Therapeutic Class Overview
Colony Stimulating Factors

Therapeutic Class Overview/Summary:
This review will focus on the granulocyte colony stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs).[1-5] Colony-stimulating factors (CSFs) fall under the naturally occurring glycoprotein cytokines, one of the main groups of immunomodulators.[6] In general, these proteins are vital to the proliferation and differentiation of hematopoietic progenitor cells.[6-8] The G-CSFs commercially available in the United States include pegfilgrastim (Neulasta®), filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), and tbo-filgrastim (Granix®). While filgrastim-sndz and tbo-filgrastim are the same recombinant human G-CSF as filgrastim, only filgrastim-sndz is considered a biosimilar drug as it was approved through the biosimilar pathway. At this time, filgrastim-sndz has not applied for the interchangeable designation from the Food and Drug Administration (FDA). When tbo-filgrastim was approved, a regulatory pathway for biosimilar drugs had not yet been established in the United States and tbo-filgrastim was filed under its own Biologic License Application.[9] Only one GM-CSF is currently available, sargramostim (Leukine®). These agents are FDA-approved for a variety of conditions relating to neutropenia or for the collection of hematopoietic progenitor cells by leukapheresis.[1-5]

The G-CSFs are generally used in patients with cancer to reduce the incidence of adverse events associated with chemotherapy, such as febrile neutropenia, infections and delayed neutrophil recovery time. Neutrophils are the body's defense system against infection and play a key role in the process of acute inflammation.[10] Chemotherapy and radiation can affect neutrophil function as well as decrease the production of neutrophils in the bone marrow. When the absolute neutrophil count (ANC) falls below 1,500 cells/µL, this is defined as neutropenia. Patients who have severe neutropenia (ANC <500 cells/µL) are at high risk for infection.[10] Endogenous G-CSF is a growth factor produced by monocytes, fibroblasts and endothelial cells that acts upon the bone marrow to increase the production of neutrophils. In addition to increasing neutrophil production, G-CSF also enhances phagocytic and cytotoxic actions of mature neutrophils.[1,2] Filgrastim, tbo-filgrastim, filgrastim-sndz and pegfilgrastim are produced by recombinant deoxyribonucleic acid (DNA) technology via the insertion of the human G-CSF gene into *Escherichia coli* (*E coli*) bacteria.[1-3,5] Pegfilgrastim, a long-acting formulation of filgrastim, is produced by conjugating filgrastim with polyethylene glycol, thereby increasing the molecular weight and delaying kidney excretion.[3]

GM-CSF is primarily used to accelerate myeloid recovery in oncology patients following myelosuppressive treatment regimens. Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes, macrophages, fibroblasts and endothelial cells.[6] In addition to increasing the production of neutrophils, GM-CSF also increases other white blood cells including monocytes, macrophages and eosinophils in the bone marrow as well as promoting their function. Like the G-CSFs, sargramostim is also produced utilizing recombinant DNA technology; however it is derived in yeast (*Saccharomyces cerevisiae*) expression system rather than from *E coli* bacteria.[4]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Filgrastim (Neupogen®)	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML, Myeloablative chemotherapy followed by BMT, Autologous	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL	a *

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	Peripheral Blood Progenitor Cell Collection and Therapy, Congenital Neutropenia, Idiopathic or Cyclic Neutropenia, Hematopoietic Syndrome of Acute Radiation Syndrome		
Filgrastim-sndz (Zarxio®*)	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML, Myeloablative chemotherapy followed by BMT, Autologous Peripheral Blood Progenitor Cell Collection and Therapy, Congenital Neutropenia, Idiopathic or Cyclic Neutropenia	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL	-
Pegfilgrastim (Neulasta®)	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies, Hematopoietic Syndrome of Acute Radiation Syndrome	Prefilled Syringe: 6 mg/0.6 mL	-
Sargramostim (Leukine®)	Induction Chemotherapy for AML, Non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Hodgkin's disease undergoing autologous BMT, Allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed, Autologous Peripheral Blood Progenitor Cell Collection and Therapy	Vial (powder for reconstitution): 250 µg Vial (solution) 500 µg/1 mL	-
Tbo-filgrastim (Granix®)	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies	Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL	-

*Zarxio® is a biosimilar to the reference drug Neupogen®.

Evidence-based Medicine

- The safety and efficacy of the granulocyte and granulocyte-macrophage colony stimulating factors have been evaluated in several clinical trials; however, there are few trials that compare G-CSFs to GM-CSFs. Agents were shown to be safe and effective for FDA-approved indications.[18-53]
- Tbo-filgrastim was evaluated in a single multi-center, placebo- and active-controlled, randomized control trial that evaluated patients with breast cancer. Patients received tbo-filgrastim, filgrastim, or placebo for cycle one. For cycle two to four, patients that received placebo were switched to tbo-filgrastim. Doses were 5µg/kg daily for both active treatment groups for all cycles. The primary efficacy endpoint was duration of severe neutropenia in cycle one. When compared to placebo, tbo-

filgrastim was provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary endpoints showed no differences between tbo-filgrastim and filgrastim during any cycle or overall.[38]

Key Points within the Medication Class

- Based on current guidelines:
  - It is important to prevent and limit the duration of febrile neutropenia.[11,12]
  - Recommend primary prophylaxis with a CSF when the risk of febrile neutropenia is >20%.
  - Recommend that the therapeutic use of a CSF be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.
  - There is currently no general consensus among the guidelines regarding the specific CSFs within the class.
  - The NCCN states that when choosing an agent for the treatment of prophylaxis of febrile neutropenia, filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.[11,13]
  - The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.[14]
  - The ASCO state that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.[12]

- Other Key Facts:
  - Due to the pathway taken, tbo-filgrastim does not share all of the same indications as filgrastim and these two products are not interchangeable. It is important to note that although filgrastim-sndz is a biosimilar product, and it was approved with all the same indications as filgrastim at the time, filgrastim has since received FDA-approval for an additional indication that filgrastim-sndz does not have, to increase survival in patients with acute exposure to myelosuppressive doses of radiation.[1-3]
  - Differences among dosing schedules also exist between the agents. Pegfilgrastim is administered at a fixed dose (6 mg subcutaneously once per chemotherapy cycle), while filgrastim, filgrastim-sndz, tbo-filgrastim, and sargramostim are dosed based on patient's body weight and are administered daily.[1-5]

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Therapeutic Class Review
Colony Stimulating Factors

Overview/Summary

This review will focus on the granulocyte colony stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs).[1-5] Colony-stimulating factors (CSFs) fall under the naturally occurring glycoprotein cytokines, one of the main groups of immunomodulators.[6] In general, these proteins are vital to the proliferation and differentiation of hematopoietic progenitor cells.[6-8] The G-CSFs commercially available in the United States include pegfilgrastim (Neulasta®), filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), and tbo-filgrastim (Granix®). While filgrastim-sndz and tbo-filgrastim are the same recombinant human G-CSF as filgrastim, only filgrastim-sndz is considered a biosimilar drug as it was approved through the biosimilar pathway. At this time, filgrastim-sndz has not applied for the interchangeable designation from the Food and Drug Administration (FDA). When tbo-filgrastim was approved, a regulatory pathway for biosimilar drugs had not yet been established in the United States and tbo-filgrastim was filed under its own Biologic License Application.[9] Only one GM-CSF is currently available, sargramostim (Leukine®). These agents are FDA-approved for a variety of conditions relating to neutropenia or for the collection of hematopoietic progenitor cells by leukapheresis.[1-5] Due to the pathway taken, tbo-filgrastim does not share all of the same indications as filgrastim and these two products are not interchangeable. It is important to note that although filgrastim-sndz is a biosimilar product, and it was approved with all the same indications as filgrastim at the time, filgrastim has since received FDA-approval for an additional indication that filgrastim-sndz does not have, to increase survival in patients with acute exposure to myelosuppressive doses of radiation.[1-3] A complete list of indications for each agent can be found in Table 2. Differences among dosing schedules also exist between the agents. Pegfilgrastim is administered at a fixed dose (6 mg subcutaneously once per chemotherapy cycle), while filgrastim, filgrastim-sndz, tbo-filgrastim, and sargramostim are dosed based on patient's body weight and are administered daily.[1-5]

The G-CSFs are generally used in patients with cancer to reduce the incidence of adverse events associated with chemotherapy, such as febrile neutropenia, infections and delayed neutrophil recovery time. Neutrophils are the body's defense system against infection and play a key role in the process of acute inflammation.[10] Chemotherapy and radiation can affect neutrophil function as well as decrease the production of neutrophils in the bone marrow. When the absolute neutrophil count (ANC) falls below 1,500 cells/µL, this is defined as neutropenia. Patients who have severe neutropenia (ANC <500 cells/µL) are at high risk for infection.[10] Endogenous G-CSF is a growth factor produced by monocytes, fibroblasts and endothelial cells that acts upon the bone marrow to increase the production of neutrophils. In addition to increasing neutrophil production, G-CSF also enhances phagocytic and cytotoxic actions of mature neutrophils.[1,2] Filgrastim, tbo-filgrastim, filgrastim-sndz and pegfilgrastim are produced by recombinant deoxyribonucleic acid (DNA) technology via the insertion of the human G-CSF gene into *Escherichia coli* (*E coli*) bacteria.[1-3,5] Pegfilgrastim, a long-acting formulation of filgrastim, is produced by conjugating filgrastim with polyethylene glycol, thereby increasing the molecular weight and delaying kidney excretion.[3]

GM-CSF is primarily used to accelerate myeloid recovery in oncology patients following myelosuppressive treatment regimens. Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes, macrophages, fibroblasts and endothelial cells.[6] In addition to increasing the production of neutrophils, GM-CSF also increases other white blood cells including monocytes, macrophages and eosinophils in the bone marrow as well as promoting their function. Like the G-CSFs, sargramostim is also produced utilizing recombinant DNA technology; however it is derived in yeast (*Saccharomyces cerevisiae*) expression system rather than from *E coli* bacteria.[4]

Based on current guidelines regarding the general use of CSFs such as the National Comprehensive Cancer Network (NCCN) Myeloid Growth Factors Clinical Practice Guideline in Oncology and the American Society of Clinical Oncology (ASCO) 2006 Update of Recommendations for the Use of White

Blood Cell Growth Factors, both recognize the importance of preventing and limiting the duration of febrile neutropenia. Similarly, both guidelines recommend primary prophylaxis with a CSF when the risk of febrile neutropenia is >20%. In addition, they recommend that the therapeutic use of a CSF be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.[11,12] There is currently no general consensus among the guidelines regarding the specific CSFs within the class. The NCCN states that when choosing an agent for the treatment of prophylaxis of febrile neutropenia, filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.[11,13] The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.[14] The ASCO state that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.[12]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Filgrastim (Neupogen®)	Granulocyte colony stimulating factor	a *
Filgrastim-sndz (Zarxio®*)	Granulocyte colony stimulating factor	-
Pegfilgrastim (Neulasta®)	Granulocyte colony stimulating factor	-
Sargramostim (Leukine®)	Granulocyte-macrophage colony stimulating factor	-
Tbo-filgrastim (Granix®)	Granulocyte colony stimulating factor	-

*Zarxio® is a biosimilar to the reference drug Neupogen®.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Indication	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Hodgkin's disease following autologous bone marrow transplantation.				a	
Acceleration of myeloid recovery in patients undergoing allogeneic bone marrow transplantation from human leukocyte antigen-matched related donors.				a	
Graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic bone marrow transplantation				a	
Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis in patients undergoing autologous peripheral blood progenitor cell collection and following transplantation of autologous peripheral blood progenitor cells	a	a			
To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever/febrile neutropenia	a	a	a		a
To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)	a		a		

Indication	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation	a	a			
To reduce the incidence and duration of sequelae of chronic neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	a *	a *			
To reduce the time to neutrophil recovery and the duration of fever, following induction chemotherapy in patients with acute myeloid leukemia	a	a		a †	
To reduce the time to neutrophil recovery and the duration of fever, following consolidation chemotherapy in patients with acute myeloid leukemia	a	a			

*Approved for chronic administration.
†Safety and efficacy has not been established in patients <55 years of age.

Although not FDA approved, filgrastim has been used for the treatment of graft failure after bone marrow transplantation, neutropenia associated with myelodysplastic syndrome, hairy cell leukemia, aplastic anemia, acquired immune deficiency syndrome and zidovudine- and other drug-induced neutropenias. Pegfilgrastim has been used for peripheral blood stem cell leukapheresis prior to autologous stem cell transplantation. Sargramostim has also been used for non-FDA approved indications. It has been most commonly used to treat Crohn's disease. Other uses of sargramostim include the treatment of melanoma, neutropenia associated with myelodysplastic syndrome or aplastic anemia, oral mucositis, pulmonary alveolar proteinosis, sepsis and neutropenia in the newborn, stomatitis, zidovudine- and other drug-induced neutropenia and wound healing. Sargramostim has also been used as a vaccine adjuvant and an adjunct to high-dose chemotherapy.[15,16]

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,17]

Generic Name(s)*	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Filgrastim	60 to 70 (SC)	Not reported	Not reported	3.5
Filgrastim-sndz	60 to 70 (SC)	Not reported	Not reported	3.5
Pegfilgrastim	Not reported	Not reported	Not reported	15 to 18
Sargramostim	Not reported	Not reported	Not reported	1 (IV) 2 to 3 (SC)
Tbo-filgrastim	33*	Not reported	Not reported	3.2 to 3.8

SC=subcutaneous, IV=intravenous
*Absolute bioavailability based on a dose of 5 µg/kg injected subcutaneously.

Clinical Trials

The safety and efficacy of the granulocyte and granulocyte-macrophage colony stimulating factors have been evaluated in several clinical trials; however, there are few trials that compare G-CSFs to GM-CSFs.[18-53]

Two retrospective trials evaluated the differences in efficacy between filgrastim and pegfilgrastim in patients with nonmyeloid malignancies who underwent chemotherapy. In Almenar et al, a multicenter,

retrospective, observational trial, pegfilgrastim was associated with fewer episodes of febrile neutropenia compared to filgrastim (10.7 vs 24.3%, respectively; P value not reported) as well as fewer hospitalizations for febrile neutropenia (9.3 vs 19.8%, respectively; P value not reported).[18] Results from Weycker et al also showed the risk of hospitalization for febrile neutropenia or infection was lower with pegfilgrastim compared to filgrastim (odds ratio, 0.64; 95% confidence interval [CI], 0.48 to 0.85; P=0.002).[19]

A multicenter, randomized, double-blind, active-control trial compared single-dose pegfilgrastim to daily filgrastim in reducing neutropenia in 310 patients who received four cycles of myelosuppressive chemotherapy for high-risk breast cancer. There were no significant differences between treatment groups in the duration of severe neutropenia and the depth of ANC nadir in all cycles. Overall, the incidence of febrile neutropenia was less in the pegfilgrastim group than in the filgrastim group (9 vs 18%; P=0.029). The difference in the mean duration of severe neutropenia between the pegfilgrastim and filgrastim treatment groups was less than one day. Adverse event profiles in the pegfilgrastim and filgrastim groups were similar. A single injection of pegfilgrastim per cycle was as safe and effective as daily injections of filgrastim in reducing neutropenia and its complications in patients who received four cycles of chemotherapy.[21]

One randomized, double-blind, multicenter trial compared filgrastim and sargramostim in 181 patients with chemotherapy-induced febrile neutropenia (ANC ≤500 cells/µL). Patients were given daily subcutaneous injections of either agent until ANC levels reached ≥1,500 cells/µL. Overall, the mean number of days patients received filgrastim (4.60±0.14 days) was significantly shorter than sargramostim (5.70±0.23 days; P=0.0001). There was no significant difference among the treatment groups in the mean number of days to reach an ANC 500 cells/µL (filgrastim, 3.60±0.16 vs sargramostim, 3.30±0.16; P=0.32); however, the mean number of days to reach an ANC 1,000 and 1,500 cells/µL was significantly lower in the filgrastim group (4.50±0.13 and 4.60±0.14, respectively) compared to the sargramostim group (5.10±0.22 and 5.70±0.23, respectively; P=0.009 and P=0.0001, respectively). In regards to the other endpoints reported, patients in the sargramostim group had fewer hospitalizations with febrile neutropenia or intravenous (IV) antibiotics (P=0.46), shorter mean length of hospitalization (P=0.58) and shorter mean duration of fever (P=0.14) compared to patients in the filgrastim group; however, these endpoints did not reach statistical significance. Overall the agents were well tolerated and had comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression in community practice.[22]

A second prospective, randomized, double-blind, multicenter trial comparing sargramostim and filgrastim published by the same author found that with the exception of a slightly higher incidence of grade 1 fever (37.1 to 38.0°C) with sargramostim compared to filgrastim (48 vs 26%, respectively; P=0.01), there were no statistically significant differences in the incidence or severity of local or systemic adverse events potentially related to CSFs. Although the study was not designed to evaluate efficacy directly, there were also no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization or days of IV antibiotic therapy during the treatment period. Both agents were well tolerated and there were no clinically significant differences between them.[23]

A Cochrane review of 13 randomized, placebo-controlled trials was performed to evaluate the efficacy and safety of G-CSF (filgrastim and lenograstim [not available in the United States]) or GM-CSF (sargramostim) compared to placebo in patients who were receiving nonmyeloablative chemotherapy for malignant lymphomas. Sensitivity analyses that were performed in this review concluded that there were no differences between G-CSF and GM-CSF in their effects on overall survival, freedom from treatment failure and risk reduction in incidence of neutropenia or febrile neutropenia.[24]

Two retrospective, case-controlled cohort trials were conducted to compare filgrastim, pegfilgrastim and sargramostim in reducing the risks of neutropenia-related hospitalizations in cancer patients receiving chemotherapies. Weycker et al found that the use of pegfilgrastim was associated with fewer hospitalizations for neutropenic complications compared to filgrastim and sargramostim (1.1, 2.1 and

2.5%, respectively; P<0.001 for both filgrastim and sargramostim compared to pegfilgrastim).[20] Heaney et al found that sargramostim was associated with fewer infection-related hospitalizations compared to filgrastim (12 vs 26%, respectively; P=0.0422) and pegfilgrastim (24%; P=0.0628). The incidence of hospitalizations for febrile neutropenia was also lower in the sargramostim group compared to the filgrastim and pegfilgrastim groups; however, these differences were not statistically significant.[25]

There were additional studies compared filgrastim to sargramostim. In these studies, efficacy favored filgrastim overall. Filgrastim had statistically significant fewer episodes of fever in nonmyeloid malignancies in patients receiving myelosuppressive anticancer drugs (P<0.001).[37] For collection of progenitor cells by leukapheresis, the filgrastim group had significantly greater CD34+ harvested than the sargramostim group (P=0.0001). Additionally, ANC recover was significantly more rapid in the filgrastim group and there were significantly fewer patients with a temperature >38.5°C, patients who received IV antibiotics or red blood cells and hospital admissions.[44] One study had mixed results that showed sargramostim improved time to ANC recover compared with filgrastim, but required a greater number of days with growth factor (P<0.001 and P=0.001, respectively). In this study, there were no differences between time to platelet recovery, number of days patients experienced fever or received IV antibiotics, the number of platelet transfusions and the number of red blood cell units received.[50]

Tbo-filgrastim was evaluated in a single multi-center, placebo- and active-controlled, randomized control trial that evaluated patients with breast cancer. Patients received tbo-filgrastim, filgrastim, or placebo for cycle one. For cycle two to four, patients that received placebo were switched to tbo-filgrastim. Doses were 5µg/kg daily for both active treatment groups for all cycles. The primary efficacy endpoint was duration of severe neutropenia in cycle one. When compared to placebo, tbo-filgrastim was provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary endpoints showed no differences between tbo-filgrastim and filgrastim during any cycle or overall.[38] Two additional studies published showed similar results but in patients with aggressive non-Hodgkin's lymphoma and small cell or non-small cell lung cancer.[39,40]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Decrease Incidence of Infection, as Manifested by Febrile Neutropenia, in Patients with Nonmyeloid Malignancies Receiving Myelosuppressive Anticancer Drugs Associated with Significant Incidence of Severe Neutropenia with Fever				
Almenar et al[18] Filgrastim or lenograstim daily (dosing not specified) vs pegfilgrastim (dosing not specified)	MC, OS, RETRO Patients with nonmyeloid tumors who underwent cytotoxic chemotherapy; tumor types included breast, lung, NHL, multiple myeloma, gastrointestinal, gynecological and others	N=186 Duration not specified	Primary: Proportion of patients with proactive vs reactive use of G-CSF, the duration of treatment with daily G-CSF, delay or reduction in chemotherapy dose (>3 days delay with respect to planned date of administration or <85% of planned dose administered), incidence of febrile neutropenia, incidence of hospitalization, antibiotic use, adverse events Secondary: Not reported	Primary: The percentage of patients receiving G-CSF as primary and secondary prophylaxis for febrile neutropenia was similar in both filgrastim and pegfilgrastim groups. Pegfilgrastim was less likely to be used to treat febrile neutropenia compared to filgrastim (17.3 vs 29.7%; P value not reported). The duration of treatment with daily G-CSF was not reported. Similar percentage of patients had a delay in chemotherapy administration in the filgrastim and pegfilgrastim groups (46.0 and 44.0%, respectively; P value not reported). However, 20.7% of patients receiving filgrastim had a chemotherapy dose reduction due to neutropenia, compared to 6.7% of patients receiving pegfilgrastim (P value not reported). There were fewer incidences of febrile neutropenia and hospitalization due to febrile neutropenia in the pegfilgrastim group compared to the filgrastim group. The incidences of febrile neutropenia in the filgrastim and pegfilgrastim groups were 24.3 and 10.7%, respectively (P value not reported), while the incidences of hospitalization due to febrile neutropenia were 19.8 and 9.3%, respectively (P value not reported). Fewer patients in the pegfilgrastim group received treatment of antibiotics due to febrile neutropenia compared to the filgrastim group (8.0 vs 17.1%; P value not reported). Bone pain was reported in 2.7 and 1.3% of patients in the filgrastim and pegfilgrastim groups, respectively. Other treatment-related adverse events were reported in 5.4 and 1.3% of patients in the filgrastim and pegfilgrastim groups, respectively (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Weycker et al[19] Filgrastim (dose not specified) for a mean of 4.5±3.3 days vs pegfilgrastim (dose not specified) G-CSFs were administered on or before day 5 of each chemotherapy cycle.	CO, RETRO Adult patients who received chemotherapy for a primary solid tumor and who received filgrastim or pegfilgrastim during the first course of chemotherapy; the most common types of malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy cycles were then identified; cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs were administered on or before day 5 of cycle; receipt of chemotherapy and diagnoses of	N=4,903 (patients with a total of 15,763 chemo-therapy cycles) Duration not specified	Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for febrile neutropenia or infection, incidence of all-cause hospitalization (hospitalizations for neutropenia, febrile neutropenia and infection were identified using corresponding ICD-9 codes) Secondary: Not reported	Primary: Pegfilgrastim was associated with lower incidence of hospitalizations for neutropenia compared to filgrastim (1.2 vs 2.1%; OR, 0.55; 95% CI, 0.36 to 0.84; P=0.005). The risk of hospitalization for neutropenic fever or infection was also lower with pegfilgrastim than filgrastim (3.1 vs 4.8%; OR, 0.64; 95% CI, 0.48 to 0.85; P=0.002). The incidence of all-cause hospitalizations was 6.3% with pegfilgrastim and 8.7% with filgrastim (OR, 0.70; 95% CI, 0.56 to 0.86; P=0.001). After adjusting for patient, cancer and chemotherapy characteristics, pegfilgrastim was still associated with a lower incidence of hospitalization for neutropenia (adjusted OR, 0.64; 95% CI, 0.41 to 0.99; P=0.043), hospitalization for neutropenic fever or infection (adjusted OR, 0.69; 95% CI, 0.52 to 0.92; P=0.012) and all-cause hospitalization (adjusted OR, 0.73; 95% CI, 0.59 to 0.91; P=0.004). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	malignancies were based on medical insurance claims			
Weycker et al[20] Pegfilgrastim vs filgrastim (dose not specified) for 4.8±3.4 days or sargramostim (dose not specified) for 6.0±4.4 days G-CSFs and GM-CSF were administered on or before day 5 of each chemotherapy cycle. The most common concomitant chemotherapy regimen was cyclophosphamide and doxorubicin for breast cancer, carboplatin and etoposide for lung cancer and cyclophosphamide, doxorubicin and	CO, RETRO Adult patients who received chemotherapy for solid tumors based on evidence of medical claims; each chemotherapy cycle was a minimum of 20 days; the most common malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy cycles were then identified; cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs and GM-CSF were administered on or before day 5 of cycle; receipt of	N=22,995 (patients with a total of 77,269 chemo-therapy cycles) Duration not specified	Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for neutropenic fever or infection, incidence of all-cause hospitalization within 60 days after the initiation of study drugs (hospitalizations for neutropenia, febrile neutropenia and infection were identified using corresponding ICD-9 codes) Secondary: Not reported	Primary: The risk of hospitalization for neutropenia was higher during chemotherapy cycles in which patients received filgrastim compared to pegfilgrastim (2.1 vs 1.1%, respectively; OR, 1.93, 95% CI, 1.63 to 2.28; P<0.001). Similarly, the same risk was higher in patients who received sargramostim during chemotherapy compared to pegfilgrastim (2.5 vs 1.1%, respectively; OR, 2.39, 95% CI, 1.76 to 3.26; P<0.001). A similar trend was seen in the risk of hospitalization for neutropenic fever or infection. Pegfilgrastim was associated with fewer hospitalizations compared to filgrastim (2.6 vs 4.0%, respectively; OR, 1.53; 95% CI, 1.35 to 1.72; P<0.001) and sargramostim (5.1%; OR, 1.98; 95% CI, 1.59 to 2.46; P<0.001). Patients receiving pegfilgrastim had fewer incidence of all-cause hospitalization (5.3%) compared to filgrastim (7.9%; OR, 1.55; 95% CI, 1.42 to 1.69; P<0.001) and sargramostim (9.6%; OR, 1.91; 95% CI, 1.62 to 2.25; P<0.001). After adjusting for patient, cancer and chemotherapy characteristics, filgrastim and sargramostim were still associated with increased risk of hospitalization for neutropenia compared to pegfilgrastim (OR, 1.8 for filgrastim; P<0.001; OR, 2.7 for sargramostim; P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vincristine for NHL.	chemotherapy and diagnoses of malignancies were based on medical insurance claims			
Holmes, O'Shaughnessy et al[21] Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥$10x10^9$ cells/µL after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 100 µg/kg SC on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >$1x10^9$ cells/µL, and platelet count >$100x10^9$ units/L.	DB, MC, RCT Subjects >18 years of age diagnosed with high risk stage II or stage III/IV breast cancer, who were naïve to chemotherapy or received adjuvant therapy and/or completed ≤1 regimen of chemotherapy for metastatic disease, completion of previous chemotherapy more than four weeks before randomization, an ECOG performance status ≤2, an ANC ≥$1.5x10^9$/L, platelet count ≥$100x10^9$/L, and adequate hepatic	N=310 4 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <$0.5x10^9$ cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia during cycles two through four, the depth of ANC nadir in each of the cycles (one to four), rates of febrile neutropenia and the time to ANC recovery in chemotherapy cycles one to four	Primary: There was no significant difference in duration of grade 4 neutropenia in cycle one between the filgrastim group (1.8 [1.4] days) and the pegfilgrastim group (1.7 [1.5] days; difference of 0.03 days; 95% CI, –0.36 to 0.30). Secondary: The duration of grade 4 neutropenia was significantly less in the pegfilgrastim group in cycles two to four compared to filgrastim: cycle two: 0.7 vs 1.1 days, respectively (difference of –0.40 days; 95% CI, –0.64 to –0.17; P=0.001); cycle three: 0.6 vs 1.2 days, respectively (difference of –0.63; 95% CI, –0.91 to –0.36; P≤0.001); cycle four: 0.9 vs 1.3 days (difference of –0.38 days; 95% CI, –0.71 to –0.07; P=0.019). The depth of ANC nadirs was similar between the two treatment groups over the course of the study (P values not reported). Febrile neutropenia occurred at least once during the study in 9% of patients in the pegfilgrastim group which was significantly less than the 18% of patients in the filgrastim group (difference of –9%; 95% CI, –16.8 to –1.1; P=0.029). The mean time to ANC recovery was 9.3 days for the pegfilgrastim group and 9.7 days for the filgrastim group (difference of –0.40 days; 95% CI, –0.88 to 0.08; P value not reported). Adverse event profiles in the pegfilgrastim and filgrastim groups were similar.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and cardiac function			
Beveridge et al[22] Filgrastim 5 µg/kg SC daily vs sargramostim 250 µg/m^2 SC daily	DB, MC, RCT Patients ≥18 years of age who developed neutropenia within four weeks of chemotherapy regimen and had an ANC <500 cells/µL	N=181 Mean duration of treatment: filgrastim, 4.60±0.14 days; sargra-mostim, 5.70±0.23 days	Primary: Number of days to reach an ANC 1,000 and 1,500 cells/µL, number of febrile neutropenic episodes, duration of hospitalization, duration of fever, duration of IV antibiotic therapy, number of episodes of chills or fever, number of events of fever in the morning, evening and four hours after injection of CSF, documented positive bacterial cultures, number of events of sepsis and adverse events Secondary: Not reported	Primary: The number of days to reach an ANC 1,000 cells/µL was significantly fewer with filgrastim compared to sargramostim (4.50±0.13 vs 5.10±0.22 days; P=0.009). Similarly, filgrastim was associated with fewer number of days to reach an ANC 1,500 cells/µL compared to sargramostim (4.60±0.14 vs 5.70±0.23 days; P=0.0001). There was no significant difference between the two treatment groups with regard to the number of days to reach an ANC 500 cells/µL (3.60±0.16 vs 3.30±0.16 days; P=0.32). There was no significant difference between filgrastim and sargramostim regarding the proportion of patients with hospitalizations for febrile neutropenia or IV antibiotic therapy (6.3 and 7.8%, respectively; P=0.46). Compared to filgrastim, sargramostim was associated with a shorter duration of hospitalization (5.60±1.10 vs 4.80±0.58 days; P=0.58), fever (3.60±0.92 vs 1.60±0.60 days; P=0.14) and IV antibiotic therapy (6.30±1.3 vs 4.70±0.67 days; P value not reported). Two patients (1.9%) in the filgrastim group and one patient (1.2%) from the sargramostim group experienced chills (P=0.60). There was no significant difference between filgrastim and sargramostim with respect to the incidence of Grade 2 fever reported in the morning (10 and 9%, respectively; P=0.53), evening (13.7 and 11.0%, respectively; P=0.41) and four hours after CSF injection (10.7 and 3.8%, respectively; P=0.07). Two patients receiving filgrastim and no patient receiving sargramostim had documented positive blood cultures, indicating bacteremia (P value not reported). However, the incidence of sepsis was not reported. Both filgrastim and sargramostim were well-tolerated, and there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant difference between the two treatment groups with regard to the incidence of adverse events. Secondary: Not reported
Beveridge et al[23] Filgrastim 7 µg/kg daily vs sargramostim 300 µg daily Study drugs were administered starting one to two days after chemotherapy, chemotherapy regimens were not specified in the protocol.	DB, MC, RCT Patients ≥18 years of age, documented malignancy and an ECOG performance status grade 0 to 2 and received cytotoxic chemotherapy	N=144 7 days	Primary: Tolerability, hospitalization and use of IV antibiotics Secondary: Not reported	Primary: Both agents were well tolerated. There were no cases of grade 4 toxicity during the treatment period in patients receiving either sargramostim or filgrastim and no instances when either drug had to be discontinued because of toxicity (P values not reported). Grade 1 fever (37.1 to 38.0°C) occurred in significantly more patients in the filgrastim group (36 patients) compared to the sargramostim group (16 patients; P<0.01). There were no statistically significant differences between treatment groups in the incidence of local reactions or in the incidence or severity of bone or joint pain, chills, nausea, vomiting, dyspnea or headache (P values not reported). There were no significant differences between the filgrastim and sargramostim groups in days of hospitalization (4.0 vs 4.6 days, respectively) and in days of IV antibiotic therapy (6.0 vs 4.4 days, respectively) during the treatment period (P values not reported). Secondary: Not reported
Bohlius et al[24] Filgrastim or lenograstim* ≥1 µg/kg/day IV or SC or sargramostim ≥1	MA of 13 PC, RCT Patients >16 years of age with NHL or HD	N=2,607 Duration not specified	Primary: Overall survival, freedom from treatment failure Secondary: Quality of life, risk and duration of neutropenia, risk	Primary: When compared to placebo, treatment with CSFs had no significant effect on the overall survival (HR, 0.97; 95% CI, 0.87 to1.09; P value not reported) or freedom from treatment failure (HR, 1.11; 95% CI, 0.91 to1.35; P value not reported). Sensitivity analyses were performed and showed that there was no significant difference between G-CSF and GM-CSF in their effects on the primary endpoints.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day IV or SC vs placebo or no treatment All patients received G-CSF or GM-CSF as primary prophylaxis during standard nonmyeloablative chemotherapy prior to the onset of neutropenia in the first- or second-line treatment of malignant lymphoma. G-CSF and GM-CSF was given within 72 hours of chemotherapy administration and in each cycle of chemotherapy.			and duration of febrile neutropenia, infection, risk and duration of IV antibiotic treatment, hospitalization, dose intensity of chemotherapy, mortality during chemotherapy, tumor response, adverse effects of CSFs, risk and duration of thrombocytopenia and anemia	Secondary: No difference in quality of life was detected between CSF and placebo. Treatment with CSFs was associated with a 33% risk reduction in developing neutropenia (RR, 0.67; 95% CI, 0.60 to 0.73; P value not reported). There was a 26% risk reduction in developing febrile neutropenia with an ANC <$1x10^9$/L (RR, 0.74; 95% CI, 0.62 to 0.89; P value not reported) and a 41% risk reduction in developing neutropenia with ANC <$0.5x10^9$/L (RR, 0.59; 95% CI, 0.48 to 0.72; P value not reported) with CSF compared to placebo. There was no significant difference with respect to G-CSF compared to GM-CSF. There was no conclusive evidence that CSFs reduce the duration of neutropenia or febrile neutropenia. The risk of developing an infection was also reduced by 26% in patients receiving CSF compared to patients receiving placebo (RR, 0.74; 95% CI, 0.64 to 0.85; P value not reported). There was a non-significant risk reduction in requiring IV antibiotic treatment with CSF compared to placebo (RR, 0.82; 95% CI, 0.57 to 1.18; P value not reported). There was no conclusive evidence to detect the effect of CSF on the duration of IV antibiotic treatment, hospitalization or dose intensity of chemotherapy. Between the two treatment groups, there was no difference in mortality during chemotherapy (RR, 0.93; 95% CI, 0.60 to 1.43; P value not reported) or complete tumor response (RR, 1.03; 95% CI, 0.95 to 1.10; P value not reported). Significantly more patients receiving CSF reported bone pain compared to patients receiving placebo (RR, 3.57; 95% CI, 2.09 to 6.12; P value not reported). GM-CSF was associated with a smaller risk of bone pain compared to G-CSF (P=0.026). Treatment with CSF did not increase the risk of thromboembolic complications compared to placebo (RR, 1.29;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95% CI, 0.56 to 3.01; P value not reported). There was no conclusive evidence showing that CSF treatment affects incidence or degree of thrombocytopenia or anemia.
Heaney et al[25] Sargramostim (dose not specified) vs filgrastim (dose not specified) or pegfilgrastim (dose not specified)	CO, RETRO Adult patients with cancer who had received chemotherapy and had at least two doses of filgrastim or sargramostim or at least one dose of pegfilgrastim; the most common types of malignancies were breast cancer, lung cancer and NHL; patients receiving sargramostim were matched 1:1 with patients receiving filgrastim and pegfilgrastim based and gender and age	N=2,962 Average duration of treatment: filgrastim and sargra-mostin, 31 days; peg-filgrastim, 58 days	Primary: Incidence of infection-related hospitalization, associated costs per patient per month Secondary: Incidence of febrile neutropenia-related hospitalization	Primary: Sargramostim was associated with fewer infection-related hospitalizations compared to filgrastim (12 vs 26%, respectively; incidence rate ratio, 0.46; 95% CI, 0.22 to 0.97; P=0.0422) and pegfilgrastim (12 vs 24%; incidence rate ratio, 0.52; 95% CI, 0.26 to 1.04; P=0.0628). Comparison on febrile neutropenia-related hospitalizations was not performed due to low event rate in each treatment group. The per-patient-per-month costs for sargramostim was 84% lower compared to filgrastim ($138/patient/month vs $866/patient/month; P=0.0380) and 62% lower compared to pegfilgrastim ($138/patient/month vs $365/patient/month; P=0.01). Secondary: Patients receiving sargramostim had fewer febrile-neutropenia-related hospitalizations compared to filgrastim and pegfilgrastim, though the differences were not statistically significant. The incidence of hospitalizations was 5% for sargramostim, 8% for filgrastim (incidence rate ratio to sargramostim, 0.58; 95% CI, 0.17 to 1.98; P=0.3837) and 6% for pegfilgrastim (incidence rate ratio, 0.85; 95% CI, 0.26 to 2.75; P=0.0628).
Grigg et al[32] Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC	MC, OL, RCT Subjects ≥60 years of age diagnosed with	N=50 6 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9/L) in cycle one	Primary: The mean duration of grade 4 neutropenia in cycle one was shorter with the patients who received cytokine (pegfilgrastim 60 µg/kg, 2.2±1.2 days; pegfilgrastim 100 µg/kg, 1.5±1.0 days; filgrastim 0.8±1.2 days) compared to the patients who received no cytokine in cycle one (mean 5.0±2.0

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
≥10x10^9 cells/µL after the expected nadir or for 14 days, whichever occurred first vs no cytokine support in cycle 1 followed by filgrastim 5 µg/kg/day SC in all other cycles vs pegfilgrastim 60 µg/kg on day 2 of each cycle vs pegfilgrastim 100 µg/kg on day 2 of each cycle Subjects received CHOP therapy repeated every three weeks for up to six cycles provided ANC >1x10^9 cells/µL, and platelet count >100x10^9 units/L.	NHL requiring treatment with standard CHOP therapy, ECOG performance status ≤2, an ANC ≥2x10^9 cells/µL, platelet count ≥100x10^9/L, bilirubin concentration ≤2xupper limit of normal, and adequate renal function		Secondary: Incidence of febrile neutropenia (ANC <0.5x10^9 cells/µL and temperature >38.2°C), the time to ANC recovery (ANC ≥2.0x10^9 cells/µL) in cycles one, three and six and the ability to deliver planned dose of chemotherapy on time	days; P values not reported). Secondary: The incidence of febrile neutropenia throughout the study was as follows: four of 13 (31%) patients treated with pegfilgrastim 60 µg/kg who received a total of 68 cycles, zero of 13 patients treated with pegfilgrastim 100 µg/kg who received a total of 62 cycles, one of 13 (8%) patients treated with filgrastim who received a total of 59 cycles and zero of nine patients who did not receive cytokine (in cycle one only) who received a total of 43 cycles (P values not reported). The median time to ANC recovery in cycles one, three and six was similar for the all the groups receiving cytokine support: pegfilgrastim 60 µg/kg, 11 days (10 to 14); pegfilgrastim 100 µg/kg, 10 days (nine to 12) and filgrastim, 10 days (one to 20) (P values not reported). In cycles two to six, eight patients experienced a delay in the start of chemotherapy of more than three days; no delays were related to neutropenia. Full dose cyclophosphamide and doxorubicin was given in 94%, 96% and 100% of cycles given to filgrastim, pegfilgrastim 60 µg/kg and pegfilgrastim 100 µg/kg patients, respectively. One filgrastim patient received reduced doses due to error and one pegfilgrastim 60 µg/kg patient received reduced doses following febrile episodes. In addition, seven patients had a reduction in vincristine dose due to neuropathy (P values not reported). Pegfilgrastim was well tolerated with a safety profile similar to daily filgrastim. Adverse events (WHO grade 1 to 4) were reported by 95% of filgrastim and 96% of pegfilgrastim patients (P value not reported).
Holmes, Jones et al[33] Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC	MC, RCT Woman ≥18 years of age diagnosed with high-risk	N=154 4 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9 cells/L) in cycle	Primary: In cycle one, the mean duration of grade 4 neutropenia for filgrastim was 1.6 days compared to 2.7 days for pegfilgrastim 30 µg/kg, two days for pegfilgrastim 60 µg/kg, and 1.3 days for pegfilgrastim 100 µg/kg (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
≥10x10^9/L after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 30 µg/kg SC on day 2 of each cycle vs pegfilgrastim 60 µg/kg SC on day 2 of each cycle vs pegfilgrastim 100 µg/kg SC on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >1x10^9 cells/µL, and platelet count >100 x 10^9 units/L.	stage II, III or IV breast cancer, ECOG performance status ≤2, WBC count ≥4x10^9 cells/µL, platelet count ≥150x10^9 units/L, adequate renal, hepatic and cardiac function		one Secondary: Duration of grade 4 neutropenia during cycles two through four, ANC profile, time to ANC recovery (ANC ≥2x10^9 cells/µL) after the expected ANC nadir, and rate of febrile neutropenia (ANC <0.5x10^9 cells/µL and temperature >38.2°C)	Secondary: The duration of grade 4 neutropenia in cycles two through four ranged between zero and one day in ≥98% for pegfilgrastim 100 µg/kg, compared to 86% for pegfilgrastim 60 µg/kg and ≥92% for filgrastim (P values not reported). Most patients in the pegfilgrastim 30 µg/kg group were escalated to higher doses of pegfilgrastim in later cycles and these values were not reported. Pegfilgrastim 100 µg/kg had similar ANC profiles as filgrastim in each of the cycles (P value not reported). The mean time to ANC recovery for cycle one was 11 days for pegfilgrastim 30 µg/kg and 10.3 days for 60 µg/kg, respectively, compared to 9.5 days for pegfilgrastim 100 µg/kg and 9.4 days for filgrastim 5 µg/kg/day. The mean time to ANC recovery was significantly longer for pegfilgrastim 30 and 60 µg/kg/cycle but not the 100 µg/kg/cycle, compared to filgrastim (P values not reported). Febrile neutropenia was experienced at least once during the study by seven patients (12%) with pegfilgrastim 60 µg/kg, five patients (11%) with pegfilgrastim 100 µg/kg and two patients (12%) with filgrastim. There were no significant differences demonstrated between the groups (P values not reported). The safety profiles of pegfilgrastim and filgrastim were similar.
Green et al[34]	DB, MC, RCT	N=157	Primary: Duration of grade	Primary: There was no significant difference in the mean duration of grade 4

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥10x10^9 cells/µL after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 6 mg SC once on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >1x10^9 cells/µL, and platelet count >100x10^9 units/L.	Subjects >18 years of age diagnosed with high-risk stage II or stage III/IV breast cancer, ECOG performance status ≤2, chemotherapy naïve or adjuvant therapy only or only one chemotherapy regimen for metastatic disease, an ANC ≥1.5x10^9 cells/µL, platelet count ≥100x10^9 units/L, and a serum creatinine <1.5 times upper limit of normal	4 cycles of chemo-therapy	4 neutropenia (ANC <0.5x10^9 cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia in each of cycles two through four, depth of the ANC nadir in each of cycles two through four, incidence of febrile neutropenia, time to neutrophil recovery (ANC ≥2x10^9 cells/µL), incidence of IV antibiotic administration and hospitalization	neutropenia in cycle one between the filgrastim group (1.6±1.1 days) and the pegfilgrastim group (1.8±1.4 days; difference of 0.23 days; 95% CI, –0.15 to 0.63). Secondary: There were no significant differences demonstrated between treatment groups in the mean duration of grade 4 neutropenia in cycles two through four. Mean duration of grade 4 neutropenia in the filgrastim vs pegfilgrastim group was as follows: cycle two: 0.9±1.0 vs 1.1±1.2 days, respectively; difference of 0.13; 95% CI, –0.20 to 0.47; cycle three: 0.9±1.1 vs 1.1±1.2 days, respectively; difference of 0.16; 95% CI, –0.20 to 0.51; cycle four: 1.0±1.3 vs 1.0±1.1 days, respectively; difference of 0.00 days; 95% CI, –0.39 to 0.39. The median ANC nadir was significantly different between the two treatment groups (P value not reported). The incidence of febrile neutropenia was not statistically significant between the filgrastim (10 [13%] patients) group and the pegfilgrastim group (15 patients [20%]; difference of –7%; 95% CI, –19 to 5). The median time to neutrophil recovery in all cycles was nine days from the day of chemotherapy administration for both the pegfilgrastim group and the filgrastim group (P values not reported). Rates of IV antibiotic administration (21 and 17%) and hospitalizations (31 and 18%) for the filgrastim and pegfilgrastim groups, respectively, were generally consistent with the results obtained for the incidence of febrile neutropenia (P values not reported). The safety profile of pegfilgrastim, assessed by adverse events, antibody formation and changes in laboratory values, was similar to that of filgrastim.
Vose et al[35]	MC, OL, RCT	N=66	Primary: Duration of grade	Primary: There was no significant difference in the duration of grade 4 neutropenia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Filgrastim 5 µg/kg/day SC starting on day 6, 1 day after completion of chemotherapy and given until ANC ≥10x10^9 cells/µL postnadir or for 12 days, whichever came first vs pegfilgrastim 100 µg/kg SC once on day 6, one day after completion of chemotherapy, of each cycle Chemotherapy consisted of etoposide, methylprednisolone, cisplatin and cytarabine and repeated every three weeks.	Subjects ≥18 years of age with an ECOG performance status ≤2, an ANC ≥1.5x10^9 cells/µL, platelet count ≥100x10^9 cells/µL, and adequate renal function who were diagnosed with relapsed or persistent HD and had treatment failure from ≥1 prior chemotherapy regimen or a diagnosis of NHL and relapsed from or were refractory to first-line CHOP chemotherapy	4 cycles of chemo-therapy	4 neutropenia (ANC <0.5x10^9 cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia in subsequent cycles, ANC profiles, time to ANC recovery, and rates of febrile neutropenia (ANC <0.5x10^9 cells/µL and temperature ≥ 38.2°C) for cycles one and two	in cycle one between the filgrastim group (68%) and the pegfilgrastim group (69%). Secondary: The mean duration of grade 4 neutropenia was not significantly different between the filgrastim group (0.6 days) and pegfilgrastim group (0.4 days; difference of –0.14; 95% CI, –0.73 to 0.44). The geometric mean ANC nadir was 0.208x10^9 cells/µL for the filgrastim group and 0.161x10^9 cells/µL for the pegfilgrastim group (95% CI, 0.326 to 1.839; P value not reported). The median time to ANC recovery was not significantly different between the filgrastim group (15 days) and pegfilgrastim group (16 days; 95% CI, –0.84 to 3.07). The rates of febrile neutropenia was not significantly different between the filgrastim group (19%) and pegfilgrastim group (21%; difference of 1.3%; 95% CI, –19.4 to 22.0). Reported side effects were similar between the two treatment groups.
Staber et al[36] Filgrastim 5 µg/kg/day SC from day 7 after transplantation until ANC >10x10^9 cells/µL vs pegfilgrastim 6 mg SC once on day 5 after	T Subjects with hematological malignancies, an ECOG performance status ≤2 and normal cardiac, pulmonary, hepatic and renal	N=54 Duration not specified	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9 cells/µL) Secondary: Incidence of febrile neutropenia (ANC <0.5x10^9 cells/µL and	Primary: The mean duration of grade 4 neutropenia was significantly shorter in the pegfilgrastim group (8.3 days [8 to 14]) compared to the filgrastim group (9.5 days [5 to 14]; P=0.047). Secondary: There was no significant difference in the incidence of febrile neutropenia between the filgrastim group (23 patients [77%]) compared to the pegfilgrastim group (24 patients [80%]; P value not reported). The mean duration of febrile neutropenia was significantly shorter in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
transplantation PBSCT was performed on day 0 with unmanipulated peripheral blood stem cells that were harvested using cyclophosphamide and G-CSF before the start of the study.	function prior to transplantation		temperature ≥38.2°C), duration of febrile neutropenia, duration of fever and incidence of documented infections	pegfilgrastim group (1.6 days [zero to five]) compared to the filgrastim group (3.0 days [zero to nine]; P=0.017). The mean duration of fever was significantly shorter in the pegfilgrastim group (1.73 days [zero to five]) compared to the filgrastim group (4.1 days [zero to 16]; P=0.003). The incidence of documented infections was significantly less in the pegfilgrastim group (eight patients [26%]) compared to the filgrastim group (17 patients [56%]; P=0.02). Bone pain was the only adverse event considered cytokine related and was reported in six patients (20%) in the pegfilgrastim group and seven patients (23%) in the filgrastim group (P value not reported).
Milkovich et al[37] Filgrastim vs sargramostim Dosages of the medications were at the discretion of the investigator. Mean doses were 369 µg (5.5 µg/kg) for filgrastim and 474 µg (6.9 µg/kg) for sargramostim.	MC, RETRO, XO Subjects ≥18 years of age who received chemotherapy for a lung, breast, lymphatic system or ovarian tumor	N=490 12 months	Primary: Frequency and severity of adverse events and the frequency of switching to the alternative CSF Secondary: Not reported	Primary: Significantly more episodes of fever ≥100.4°F occurred in the sargramostim group (57 cycles [9%]) compared to the filgrastim group (39 cycles [4%]; P<0.001). Although skeletal muscle pain was the most frequently reported adverse event, there was no significant difference between the filgrastim group and the sargramostim group (11 vs 8%; P=0.06). Several adverse events occurred significantly more frequently in the sargramostim group compared to the filgrastim group: fatigue (4 vs 2%; P<0.05), diarrhea (3 vs 2%; P<0.05), injection site reaction (6 vs <1%; P<0.01), other dermatologic disorders (3 vs <1%; P<0.01) and edema (2 vs <1%; P<0.01). Significantly more patients switched from sargramostim to filgrastim (74 patients [29%]) compared to the number of patients who switched from filgrastim to sargramostim (two patients [1%]; P<0.001). The most common reason for switching from sargramostim to filgrastim was due to an adverse event (45 patients [18%]) compared to zero patients who switched from filgrastim to sargramostim (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
del Giglio et al[38] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days vs placebo Patients who received placebo were switched to tbo-filgrastim therapy after cycle one. All patients underwent a maximum of four cycles of chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2)	AC, MC, PC, RCT Patients ≥18 years of age with breast cancer high risk stage II, III, or IV, planned treatment with docetaxel and doxorubicin, chemotherapy-naïve, Eastern Cooperative Oncology Group performance status ≤ 2, an ANC ≥1.5 x 10^9/L, platelet count ≥100 × 10^9/L, and adequate cardiac, hepatic and renal function	N=348 One cycle (primary endpoint) Four cycles (other endpoints)	Primary: Duration of severe neutropenia in cycle one Secondary: Duration of severe neutropenia in cycles two to four, incidence of observed and protocol febrile neutropenia by all cycles and across all cycles, depth of ANC nadir in cycles one to four, and time to ANC recovery in cycles one to four	Primary: Duration of severe neutropenia in the per-protocol groups were 1.1 days for both the tbo-filgrastim and filgrastim groups and 3.9 days for the placebo group. When compared to placebo, tbo-filgrastim provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary: The mean duration of severe neutropenia in cycles two to four were similar in all treatment groups. Mean duration was 0.7, 0.7, and 0.5 days in cycle two, 0.6, 0.7, and 0.6 days in cycle three, and 0.7, 0.7, and 0.6 days in cycle four in the tbo-filgrastim, filgrastim, and placebo/tbo-filgrastim group (treated with tbo-filgrastim in cycles two to four), respectively. In cycle one, the incidence of observed or protocol defined febrile neutropenia was numerically lower in the tbo-filgrastim and filgrastim groups (12.1% and 12.5%, respectively) compared to the placebo group (36.1%); however, there were no significant differences with regard to febrile neutropenia incidence between the tbo-filgrastim and filgrastim groups neither in cycle one nor across all cycles. In cycle one in the placebo group, mean ANC values decreased after day two and reached a nadir on day 11, whereas in the tbo-filgrastim and filgrastim groups, mean values increased, reaching a maximum on day three, and then decreased to a nadir on day seven. Thereafter, mean values in the active treatment groups distinctly increased again, reaching a maximum on day 11. On day 21, mean values returned to values as observed on day one in all treatment groups. In the subsequent cycles, all treatment groups demonstrated the same trends as for tbo-filgrastim

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and filgrastim in cycle one. In cycle one, the mean ANC nadir was deeper in the placebo group (0.2 x 10^9/L) compared to tbo-filgrastim and filgrastim groups (0.7 x 109/L). In cycles two, three, and four, the mean ANC nadir was not as deep as in cycle one and was similar across treatment groups with a mean value of approximately 1.0 x 109/L. In cycle one, the median time to ANC recovery was shorter in the tbo-filgrastim and filgrastim groups (8.0 and 8.0 days) compared to the placebo group (15.0 days). In cycles two, three, and four, the time to ANC recovery was similar in all treatment groups with a median of 8.0 days.
Engert et al[39] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days Patients that received filgrastim were switched to tbo-filgrastim therapy in subsequent cycles.	AC, MC, PC, RCT Patients ≥18 years of age with aggressive non-Hodgkin's lymphoma, planned/eligible to receive the CHOP regimen as routine chemotherapy, were chemotherapy-naïve, had a life-expectancy of at least six months, had an IPI score 3, ANC 1.5 x 109/L, platelet count 100x109/L, and adequate hepatic, cardiac, and renal function	N=92 Six cycles	Primary: Duration of severe neutropenia in cycles one and four, incidence of observed and protocol defined febrile neutropenia by cycle and across all cycles, depth of ANC nadir in cycles one and four and time to ANC recovery in cycles one and four Secondary: Not reported	Primary: Mean duration of severe neutropenia was 0.5 and 0.9 days in cycle one for tbo-filgrastim and filgrastim, respectively, and 0.2 and 0.7 days in cycle four after the switch from filgrastim to tbo-filgrastim in the reference group. The estimated treatment difference was -0.378 days (95% CI, -0.837 to 0.081, P=0.1055). In cycle one, incidences of observed or protocol defined febrile neutropenia were 11.1% for tbo-filgrastim group and 20.7% for filgrastim group (P=0.1232). Across all cycles, the incidence of observed or protocol defined febrile neutropenia was 31.7% and 41.4% in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively (P=0.2094). In cycle one in both treatment groups, mean ANC values increased after day two, reaching a maximum on day four and then decreased to a nadir on day nine. Thereafter, mean values increased again, reaching a maximum on day 11. On day 21, mean values approached those observed on day 1 in both treatment groups. The ANC profile was similar in cycles two to six. In cycle one, mean ANC nadir values were 1.7 x 109/L in the tbo-filgrastim group and 1.1 x 109/L in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim, mean ANC nadir values were 2.1 x

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				109/L and 1.8 x 109/L in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one, mean time to ANC recovery was 6.0 days in the tbo-filgrastim group and 6.7 days in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean time to ANC recovery was 4.9 days and 6.1 days in the tbo-filgrastim and filgrastim tbo-filgrastim groups, respectively. Secondary: Not reported
Gatzemeir et al[40] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days Patients that received filgrastim were switched to tbo-filgrastim therapy in subsequent cycles.	AC, MC, PC, RCT Patients ≥18 years of age with small cell or non-small cell lung cancer planned/eligible to receive a platinum-based myelosuppressive chemotherapy, were chemotherapy-naive or had received no more than one previous chemotherapy regimen, had Eastern Cooperative Oncology Group performance status 2, an ANC	N=240 Six cycles	Primary: Duration of severe neutropenia in cycles one and four, the incidence of observed or protocol defined febrile neutropenia by cycle and across all cycles, the depth of ANC nadir in cycles one and four, and the time to ANC recovery in cycles one and four Secondary: Not reported	Primary: Mean duration of severe neutropenia was 0.5 and 0.3 days in cycle one for tbo-filgrastim and filgrastim groups, respectively, and 0.4 and 0.3 days in cycle four after the switch from filgrastim to tbo-filgrastim in the reference group. In the analysis of covariance for duration of severe neutropenia in cycle one, the estimated treatment difference was 0.157 days (95% CI, -0.114 to 0.428, no P value reported). In cycle one, incidences of observed or protocol defined febrile neutropenia were 15.0% for the tbo-filgrastim group and 8.8% for filgrastim group (P=0.2347), and in cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, incidences were 4.3% and 3.3%, respectively (P=0.9036). Across all cycles, the incidence of observed or protocol defined febrile neutropenia was 33.1% and 23.8% in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one in both treatment groups, mean ANC values increased after day two, reaching a maximum on day five and then decreased to a nadir on day 11 (day 12 for filgrastim group). Thereafter, mean values increased again, reaching a maximum on day 14. On day 21, mean values approached those observed on day one in both treatment groups. The ANC profile was similar in cycles 2 to 6.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	1.5 x 109/L, platelet count 100 x 109/L, and adequate hepatic, cardiac, and renal function			In cycle one, mean ANC nadir values were 2.1 x 109/L in the tbo-filgrastim group and 2.9 x 109/L in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean ANC nadir values were 2.3 x 109/L and 3.2 x 109/L in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one, mean time to ANC recovery was 6.3 days in the tbo-filgrastim group and 4.5 days in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean time to ANC recovery was 6.4 days and 4.5 days in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. Secondary: Not reported
Acceleration of Myeloid Recovery in Patients with Non-Hodgkin's Lymphoma, Acute Lymphocytic Leukemia and Hodgkin's Disease Undergoing Autologous Bone Marrow Transplant				
Nemunaitis et al[26] Sargramostim 250 µg/m^2/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days vs placebo Preparative regimens used before transplantation differed among the participating institutions.	DB, MC, PC, RCT Patients with relapsed NHL, HD and ALL who were undergoing an autologous BMT	N=128 100 days	Primary: Neutrophil recovery (ANC ≥500x10^6 cells/L) Secondary: Infections, duration of IV antibiotics, duration of hospitalization	Primary: The patients in the sargramostim group had a significantly shorter time to ANC recovery compared to the patients in the placebo group (19 vs 26 days, respectively; P<0.001). Secondary: The patients in the sargramostim group had significantly fewer non-streptococcal infections compared to the patients in the placebo group (P<0.004). The patients in the sargramostim group had a significantly shorter duration of IV antibiotic use compared to the patients in the placebo group (24 vs 27 days, respectively; P=0.009). The patients in the sargramostim group had a significantly shorter duration of hospitalization compared to the patients in the placebo group (27 vs 33 days, respectively; P=0.01). There were no significant differences in incidence and duration of fever,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				frequency of other side effects or 100-day survival rate between the two groups.
Lazarus et al[27] RhGM-CSF 11 µg/kg/day IV beginning three hours after completion of marrow infusion then daily thereafter over four hours until either recovery of both neutrophil count (>1,500 cells/µL) and platelet count (>50,000 units/µL, untransfused) occurred, or CSF therapy was administered for a total of 30 days vs historical control group Treatment consisted of involved-field radiotherapy, cyclophosphamide 60 mg/kg/day IV for two days, fractionated total body irradiation and autologous BMT.	MC Patients 15 to 60 years of age with histologically confirmed NHL in relapse	N=16 Duration not specified	Primary: Neutrophil recovery (ANC $\geq$500 cells/mm^3), time to self-sustaining platelet count >20,000 units/µL, toxicity, hematopoietic reconstitution Secondary: Not reported	Primary: Neutrophil recovery was significantly faster in the rhGM-CSF group (14 days [9 to 30 days]) compared to the control group (20 days [12 to 51 days]; P=0.00002). Time to self-sustaining platelet count >20,000 units/µL was not significantly different between the rhGM-CSF group (23.5 days [12 to 100 days]) and the control group (26 days [7 to 149]; P=0.38). Toxicities encountered were mild and included fever, chills, hypertension, alopecia, rash, diarrhea, stomatitis, myalgias and synovial (knee) effusions. All patients showed early regeneration of hematopoietic precursors in the bone marrow between days 10 and 22 after transplantation and increased in proportion to peripheral blood counts, but by 30 to 60 days still remained much lower than before transplant. Neutrophils transiently decreased in 13 of 16 patients (median decrease, 42%) within 24 to 72 hours of discontinuing rhGM-CSF infusions. Secondary: Not reported
Rabinowe et al[28]	ES	N=128	Primary: Long-term	Primary: There were no significant differences between the sargramostim group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sargramostim 250 µg/m^2/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days vs placebo Patients originally participated in an efficacy study conducted by Nemunaitis et al.[23]	Patients with relapsed NHL, HD and ALL who underwent an autologous BMT	36 months	toxicities, clinical variables likely to predict for the speed of neutrophil engraftment and the independent predictive effect of sargramostim on neutrophil recovery Secondary: Not reported	and the placebo group in disease-free survival (P=0.58) or in overall survival (P=0.55). Those patients with the diagnosis of HD demonstrated delayed neutrophil recovery to both an ANC ≥100 and ≥500 cells/µL (P=0.07) in comparison to patients with NHL or leukemia. Patients with HD and previous exposure to stem cell depleting agents experienced a significant delay in neutrophil recovery to an ANC of ≥500/µL (P=0.0008). Sargramostim accelerated neutrophil recovery following marrow infusion regardless of disease type (P=0.0011), previous exposure to agents that deplete stem cells (P=0.0028), prior number of drugs (P=0.0035), radiotherapy exposure (P=0.0024), marrow purging (P=0.0028), type of preparative regimen (P=0.0023) or relapse status at autologous BMT (P=0.0031). Secondary: Not reported
Acceleration of Myeloid Recovery in Patients Undergoing Allogeneic Bone Marrow Transplant from Human Leukocyte Antigen-Matched Related Donors				
Nemunaitis et al[29] Sargramostim 250 µg/m^2/day by 4-hour infusion starting on the day of marrow infusion and continuing to day 20 vs placebo	DB, MC, PC, RCT Patients of all ages and of either sex undergoing HLA-identical sibling BMT for hematologic malignancy	N=109 1 year	Primary: Time to myeloid engraftment (ANC ≥500 cells/mm^3), time to ANC ≥1,000/mm^3, median days of hospitalization Secondary: Rate of infections, rate of bacteremia, rate	Primary: The median time to myeloid engraftment was significantly less in the sargramostim group (13 days) compared to the placebo group (17 days; P=0.0001). The median time to ANC ≥1,000/mm^3 was significantly less in the sargramostim group (14 days) compared to the placebo group (19 days; P=0.0001). The median days of hospitalization was significantly less in the sargramostim group (25 days) compared to the placebo group (26 days; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received HLA-identical sibling marrow and cyclosporine and prednisone for GVHD prophylaxis.			of grade 3 or 4 mucositis	Secondary: The rate of infections was significantly less in the sargramostim group (34 patients) compared to the placebo group (51 patients; P=0.001). The rate of bacteremia was significantly less in the sargramostim group (9 patients) compared to the placebo group (19 patients; P=0.043). The rate of grade 3/4 mucositis was significantly less in the sargramostim group (four patients) compared to the placebo group (16 patients; P=0.005). There were no significant differences between the two groups in platelet recovery, erythrocyte recovery, and incidence of veno-occlusive disease, GVHD severity, relapse or survival.
Chronic Administration to Reduce Incidence and Duration of Sequelae of Neutropenia in Symptomatic Patients with Congenital, Cyclic or Idiopathic Neutropenia				
Bernini et al[30] RhG-CSF 5 µg/kg SC once daily until ANC >1.5x10^9 cells/L The rhG-CSF dosage, interval and amount were then increased and decreased, respectively, in an alternating fashion until the lowest rhG-CSF dose that would maintain the ANC >1x10^9 cells/L was reached.	T Children with symptomatic chronic idiopathic neutropenia with an ANC <0.5×10^9 cells/L documented repeatedly (and confirmed as not varying in a cyclic fashion) for less than six months, ≥12 infections that required antibiotic therapy within the previous	N=6 Mean of 14 months	Primary: Neutrophil response, clinical response, complications, expense comparison Secondary: Not reported	Primary: RhG-CSF 5 µg/kg daily resulted in a mean 44-fold increase (25- to 143-fold increase) in the ANC by the end of the first week of treatment. At 14 months, the minimal rhG-CSF dose requirements ranged from 1 µg/kg once weekly to 5 µg/kg every other day to maintain an ANC >1x10^9 cells/L, but all patients were able to maintain this goal. A significant reduction in the incidence of infections was observed after the initiation of rhG-CSF therapy (P<0.001). A significant reduction in number of days of antibiotic therapy and number of clinical visits was observed after the initiation of rhG-CSF therapy (P<0.001 for both). Low-dose rhG-CSF therapy was well tolerated and no side effects were noted. Although not statistically significant, treatment with the lowest effective

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	12 months, use of prophylactic antibiotics to prevent recurrent infections, one or more life-threatening infections or any combination of these factors, no underlying conditions and availability of medical records			dose of rhG-CSF demonstrated a total mean annual expense of $4,337 compared to the expense of $12,074 annually prior to rhG-CSF treatment (P=0.09). The mean annual savings per patient was $12,000 ($5,124 to $23,406). Secondary: Not reported
Welte et al[31] RhGM-CSF 3 to 30 µg/kg/day IV for 42 days and subsequently, one to three months later, rhG-CSF 3 to 15 µg/kg/day SC for 142 days All patients were started on 3 µg/kg/day; if no response was seen after 14 days, the dose was increased to the next dose level for 14 days. If after 14 days at the maximal dose no response was	T Patients >1 month old with a diagnosis of severe congenital neutropenia, normal kidney and liver function as judged by creatinine, bilirubin, transaminases and coagulation function, normal electrocardiogram, not on experimental therapy, chemotherapy,	N=5 Duration not specified	Primary: Effects of rhGM-CSF and rhG-CSF on blood cells, maintenance therapy, bone marrow, clinical responses, side effects of treatment Secondary: Not reported	Primary: Treatment with rhGM-CSF increased the ANC count in only one of the five patients in the study (up to 10,296/µL [oscillated between 1,000 and 6,000 cells/µL]). In four patients, the absolute eosinophil count increased from values below 1,000 cells/µL to 3,200 to 5,700 cells/µL. AMC increased two to six fold in four of the five patients as well. Other blood cells such as erythrocytes, platelets or lymphocytes did not change significantly during rhGM-CSF treatment (P values not reported). Treatment with rhG-CSF increased ANC levels to >1,000 cells/µL in all five patients. The absolute eosinophil count was not significantly augmented in all patients (one patient increased fivefold from baseline [oscillation between 100 and 800 cells/µL]). AMC increased two to eight fold in three of the five patients. Four of the five patients maintained an ANC count >1,000 cells/µL during days 43 to 142 of rhG-CSF therapy. The number of promyelocytes before and during rhGM-CSF treatment did not change significantly in four patients. Two patients in the rhG-CSF showed increases in promyelocytes (2 to 12% and 9 to 12%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
observed (no increase in ANC), the therapy was discontinued. All patients also received prophylactic antibiotic therapy with co-trimoxazal, amoxicillin, rifampicin or flucloxacillin.	hormonal therapy or immunotherapy, absence of serious infections uncontrolled on antibiotic therapy or requiring white cell transfusion, and absence of anti-neutrophil antibodies			All patients' experienced recurrent bacterial and fungal infections prior to rhGM-CSF therapy, and after therapy, no new episodes of severe bacterial infections occurred. Two patients had resolved their infections, one patient had no change and one patient developed Staphylococcus aureus induced paronychia. The one patient who had no change in their infection with rhGM-CSF therapy had their infection resolved within six weeks of rhG-CSF therapy. The other four patients did not experience any bacterial infections during rhG-CSF therapy. Both rhGM-CSF and rhG-CSF were tolerated well by all patients. During the highest dose level of rhGM-CSF treatment (30 µg/kg/day), a mild local phlebitis at the infusion site was observed in all patients. The only serious side effect occurred with rhG-CSF treatment in one patient who suffered from a cutaneous necrotizing vasculitis on both lower legs which resolved with a lowering of the dose. One patient had an increase in serum alkaline phosphatase from 285 U/L before rhG-CSF therapy to 441 units/L after rhG-CSF therapy. The other four patients had no change. Liver and renal functions remained normal. Secondary: Not reported
Delayed or Failed Engraftment in Patients Undergone Allogeneic or Autologous Bone Marrow Transplant				
Weisdorf et al[41] Sargramostim 250 µg/m^2/day SC for 14 days vs sargramostim 250 µg/m^2/day SC for 7 days followed by	RCT Subjects with graft failure after BMT (failure to achieve a leukocyte count of ≥100 cells/µL by day 21 after transplantation, failure to achieve a leukocyte count	N=47 Duration not specified	Primary: Development of a sustained ANC ≥500 cells/µL for three consecutive days Secondary: Recovery of red cells and platelets to	Primary: There was no significant difference in development of a sustained ANC ≥500 cells/µL for three consecutive days between the sargramostim alone group (eight days [two to 61]) and the sequential treatment group (six days [one to 36]; P=0.39). Secondary: There was no significant difference in recovery of red cells to transfusion-independence between the sargramostim alone group (30 days [six to 124]) and the sequential treatment group (42 days [11 to 250]; P=0.24).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
filgrastim 5 µg/kg/day SC for 7 days	≥300 cells/µL or an ANC ≥200 cells/µL by day 28; or failure to maintain a mean ANC ≥500 cells/µL for 7 days after having previously achieved an ANC ≥500 cells/µL at any time beyond day 28		transfusion-independence, adverse reactions to cytokine infusions and 100-day survival	There was no significant difference in recovery of platelets to transfusion-independence between the sargramostim alone group (28 days [6 to 127]) and the sequential treatment group (42 days [four to 249]; P=0.38). No significant adverse reactions (e.g., fevers, rash, serositis, bone pain) led to discontinuation of either treatments. GVHD was similarly frequent in both treatment arms (P values not reported). Significantly fewer patients died in the sargramostim alone group (one of 23 patients) compared to the sequential treatment group (seven of 24 patients; P=0.026).
Nemunaitis, Singer et al[42] RhGM-CSF 60 to 1,000 µg/m^2/day as a single two-hour IV infusion daily for 14 or 21 days A second course at twice the dose of the first course was allowed if after two weeks from the treatment course, the ANC remained <0.500x10^9 cells/µL and there was no life-threatening toxicity from the rhGM-CSF and no evidence of leukemic relapse.	DE Patients with malignancy or aplastic anemia who underwent allogeneic, autologous or syngeneic BMT and subsequently developed graft failure	N=37 Duration not specified	Primary: Patient response (ANC ≥500x10^9 cells/µL within 14 days of starting the final course of rhGM-CSF) by type of BMT, effect on infection, effects on GVHD, toxicities and survival Secondary: Not reported	Primary: Nine of 15 patients who underwent an allogeneic BMT increased their ANC to ≥0.500x10^9 cells/µL within 14 days of starting rhGM-CSF. Six patients did not respond to therapy. The mean ANC value in the allogeneic BMT subgroup increased from 0.153±0.140x10^9 cells/µL (zero to 0.360x10^9 cells/µL) at the start of treatment to a mean of 2.545±3.944x10^9 cells/µL (zero to 11.970x10^9 cells/µL) on the last day of the final course (P=0.03). Eleven of the 21 autologous and one syngeneic BMT patient increased their ANC to ≥0.500x10^9 cells/µL within 14 days of starting rhGM-CSF. Ten patients did not respond to therapy. The mean ANC value in the autologous or syngeneic BMT group increased from 0.104±0.130x10^9 cells/µL (zero to 0.472x10^9/L) at start of treatment to 0.964±1.010x10^9 cells/µL (zero to 4.190x10^9 cells/µL) on the last day of the final course of rhGM-CSF (P=0.00047). Fevers (temperature >38°C) were present in 13 of 15 allogeneic BMT patients before treatment with rhGM-CSF. Five patients had bacteremia or fungemia, two had viral infections, and one had liver, spleen, and brain

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A maximum of three courses of rhGM-CSF was administered to each patient.				abscesses. Fever was present in 16 of 22 autologous and syngeneic BMT patients before treatment with rhGM-CSF. Five of the 22 patients had bacteremia or fungemia, three had pneumonia and one had a cellulitis. Three patients had graft rejection (only host cells in circulation), two of which responded to rhGM-CSF therapy with recovery of host hematopoiesis. Four patients had only donor hematopoietic cells detected at the time of treatment and all responded to rhGM-CSF. Prior to initiating rhGM-CSF therapy, seven patients had evidence of grade I or II GVHD and none had a GVHD exacerbation. Of the seven patients who received chemically purged autologous marrow, none responded to rhGM-CSF therapy. The four autologous BMT recipients who were administered doses of rhGM-CSF $\geq$500 µg/m^2/day developed myalgias and bone pain during the infusion which resolved within two hours after completion of the rhGM-CSF infusion. At doses $\leq$250 µg/m^2/day, toxicity thought to be associated with rhGM-CSF was observed in one patient who developed sternal and joint pain. In addition, bilirubin increased in three patients and diminished in two others. Overall, 19 patients remained alive after follow-up. The actuarial survival of the 37 patients 100 days and one year after the day they received rhGM-CSF was 59% (95% CI, 44 to 75) and 50% (95% CI, 36 to 60), respectively. Three of the nine allogeneic BMT patients who responded to rhGM-CSF and four of the 12 responders after autologous BMT died. Secondary: Not reported
Mobilization of Hematopoietic Progenitor Cells into Peripheral Blood Collection by Leukapheresis				
Putkonen et al[43]	HC, RETRO	N=114	Primary: Blood CD34+ cell	Primary: The median blood CD34+ cell count at the onset of leukapheresis was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Filgrastim 5 µg/kg/day SC starting on day 2 post-myeloablative therapy until the end of leukapheresis vs pegfilgrastim 6 to 18 mg once on day 2 post-myeloablative therapy	Patients with lymphoproliferative malignancies (multiple myeloma, lymphomas and chronic lymphocytic leukemia) requiring stem cell mobilization prior to APBSCT and who had successful mobilization with pegfilgrastim	Median duration to leuk-apheresis onset was 10 days (10 to 18 days)	count at the onset of leukapheresis Secondary: Not reported	comparable between the filgrastim and pegfilgrastim groups (79x10^6 cells/µL [10 to 390x10^6/L] vs 64x10^6 cells/µL [17 to 805x10^6/L], respectively; P=0.44). The median onset of leukapheresis was similar between the two treatment groups (10 days for both [10 to 18 days for both]; P=0.75). Fifty-three percent of patients in the pegfilgrastim group obtained target yield of CD34+ cells following one leukapheresis cycle, compared to 36% of patients in the filgrastim group (P value not reported). Secondary: Not reported
Weaver et al[44] Filgrastim 5 µg/kg/day SC until PBSC harvests were completed vs sargramostim 250 µg/m^2/day SC until PBSC harvests were completed vs sargramostim 250 µg/m^2/day SC for 5 days followed by	MC, OL, RCT Subjects with multiple myeloma, breast cancer or lymphoma	N=156 Duration not specified	Primary: CD34+ cell yields, hematological recovery, morbidity and resource utilization Secondary: Not reported	Primary: Significantly greater CD34+ cells were harvested in the filgrastim alone group (7.1 cells/kg/apheresis [0.03 to 27.00]) and in the sequential dosing group (5.5 cells/kg/apheresis [0.12 to 48.00]) compared to the sargramostim group (2.0 cells/kg/apheresis [0.01 to 31.00]; P=0.0001 and P=0.0002, respectively). ANC recovery was significantly more rapid in those who received filgrastim alone (11 days [zero to 19]) compared to sargramostim alone (14 days [10 to 19]; P=0.001); also the sequential dosing of filgrastim and sargramostim (12 days [10 to 15]) was significant compared to sargramostim alone (P=0.001). Significantly fewer patients had a temperature >38.5° in the filgrastim alone group (9 patients [18%]) and in the sequential dosing group (eight patients [15%]) compared to the sargramostim group (27 patients [52%]; P=0.001 for both comparisons). Significantly fewer subjects received IV antibiotics in the filgrastim alone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
filgrastim 6 µg/kg/day SC until PBSC harvests were completed Subjects received myelosuppressive chemotherapy with either paclitaxel and cyclophosphamide or etoposide and cyclophosphamide.				group (12 patients [24%]) and in the sequential dosing group (13 patients [25%]) compared to the sargramostim group (36 patients [69%]; P=0.001 for both comparisons). Significantly fewer subjects had hospital admissions occurred in the filgrastim alone group (10 patients [20%]) and in the sequential dosing group (11 patients [21%]) compared to the sargramostim group (22 patients [42%]; P=0.013 and P=0.017, respectively). Significantly fewer subjects received red blood cells in the filgrastim alone group (11 patients [22%]) compared to the sargramostim group (24 patients [46%]; P=0.008). There were no significant differences between treatment groups in the number of febrile days, number with bacteremia, days of IV antibiotics, days in the hospital, number of receiving platelets and number of days red blood cells were infused. Secondary: Not reported
Reduce Duration of Neutropenia and Neutropenia-Related Sequelae in Patients with Nonmyeloid Malignancies Undergoing Myeloablative Chemotherapy Followed by Marrow Transplantation				
Martino et al[45] Filgrastim 5 µg/kg/day starting on day 5 until neutrophil engraftment vs pegfilgrastim 6 mg once on day 1 post-transplant All subjects were	RCT Subjects with a de-novo diagnosis of multiple myeloma, stages II to III Durie–Salmon classification	N=37 Duration not specified	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9/L) Secondary: Incidence of febrile neutropenia (ANC <2x10^9/L and temperature 38.2°C), duration of febrile neutropenia,	Primary: There was no significant difference in the duration of grade 4 neutropenia between the pegfilgrastim group (five days [three to 15]) and the filgrastim group (six days [four to 10]; P value not reported). Secondary: The incidence of febrile neutropenia was significantly less in the pegfilgrastim group (61.1%) compared to the filgrastim group (100%; P=0.003). The duration of febrile neutropenia was significantly less in the pegfilgrastim group (1.5 days [zero to seven]) compared to the filgrastim group (four days [one to nine]; P=0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treated with three cycles of vincristine, adriamycin and dexamethasone, followed by cyclophosphamide and G-CSF and PBCS collection. After PBCS collection, patients received high dose melphalan as the conditioning regimen for the APBSCT.			duration of fever, incidence of documented infections and platelet engraftment	The incidence of fever of unknown origin was significantly less in the pegfilgrastim group (44.0%) compared to the filgrastim group (84.2%; P=0.029). One patient in each of the treatment groups experienced catheter related infections and two patients in each of the treatment groups developed documented infections with positive blood cultures. None of patients developed documented fungal infections. There was no significant difference in mean time to platelet engraftment between the pegfilgrastim group (11 days [nine to 25]) and the filgrastim group (11 days [eight to 22]; P value not reported). Bone pain was the only adverse event considered cytokine related and was reported in 10% of subjects in the pegfilgrastim group and 12% in the filgrastim group (P value not reported).
Castagna et al[46] Filgrastim 5 µg/kg/day SC starting on day 1 post-transplant until ANC recovery to >0.5x10^9/L for two consecutive days vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients were treated with high-dose chemotherapy before	MC, OL, RCT Adult patients with hematological malignancies and solid tumors who had an adequate harvest of CD34-positive cells (≥3x10^6/kg)	N=80 Duration not specified	Primary: Duration of severe neutropenia (ANC <0.5x10^9/L), number of days to achieve an ANC >0.5x10^9/L starting on day one Secondary: Number of days to achieve an ANC >1x10^9/L starting on day one, number of days with fever >38ºC, duration of	Primary: Pegfilgrastim was not inferior to filgrastim in the duration of severe neutropenia (6.20 vs 5.97 days, respectively; mean difference, 0.23 days; 95% CI, -0.77 to 1.22; P value not reported) and the number of days needed to achieve an ANC >0.5x10^9/L (10.75 vs 11.53 days, respectively; mean difference, -0.78 days; 95% CI, -2.97 to 1.42; P value not reported). Secondary: There was no difference between the filgrastim and pegfilgrastim groups with regard to time to reach ANC >1x10^9/L (12.16 and 11.98 days, respectively; P value not reported) or days with fever (1.63 days and 0.95 days, respectively; P value not reported). The duration of antibiotic therapy was also comparable between the two treatment groups (4.0 days for filgrastim and 5.7 days for pegfilgrastim; P=0.152).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
receiving APBSCT on day 0. The most utilized chemotherapy regimens in the study were carmustine, etoposide, cytarabine and melphalan for lymphomas and high-dose melphalan 200 mg/m^2 for multiple myelomas.			antibiotic and antimycotic therapy, number of documented infections	The result on the number of documented infections was not reported.
Mathew et al[47] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients were treated with high-dose chemotherapy before receiving autologous SCT on day 0; regimens differed based on malignancies.	CO, RETRO Adult patients with NHL, HD or multiple myeloma who received an induction chemotherapy followed by autologous SCT	N=164 Mean duration of filgrastim therapy ranged from 5 to 21 days	Primary: Time to neutrophil recovery with ANC ≥0.5x10^9/L once, total days with an ANC <0.5 x 10^9/L, incidence of febrile neutropenia, number of definitive infections, days of IV antibiotic treatment, number of doses of filgrastim and pegfilgrastim given, reported episodes of bone pain, incidence of engraftment syndrome	Primary: The time to neutrophil recovery was 10.9 days with filgrastim and 9.6 days with pegfilgrastim (P<0.0001). The total number of days with an ANC <0.5x10^9/L with filgrastim was 7.6 days and 6.4 days with pegfilgrastim (P<0.001). Pegfilgrastim was associated with fewer incidences of febrile neutropenia compared to filgrastim (59 vs 78%; P=0.012). The mean duration of febrile neutropenia was similar between the two treatment groups (3.2 days for filgrastim and 2.5 days for pegfilgrastim; P=0.08). The filgrastim and pegfilgrastim had similar incidence of definitive infections (32 and 23%, respectively; P=0.294). The duration of IV antibiotic treatment was shorter with pegfilgrastim compared to filgrastim (6.3 vs 9.6 days; P=0.006). Patients in the filgrastim group received an average of nine doses of filgrastim (five to 21 doses), whereas 76 of 82 patients in the pegfilgrastim group received a single dose of pegfilgrastim. Six patients who received pegfilgrastim also received additional filgrastim. Two patients in the pegfilgrastim group and none in the filgrastim group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	reported bone pain, while engraftment syndrome occurred in one patient in each group. Secondary: Not reported
Samaras et al[48] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant until ANC recovery to ≥0.5x10^9/L for three consecutive days vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients received high-dose carmustine, etoposide, cytarabine and melphalan followed by APBSCT.	RETRO Patients with NHL or HD receiving high-dose BEAM followed by APBSCT	N=54 Duration not specified	Primary: Length of hospital stay, time to engraftment, duration of neutropenia and thrombo-cytopenia, incidence and duration of fever, use of IV antibiotics, need for red blood cell and platelet transfusion during hospital stay	Primary: The length of hospital stay was similar between the filgrastim and pegfilgrastim groups (16.0 vs 16.5 days, respectively; P=0.27). No differences were observed between the filgrastim and pegfilgrastim groups with regard to the time to engraftment (nine days for both; P=0.55), duration of neutropenia (eight vs seven days, respectively; P=0.13) and duration of thrombocytopenia (9.5 vs 7.0 days, respectively; P=0.21). Fever was reported in 80 and 97% of patients in the filgrastim and pegfilgrastim groups, respectively (P=0.057). The duration of fever also appeared similar between the two treatment groups (two days for filgrastim and 4.5 days for pegfilgrastim; P=0.057). Similar percentage of patients in the filgrastim and pegfilgrastim groups received IV antibiotics (90 vs 100%, respectively; P=0.13). The duration of IV antibiotic treatment was also comparable between the two groups (10 days for filgrastim and 11 days for pegfilgrastim; P=0.75). The need for red blood cell and platelet transfusions was similar between the two groups (P=0.27 for red blood cell transfusions; P=0.78 for platelet transfusions).
Samaras et al[49] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant until ANC recovery to ≥0.5x10^9/L for three consecutive days	RETRO Patients with multiple myeloma who received melphalan 200 mg/m^2 followed by APBSCT	N=72 Median duration of filgrastim use was 9 days (3 to 14 days)	Primary: Length of hospital stay, time to engraftment, duration of neutropenia and thrombocytopenia, incidence and	Primary: Pegfilgrastim had a shorter hospital stay than filgrastim (14.5 days [11 to 47] vs 15.5 days [12 to 64]; P=0.024). The median time to neutrophil engraftment appeared to be faster with pegfilgrastim compared to filgrastim (nine days [eight to 18] vs 10 days [eight to 12]; P=0.032). The median duration of neutropenia was also shorter with pegfilgrastim compared to filgrastim (five days [three to 14]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients received high-dose melphalan 200 mg/m^2 followed by APBSCT.			duration of fever, use of IV antibiotics, need for red blood cell and platelet transfusion during hospital stay Secondary: Not reported	vs six days [three to nine]; P=0.0079). The duration of thrombocytopenia was similar between filgrastim and pegfilgrastim (3.0 and 3.5 days, respectively; P=0.39). Seventy-two percent and 63% of patients in the filgrastim and pegfilgrastim groups, respectively, reported incidence of fever (P=0.51). The median duration of fever was similar between the two treatment groups (two days [zero to 12] for filgrastim and one day [zero to 19] for pegfilgrastim; P=0.13). The proportion of patients requiring IV antibiotics were similar in the two treatment groups (89% for filgrastim and 90% for pegfilgrastim; P=0.38). The median duration of treatment was also comparable in filgrastim and pegfilgrastim (six days [zero to 22] and 5.5 days [zero to 36], respectively; P=0.12). There was no difference between the two groups in the need for platelet transfusion (P=0.92); however, more patients in the filgrastim group required platelet transfusions compared to the pegfilgrastim (0.5 [0 to 9] vs 0 [0 to 10]; P=0.00065) Secondary: Not reported
Reducing Time to Neutrophil Recovery and Duration of Fever Following Induction or Consolidation Chemotherapy Treatment of Adults with Acute Myelogenous Leukemia				
Jansen et al[50] Filgrastim 5 µg/kg/day SC from day 0 until neutrophil recovery (ANC >1,500 cells/mm^3) vs	T Subjects with metastatic (stage IV) or locally advanced (stage II or III) breast cancer or myeloma who	N=46 Duration not specified	Primary: Time to ANC recovery >500 cells/mm^3 and ANC >1,000 cells/mm^3, time to platelet recovery >20,000 and >50,000, days	Primary: Time to ANC recovery >500/mm^3 was significantly faster in the sargramostim group (10.5±1.5 days) compared to the filgrastim group (8.8±1.2 days; P<0.001). In addition, time to ANC recovery >1,000/mm^3 was significantly faster in the sargramostim group (11.0±1.7 days) compared to the filgrastim group (8.9±2.2 days; P=0.001). There were no significant differences in time to platelet recovery >20,000 or >50,000 in the sargramostim group (9.9±1.1, 11.8±2.1 days,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sargramostim 500 µg/kg from day 0 until neutrophil recovery (ANC >1,500 cells/mm^3) Subjects underwent chemotherapy treatment with cyclophosphamide and etoposide and all patients started G-CSF 10 mg/kg/day SC followed by PBSC transplant.	were acceptable candidates for high-dose chemotherapy with PBSC rescue		with growth factor, days with temperature >38.3°C, days of IV antibiotics, number of platelet transfusions and number of red cell units Secondary: Not reported	respectively) compared to the filgrastim group (11.2±4.7, 14.9±9.3 days, respectively; P=0.40 and P=0.37, respectively). Subjects in the filgrastim group experienced significantly fewer days with growth factor compared to those in the sargramostim (10.8±2.1 vs 12.2±1.5 days; P=0.001). There was no significant difference in the number of days subjects experienced a temperature >38.3°C between the sargramostim and filgrastim groups (2.3±2.4 days vs 1.8±2.1 days; P=0.46). There was no significant difference in the number of days subjects received IV antibiotics between the sargramostim and filgrastim groups (4.3±2.7 vs 4.6±4.3 days; P=0.84). There was no significant difference in the number of platelet transfusions subjects received between the sargramostim and filgrastim groups (2.4±1.7 days vs 3.1±3.2 days; P=0.80). There was no significant difference in the number of red cell units subjects received between the sargramostim and filgrastim groups (2.8±1.6 vs 2.3±2.2; P=0.21). Secondary: Not reported
Shorten Time to Neutrophil Recovery and Reduce Incidence of Infection Following Induction Chemotherapy in Older Adult Patients with Acute Myelogenous Leukemia				
Stone et al[51] GM-CSF 5 µg/kg/day IV given daily until the neutrophil count was at least 1,000 cells/cm^3, there was evidence of the regrowth of	DB, RCT Patients ≥ 60 years of age with the diagnosis of primary AML as defined morphologically by	N=388 Duration not specified	Primary: Rate of complete remission Secondary: Therapeutic failure, overall survival, duration	Primary: There was no significant difference among the rate of complete remission between the GM-CSF group (51%; 95% CI, 44 to 59) and the placebo group (54%; 95% CI, 47 to 61; P=0.61). Secondary: The reasons for therapeutic failure of remission (i.e., resistant disease or death during marrow hypoplasia) were similar in both treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
leukemia, or severe toxic effects attributable to the study infusion occurred vs placebo given daily until the neutrophil count was at least 1,000/mm^3, there was evidence of the regrowth of leukemia, or severe toxic effects attributable to the study infusion occurred Induction chemotherapy consisted of daunorubicin and cytarabine.	the FAB system of classification		of neutropenia and duration of hospitalization	(P=0.79). The median survival was not significantly different between the two groups (9.4 months; 95% CI, 7.6 to 11.2). The median duration of neutropenia was significantly shorter in the GM-CSF group (15 days; 95% CI, 15 to 1) than in placebo group (17 days; 95% CI, 16 to 19; P=0.02). The median length of hospitalization was not significantly different between the CM-CSF group (28 days; 95% CI, 26 to 31) and the placebo group (30 days; 95% CI, 28 to 33; P=0.11).
Rowe et al[52] Sargramostim 250 µg/m^2 over 4 hours and administered daily until the ANC was >1,500 cells/µL for 3 consecutive days or for a maximum of 42 days vs placebo	DB, RCT Adult patients >55 but not exceeding 70 years of age with adequate hepatic, renal and cardiac function (bilirubin 52 mg/dL; creatinine <2 mg/dL; and normal cardiac left	N=124 Duration not specified	Primary: Hematologic response (ANC recovery, platelet recovery and red blood cell recovery) and rate of complete remission Secondary: Treatment-related toxicity, infectious	Primary: The median time to ANC recovery was significantly shorter in the sargramostim group compared to the placebo group. Median time to ANC recovery of >500 cells/µL in the sargramostim group was 13 days compared to 17 days for the placebo group (P=0.001) and the median time to ANC recovery of >1,000 cells/µL was 14 vs 21 days, respectively (P=0.001). There was no significant differences between the sargramostim and placebo groups in median recovery rates of platelets (11 vs 12 days, respectively; P=0.11) and red blood cells (13 vs 14 days, respectively; P=0.39).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Induction consisted of standard daunorubicin and cytarabine.	ventricular ejection fraction), no previous cytotoxic or radiation therapy, morphologic proof of AML, no known antecedent myelody-splasiacytogenetic and immunophenotypic analysis performed on prestudy specimens		toxicity and median survival	There were significantly more patients who experienced complete remission in the sargramostim group (36 patients [60%]) compared to the placebo group (25 patients [45%]; P=0.08). Secondary: The treatment-related mortality was not significantly different between the sargramostim group (three patients [6%]) compared to the placebo group (seven patients [15%]; P=0.18). There were no differences between the groups for any other toxicities, including weight gain (8% on sargramostim and 21% on placebo), cardiac events, or pulmonary events, and no patient withdrew from study drug because of toxicity or leukemia regrowth. Grade 4 and 5 infections occurred significantly less in the sargramostim group (five patients [10%]) compared to the placebo group (17 patients [36%]; P=0.002); however there was no significant difference in occurrence of the combination of grade 3, 4 and 5 infections (27 [52%] vs 33 patients [70%], respectively; P=0.068). Death associated with pneumonia occurred significantly less in the sargramostim group (two patients [14%]) compared to the placebo group (seven patients [54%]; P=0.046). The median survival time was significantly longer in the sargramostim group (10.6 months) compared to the placebo group (4.8 months; P=0.048).
Büchner et al[53] Sargramostim 250 $\mu g/m^2$/day continuous IV infusion started on day 4 vs	HC Adult patients at all ages with early relapse occurring in the first 6 months of remission and with	N=92 Duration not specified	Primary: Complete remission rate Secondary: Death rate, definite nonresponse rate,	Primary: There was no statistical difference among complete remission rates between the sargramostim group (18 patients [50%]) and the control group (18 patients [32%]; P=0.09). Secondary: The sargramostim group had significantly fewer early (within six weeks) deaths (five patients [14%]) compared to the control group (22 patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
control group (sequential patients treated by the identical chemotherapy at the same situations) Early or multiple relapses were treated with one course S-HAM and newly diagnosed AML and AML late relapses in the higher age group were treated with TAD9.	multiple relapse, and patients ≥65 years with newly diagnosed AML or late relapse		adverse events, duration of remission	[39%]; P=0.009); however there was no significant difference among later hypoplastic deaths between the two groups (seven [19%] vs seven patients [13%]; P not reported). There was no significant difference in the number of definite nonresponders between the sargramostim group (six patients [17%]) and the control group (nine patients [16%]; P value not reported). The sargramostim group showed a higher overall frequency, including all grades of decrease in serum protein (P=0.02), prothrombin (P=0.02) and pseudo-cholinesterase levels (P=0.008). In the control group, elevation of serum transaminases was more frequent overall (P=0.008) and in lower-grade elevations and showed more frequent cardiac events (P=0.018). Remission duration does not seem to be reduced after GM-CSF compared to the control group (P value not reported).

Drug regimen abbreviations: IV=intravenous, SC=subcutaneous
Study abbreviations: CO=cohort, DB=double blind, DE=dose-escalation, ES=extension study, HC=historical control, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observation study, PC=placebo controlled, RCT=randomized controlled trial, RETRO=retrospective, T=trial, XO=crossover
Miscellaneous abbreviations: ALL=acute lymphocytic leukemia, AMC=absolute monocytes count, AML=acute myelogenous leukemia, ANC=absolute neutrophil count, APBSCT=autologous peripheral blood stem cell transplantation, BEAM= carmustine, etoposide, cytarabine, melphalan, BMT=bone marrow transplant, CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone, CI=confidence interval, CSF=colony-stimulating factor, ECOG=Eastern Cooperative Oncology Group, FAB=French-American-British, G-CSF=granulocyte-colony-stimulating factor, GM-CSF=granulocyte-macrophage-colony stimulating factor, GVHD=graft-versus-host disease, IPI=international prognostic index, HD=Hodgkin's disease, HLA=human leukocyte antigen, NHL=non-Hodgkin's lymphoma, OR=odds ratio, PBC=peripheral blood count, PBSC=peripheral blood stem cell, PBSCT=peripheral blood stem cell transplant, rhG-CSF=recombinant human granulocyte colony-stimulating factor, rhGM-CSF=recombinant human granulocyte-macrophage colony-stimulating factor, RR=relative risk, SCT=stem cell transplant, SD=standard deviation, S-HAM=sequential high-dose cytosine arabinoside and mitoxantrone,TAD9=9-day 6-thioguanine with cytosine arabinoside and daunorubicin, WBC=white blood cell, WHO=World Health Organization

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Filgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. FDA-approved for use in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
Filgrastim-sndz	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. FDA-approved for use in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
Pegfilgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.
Sargramostim	Safety and efficacy in elderly patients have not been established.* Safety and effectiveness in pediatric patients have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Tbo-filgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required for creatinine clearance ≥60 mL/min. Not studied in patients with creatinine clearance <60 mL/min.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[1-5]

Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Cardiovascular System					
Cardiac	-	-	-	23	-
Hemorrhage	-	-	-	23 to 29	-
Hypertension	-	-	-	25 to 34	-
Hypotension	-	-	-	13	-
Tachycardia	-	-	-	11	-
Central Nervous System					
Anxiety	-	-	-	11	-
Central nervous system disorder	-	-	-	11	-
Chills	-	-	-	19 to 25	-
Fatigue	11	11	-	-	-
Fever	12	12	-	77 to 96	-
Headache	-	-	16	36	a
Insomnia	-	-	-	11	-
Neuro-clinical	-	-	-	42	-
Neuro-motor	-	-	-	25	-
Neuro-psych	-	-	-	15	-
Neutropenic fever	13	13	-	-	-
Paresthesia	-	-	-	11	-
Pyrexia	-	-	23	-	-
Dermatological					
Alopecia	18	18	48	37 to 73	-
Pruritus	-	-	-	23	-
Rash	-	-	-	44 to 70	-
Skin	-	-	-	77	-
Sweet's Syndrome	-	-	-	-	a
Gastrointestinal					
Abdominal pain	-	-	-	38	-
Anorexia	-	-	-	13 to 54	-
Constipation	-	-	10	-	-

Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Diarrhea	14	14	29	52 to 89	-
Dyspepsia	-	-	-	17	-
Dysphagia	-	-	-	11	-
Gastrointestinal disorder	-	-	-	37	-
Gastrointestinal hemorrhage	-	-	-	11 to 27	-
Hematemesis	-	-	-	13	-
Mucositis	12	12	-	-	-
Nausea/vomiting	57	57	13	46 to 90	a
Stomatitis	-	-	-	24 to 62	-
Laboratory Test Abnormalities					
Bilirubinemia	-	-	-	30	-
Blood dyscrasia	-	-	-	25	-
Coagulation	-	-	-	19	-
High blood urea nitrogen	-	-	-	23	-
High cholesterol	-	-	-	17	-
Hyperglycemia	-	-	-	25 to 41	-
Hypomagnesemia	-	-	-	15	-
Increased creatinine	-	-	-	15	-
Increased serum glutamic pyruvic transaminase	-	-	-	13	-
Leukopenia	-	-	-	17	-
Liver damage	-	-	-	13	-
Low albumin	-	-	-	27	-
Thrombocytopenia	-	-	-	19	a
Respiratory					
Dyspnea	-	-	-	15 to 28	-
Epistaxis	-	-	-	17	-
Lung disorder	-	-	-	20	-
Pharyngitis	-	-	-	23	-
Pulmonary	-	-	-	48	-
Rhinitis	-	-	-	11	-
Other					
Allergy	-	-	-	12	-
Arthralgia	-	-	16	11	-
Asthenia	-	-	13	17 to 66	-
Bone pain	-	-	31	21	3.4
Chest pain	-	-	-	15	-
Cutaneous vasculitis	-	-	-	-	a
Edema	-	-	-	13 to 34	-
Eye hemorrhage	-	-	-	11	-
Infection	-	-	-	65	-
Liver	-	-	-	77	-
Malaise	-	-	-	57	-
Metabolic	-	-	-	58	-
Mucous membrane disorder	-	-	-	75	-

Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Myalgia	-	-	21	-	a
Pain	-	-	-	17	-
Peripheral edema	-	-	12	11 to 15	-
Sepsis	-	-	-	11	-
Skeletal pain	22	-	-	-	-
Urinary tract disorder	-	-	-	14	-
Weight loss	-	-	-	27	-

CNS=central nervous system, GI=gastrointestinal
- Event not reported or incidence ≤10%.
a Rate not reported

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Concurrent chemotherapy and radiotherapy use.				a	
Excessive leukemic myeloid blasts in the bone marrow or peripheral blood (≥10%)				a	
Known hypersensitivity to acrylic.			a		
Know hypersensitivity to human granulocyte colony-stimulating factors or any inactive component.	a	a	a	a	a
Known hypersensitivity to yeast-derived products.				a	
Use in neonatal patients.				a	

Warnings/Precautions

Table 8. Warnings and Precautions[1-5]

Warnings and Precautions	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Acute Respiratory Distress Syndrome (ARDS) has been reported. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue use in patients with ARDS.	a	a	a	a	a
Allergy to Acrylics; the injection device uses acrylic adhesives; serous allergic reactions may occur in patients allergic to acrylic.			a		
Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in peripheral blood progenitor cell collection mobilization.	a	a			
Benzyl Alcohol is a constituent and is associated with “Gasping Syndrome” in premature infants. Do not administer to neonates				a	

Warnings and Precautions	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Capillary leak syndrome has been reported after G-CSF administration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Closely monitor and provide standard symptomatic treatment, which may include intensive care.	a	a		a	a
Cardiovascular symptoms of transient supraventricular arrhythmia have been reported, particularly in patients with a history of arrhythmia. Use with caution in patients with preexisting cardiac disease.				a	
Cutaneous Vasculitis has been reported; hold therapy and restart with a reduced dose when symptoms resolve and ANC has decreased.	a	a			
Glomerulonephritis has occurred. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy.	a	a	a		
Leukocytosis; Discontinue use if white blood cell count >10,000/mm^3 in patients with cancer receiving myelosuppressive chemotherapy.	a	a			
Leukocytosis; Discontinue use if white blood cell count >100,000/mm^3 if being used for peripheral blood progenitor cell collection and therapy.	a	a			
Leukocytosis; White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood count during therapy is recommended.			a		
Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated for severe chronic neutropenia (SCN). Confirm the diagnosis of SCN before initiating therapy.	a	a			
Nuclear Imaging; transient positive bone-imaging changes have been associated with use; considerations should be made when interpreting bone-imaging results.	a	a			
Potential Effect on Malignant Cells; may act as a growth factor in tumor cells; safety and efficacy in chronic myeloid leukemia and myelodysplasia has not been established.	a	a	a		a
Renal and Hepatic Dysfunction; in patients with preexisting renal or hepatic dysfunction increases in serum creatinine, bilirubin, or hepatic enzymes have been reported. Dose reduction has resulted in a decrease to pre-treatment levels. Monitor patients with preexisting dysfunction at least every other week during therapy.				a	
Serious allergic reactions, including anaphylaxis, have been reported; can recur within days after the discontinuation of allergy treatment. Permanently discontinue in patients with serious allergic reactions.	a	a	a		a
Sickle cell crisis has been reported in patients with sickle cell trait or sickle cell disease.	a	a	a		a
Simultaneous use with chemotherapy and radiation therapy is not recommended. Do not administer within 24 hours before and after administration of cytotoxic chemotherapy. Avoid simultaneous use with radiation. Safety and efficacy with simultaneous use has not been established for chemotherapy or radiation.	a	a			

Warnings and Precautions	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-filgrastim
Splenic rupture has been reported. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or rupture.	a	a	a		a
Thrombocytopenia has been reported. Monitor platelet counts.	a	a			

Drug Interactions

There are no specific drug interactions reported with the use of granulocyte colony-stimulating factors and associated agents.[1-5] It is recommended to use caution when granulocyte colony-stimulating factor agents are used in combination with other agents which may potentiate the release of neutrophils, such as lithium and corticosteroids.[1-5]

Dosage and Administration

Table 9. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Filgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML: Vial, prefilled syringe: initial, 5 µg/kg/day via SC, short IV infusion (15 to 30 minutes), or continuous IV infusion daily; maintenance, increase dose by 5 µg /kg for each chemotherapy cycle based on ANC Myeloablative chemotherapy followed by BMT: Vial, prefilled syringe: initial, 10 µg/kg/day via IV infusion (over <24 hours) daily; maintenance, titrate dose based on neutrophil response Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial, prefilled syringe: 10 µg/kg/day SC for at least four days before leukapheresis and continue until the last leukapheresis. Congenital Neutropenia: Vial, prefilled syringe: initial, 6 µg/kg SC twice daily; maintenance, dose should be individualized; maximum, doses up to 100 µg/kg/day have been required rarely. Idiopathic or Cyclic Neutropenia: Vial, prefilled syringe: initial, 5 µg/kg SC	Refer to adult dosing.	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	daily; maintenance, dose should be individualized. Hematopoietic Syndrome of Acute Radiation Syndrome: Vial, prefilled syringe: initial, 10 µg/kg SC daily as soon as possible after confirmed exposure to radiation doses greater than 2 gray (Gy) until ANC >1,000 mm^3 for three consecutive CBCs obtained approximately every three days or ANC>10,000 mm^3 after radiation-induced nadir.		
Filgrastim-sndz	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML: Vial, prefilled syringe: initial, 5 µg/kg/day via SC, short IV infusion (15 to 30 minutes), or continuous IV infusion daily; maintenance, increase dose by 5 µg /kg for each chemotherapy cycle based on ANC Myeloablative chemotherapy followed by BMT: Vial, prefilled syringe: initial, 10 µg/kg/day via IV infusion (over <24 hours) daily; maintenance, titrate dose based on neutrophil response Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial, prefilled syringe: 10 µg/kg/day SC for at least four days before leukapheresis and continue until the last leukapheresis. Congenital Neutropenia: Vial, prefilled syringe: initial, 6 µg/kg SC twice daily; maintenance, dose should be individualized; maximum, doses up to 100 µg/kg/day have been required rarely. Idiopathic or Cyclic Neutropenia: Vial, prefilled syringe: initial, 5 µg/kg SC daily; maintenance, dose should be individualized.	Refer to adult dosing.	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL
Pegfilgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies: Prefilled syringe: 6 mg SC once per chemotherapy cycle. Hematopoietic Syndrome of Acute Radiation Syndrome:	Safety and efficacy have not been established in pediatric patients.	Prefilled Syringe: 6 mg/0.6 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	Prefilled syringe: 6 mg SC followed by 6 mg SC one week later.		
Sargramostim	Induction Chemotherapy for AML: Vial (powder, solution): 250 µg/m^2/day IV over four hours daily starting approximately on day 11 or four days following the completion of induction chemotherapy until ANC>1,500 mm^3 for three consecutive days or a maximum of 42 days. If a second cycle of chemotherapy is required, administer approximately four days after the completion of chemotherapy. Non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Hodgkin's disease undergoing autologous BMT: Vial: 250 µg/m^2/day IV beginning two to four hours after bone marrow infusion and not less than 24 hours after the last dose of chemotherapy or radiotherapy and continued until absolute neutrophil count >1,500 cells/mm3 for three consecutive days Allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed: Vial: initial, 250 µg/m^2/day IV for 14 days; treatment may be repeated after seven days off therapy; if a third course is necessary, dose is increased to 500 µg/m^2/day. Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial (powder, solution): 250 µg/m^2/day IV over 24 hours or SC once daily, The optimal schedule for collection has not been established. Immediately following infusion of progenitor cells, give 250 µg/m^2/day IV over 24 hours or SC once daily and continue until ANC>1,500 cells/mm^3 for three consecutive days.	Safety and efficacy have not been established in pediatric patients.	Vial (powder for reconstitution): 250 µg Vial (solution) 500 µg/1 mL
Tbo-filgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies: Prefilled syringe: 5 µg/kg SC daily until the expected neutrophil nadir is passed and neutrophil count has recovered to the normal range.	Safety and efficacy have not been established in pediatric patients.	Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL

AML=acute myeloid leukemia, ANC=absolute neutrophil count, BMT=bone marrow transplant, IV=intravenous, SC=subcutaneous

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network: **Myeloid Growth Factors Clinical Practice Guidelines in Oncology (2010)**[11]	Prophylactic use of colony-stimulating factors (CSFs) · For patients at high risk of febrile neutropenia, prophylactic CSFs is recommended if the risk of febrile neutropenia is 20% or greater and for any patient considered at high risk, regardless of whether the treatment is intended to be curative, to prolong survival or to manage symptoms. · Patients at intermediate risk of febrile neutropenia: o Intermediate risk is defined as a 10 to 20% probability of developing febrile neutropenia or a neutropenic event that would compromise treatment. o Whether the treatment is intended to be curative, to prolong survival or to manage symptoms, it is recommended that individualized consideration of CSF therapy be based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing febrile neutropenia, the potential consequences of a neutropenic event and the implications of reduced chemotherapy doses. o If patient risk factors determine the risk, CSF is a reasonable prophylactic option. o If the risk is due to the chemotherapy regimen and the treatment is intended to prolong survival or to manage symptoms, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored. · Patients at low risk of febrile neutropenia: o In patients at low risk of febrile neutropenia, defined as <10% risk, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate. o CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of febrile neutropenia, including death. · Evaluation of subsequent chemotherapy cycles: o Patient evaluation should occur prior to each subsequent chemotherapy cycle to determine the risk categorization and treatment intent. o If a patient experiences an episode of febrile neutropenia or a dose-limiting neutropenic event despite receiving CSF therapy, it is recommended that a chemotherapy dose reduction or change in treatment regimen occurs unless there is an impact on patient survival. · Chemotherapy regimens and risk of febrile neutropenia: o CSF prophylaxis is recommended when using a chemotherapy regimen with an incidence of >20% of febrile neutropenia. o Benefits of pegfilgrastim have not been shown in regimens given under two week duration; therefore, it should be avoided in patients receiving weekly chemotherapy. Therapeutic uses of CSFs · Patients with febrile neutropenia who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegfilgrastim is long-acting, those who have received prophylaxis with

Clinical Guideline	Recommendations
	pegfilgrastim should not be treated with an additional CSF. · Due to the lack of evidence supporting the therapeutic use of pegfilgrastim, only filgrastim and sargramostim should be used in this therapeutic setting. · It is recommended for those who have not received prophylactic CSFs to be evaluated for risk factors for infection-related complications or poor clinical outcome. These include: old age (>65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] <100 cells/μL) or anticipated prolonged (>10 days) neutropenia, pneumonia, invasive fungal infection or other clinically-documented infections. If risk factors are present, CSFs should be considered. Dosing and administration · Based on available data regarding the CSFs in prophylaxis of febrile neutropenia, when choosing among the myeloid growth factors, filgrastim and pegfilgrastim are considered to have more evidence than sargramostim. · Initial doses of filgrastim are started at a daily dose of 5 μg/kg beginning within one to three days after completion of chemotherapy until post-nadir ANC recovery to normal or near-normal ANC levels by laboratory standards. · There is evidence to support the use of pegfilgrastim 24 hours after completion of chemotherapy given every three weeks in one dose of 6 mg per cycle of treatment. · Administration of filgrastim or pegfilgrastim within 24 hours after completion of chemotherapy is not recommended. · There is insufficient evidence to support a strong recommendation for sargramostim in nonmyeloid malignancies. · Subcutaneous administration is preferred for filgrastim, pegfilgrastim and sargramostim. Severe chronic neutropenia · Granulocyte CSF (G-CSF) is an established effective treatment for cyclic, congenital and idiopathic neutropenia.
The American Society of Clinical Oncology: **2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-based Clinical Practice Guideline (2006)**[12]	· Reduction in febrile neutropenia is an important clinical outcome that justifies the use of CSFs, regardless of their impact on other factors, when the risk of febrile neutropenia is approximately 20% and no other equally effective regimen that does not require CSFs is available. Primary prophylactic CSF administration (first and subsequent-cycle use) · Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics and myelotoxicity of the chemotherapy regimen. · For “dose dense” regimens, CSFs are required and recommended. · The standard of care is to use chemotherapy regimens that do not require CSFs because of equal efficacy and lower risk of febrile neutropenia if such regimens are available. · Current data demonstrates effectiveness and supports the use of CSFs when regimens that have a febrile neutropenia incidence of >20% are used; therefore, this practice is recommended. Secondary prophylactic CSF administration · Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy

Clinical Guideline	Recommendations
	(for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. Therapeutic use of CSF · CSFs should not be routinely used for patients with neutropenia who are afebrile. · CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with febrile neutropenia. However, CSFs should be considered in patients with febrile neutropenia who are at high-risk for infection associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. Use of CSFs to increase chemotherapy dose-intensity and dose-density · Use of CSFs allows a modest to moderate increase in dose density and/or dose-intensity of chemotherapy regimens. · A survival benefit is suggested by the current data when CSFs are used with dose-dense regimens in specific settings (e.g., node-positive breast cancer and possibly non-Hodgkin's lymphoma [NHL]), but this data cannot be applied to other diseases. · It is recommended to only use dose dense regimens within an appropriately designed clinical trial or when use is supported by convincing efficacy data. Use of CSFs as adjuncts to progenitor-cell transplantation · The current standard of care is the administration of CSFs to mobilize peripheral-blood progenitor cell (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplantation. Use of CSFs in patients with acute leukemia and myelodysplastic syndromes · For acute myeloid leukemia (AML), CSF use following initial induction therapy is reasonable, as studies have demonstrated a decrease in neutropenia duration, although there has been no favorable impact on remission rate, remission duration or survival. Patients older than 55 years of age may be most likely to benefit from CSF use. · For priming of leukemia cells in patients with AML, use of CSFs is not recommended. · After the completion of consolidation chemotherapy, CSF use can be recommended to possibly decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post-remission chemotherapy. · Due to the lack of information regarding pegylated CSFs in patients with myeloid leukemia, it is recommended that they not be used in such patients outside of clinical trials. · For myelodysplastic syndromes, intermittent administration of CSFs may be considered in certain patients with severe neutropenia and recurrent infection; however, there is a lack of data supporting the routine long-term continuous use of CSFs in these patients. · For acute lymphocytic leukemia (ALL), to reduce the duration of neutropenia, CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post remission course. · For acute leukemia in relapse it is recommended that CSFs be used

Clinical Guideline	Recommendations
	judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia due to the lack of expected response. Use of CSFs in patients receiving radiotherapy with or without concurrent chemotherapy · In those patients who are expected to have prolonged delays in radiation treatment due to neutropenia and are not receiving chemotherapy, CSFs may be considered. · In those patients receiving concurrent chemotherapy and radiation of the mediastinum, CSFs should be avoided. Use of CSFs in older patients · To reduce the incidence of febrile neutropenia and infections, prophylactic CSFs should be given to patients 65 years of age and older with diffuse aggressive lymphoma treated with curative chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or more aggressive regimens). Use of CSFs in the pediatric population · The use of CSFs in pediatric patients will almost always be guided by clinical protocols. The use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a likelihood of febrile neutropenia. · The use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. · Due to the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with CSFs, their use represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSFs in children with ALL should be considered with caution. CSF initiation, duration, dosing and administration · CSFs should be given 24 to 72 hours after the administration of myelotoxic chemotherapy and should be continued until the ANC reaches at least 2 to $3x10^9$ cells/L. · For PBPC mobilization, CSFs should be started at least four days before the first leukapheresis procedure and continued until the last leukapheresis. · In adults, the recommended CSF doses are 5 µg/kg/day for G-CSF and 250 $\mu g/m^2$/day for granulocyte macrophage CSF (GM-CSF) for all clinical settings other than PBPC mobilization. · In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 µg/kg/day maybe preferable. · The preferred route of CSF administration is subcutaneous. Pegylated G-CSF initiation, duration, dosing and administration · Pegfilgrastim 6 mg should be given once 24 hours after completion of chemotherapy. · The 6 mg formulation should not be used in infants, children or small adolescents weighing less than 45 kg. Special comments on comparative clinical activity of G-CSF and GM-CSF · No guideline recommendation can be made regarding the equivalency of the two CFSs. · Further trials are recommended to study the comparative clinical activity,

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	toxicity and cost-effectiveness of G-CSF and GM-CSF. Special comments on growth factors as a treatment for radiation injury · Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.
European Organization for Research and Treatment of Cancer: **2010 Update of European Organization for Research and Treatment of Cancer Guidelines for the Use of Granulocyte-Colony Stimulating Factor to Reduce the Incidence of Chemotherapy-Induced Febrile Neutropenia in Adult Patients with Lymphoproliferative Disorders and Solid Tumors (2010)**[14]	Patient-related risk factors for increased risk of febrile neutropenia · Prevention of chemotherapy-induced febrile neutropenia should be considered a clinical priority. · Prior to administering each cycle of chemotherapy, evaluation of patient-related risk factors should be included in the overall assessment. · Other risk factors that should be evaluated for include: elderly age (aged 65 and over), advanced stage of disease, experience of previous episode(s) of febrile neutropenia, lack of G-CSF use and lack of antibiotic prophylaxis. · Indiscriminate use of antibiotic prophylaxis is not recommended. Chemotherapy regimens associated with increased risk of febrile neutropenia · Chemotherapy regimens are categorized based on their potential to cause febrile neutropenia (>20%, 10 to 20%, <10%); therefore, this risk should be taken into consideration when using certain chemotherapy regimens. G-CSF to support chemotherapy · G-CSF prophylaxis should be used as supportive treatment in cases when dose-dense or dose-intense chemotherapy regimens have demonstrated survival benefits. · G-CSF should be used as primary prophylaxis to maintain a chemotherapy regimen if dose or intensity reduction has demonstrated poor prognosis when the treatment is potentially curative or intended to prolong survival. · When the treatment is palliative, the use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. Impact of the overall febrile neutropenia risk on G-CSF use · At the beginning of each cycle, each patient should be individually assessed for the risk of complication related to febrile neutropenia which should include patient-related risk factors, the chemotherapy regimen and associated complications and treatment intent. · Prophylactic G-CSF therapy is recommended in patients whose overall risk of febrile neutropenia is >20%. · When a chemotherapy regimen associated with a febrile neutropenia risk of 10 to 20% is used, patient characteristics should be taken into account when reviewing the overall risk of febrile neutropenia. G-CSF in patients with existing febrile neutropenia · G-CSF treatment in patients with solid tumors and malignant lymphoma should be reserved for those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infections (such as severe sepsis or septic shock). Choice of formulation · Where indicated, filgrastim, lenograstim* and pegfilgrastim are all recommended to prevent febrile neutropenia and febrile neutropenia related

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	complications due to their clinical efficacy and studies demonstrating comparable efficacy.
British Committee for Standards in Hematology: **Guidelines on the Use of Colony-stimulating Factors in Hematological Malignancies (2003)**[54]	· Due to the lack of comparative trials and clinical trial data, there seems to be no evidence demonstrating efficacy or outcome differences between the G-CSF and GM-CSF products when administered at recommended doses. These guidelines do not differentiate between the agents. Prophylactic and adjunctive use · Primary prophylaxis is not routinely recommended unless the expected incidence of febrile neutropenia is >40%. · Secondary prophylaxis cannot be routinely justified because of a lack of available evidence but is indicated for tumors in which dose reduction or dose delay would compromise overall survival. · Adjunctive treatment is not recommended for patients with uncomplicated febrile neutropenia but should be considered in patients with poor prognostic factors. Use of CSFs in association with chemotherapy · AML: The routine use of CSF is recommended after consolidation chemotherapy. CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. · ALL: G-CSF is indicated to reduce the severity of neutropenia following intensive phases of therapy. · Myelodysplastic syndromes: CSFs are indicted to reduce the severity of neutropenia in patients receiving intensive chemotherapy. CSFs are also recommended on an intermittent basis for patients with neutropenia and infection, but continuous prophylactic use is not routinely justified. · Aplastic anemia: There is insufficient evidence to make any general recommendations. Hence patients should be given CSFs only on an individual therapeutic trial basis. · Bone marrow failure syndromes: G-CSF is recommended when improvement of neutrophil count is appropriate. · Malignant lymphomas: There is evidence to support the routine use of CSFs to reduce the incidence of infection, chemotherapy delay and hospitalization, especially when the risk of febrile neutropenia exceeds 40%. There is also emerging evidence of improved survival with G-CSF-supported dose intensification in elderly patients with high-grade NHL. At present, this evidence is insufficient to justify a change in policy in all patients with lymphoma, but elderly patients may benefit from G-CSF support. CSFs for PBPC mobilization · CSFs are indicated for the mobilization of PBPCs. CSFs after PBSC and marrow transplantation · CSFs are indicated to accelerate reconstitution after allogeneic and autologous PBPC transplantation or bone marrow transplant.
National Comprehensive Cancer Network: **Acute Myeloid Leukemia Clinical Practice**	Monitoring and supportive care · Growth factor support may be considered in the elderly once chemotherapy is complete. · Recommendations regarding the use of cytokines for infection or for slow marrow recovery are left to institutional policy. · G-CSF or GM-CSF should be discontinued for a minimum of seven days

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Guidelines in Oncology (2011)[13]	before obtaining bone marrow to document remission as CSF therapy may confound interpretation of the bone marrow. · Growth factors should not be used in patients with acute promyelocytic leukemia.
British Committee for Standards in Hematology: **Guidelines on the Management of Acute Myeloid Leukemia in Adults (2006)[55]**	Growth factors · Growth factors following AML chemotherapy have shown no survival benefit but have demonstrated reduction in the duration of neutropenia, antibiotic use and hospital stay. · The cost-benefit advantages of routine growth factor use are uncertain. · G-CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. · The routine use of growth factor therapy in AML is not recommended. Standard chemotherapy · There is insufficient evidence to support routine use of G-CSF or GM-CSF with induction chemotherapy in patients over 60 years of age, although this may be appropriate if it is desirable to reduce hospitalization or antibiotic usage. Management of AML in patients who are pregnant · Pregnant patients with other forms of AML, other than promyelocytic leukemia-retinoic acid receptor-positive acute promyelocytic leukemia, and with stable disease may defer chemotherapy and be supported with growth factors and blood products until delivery can be safely induced at about 30 weeks.
National Comprehensive Cancer Network: **Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (2011)[56]**	Supportive care · Use of G-CSF or GM-CSF is not recommended for routine infection prophylaxis. · Use of G-CSF or GM-CSF may be considered in a neutropenic patient who has recurrent or resistant infections. · Low-dose G-CSF or GM-CSF may be combined with recombinant human erythropoietin for anemia when indicated, particularly in patients who are not responding to erythropoiesis-stimulating agents and have serum erythropoietin level of 500 mUnits/mL or less.
United Kingdom Myelodysplastic Syndromes Guideline Group: **Guidelines for the Diagnosis and Therapy of Adult Myelodysplastic Syndromes (2003)[57]**	Erythropoietin with or without G-CSF · Many studies have clearly demonstrated that erythropoietin±G-CSF can increase hemoglobin levels and reduce or eliminate red blood cell transfusion in selected myelodysplastic syndromes patients. · It is recommended that patients with refractory anemia and refractory anemia with excess blasts who are not eligible for chemotherapy or stem cell transplantation and are symptomatic of anemia, with no or low transfusion requirement (<2 units/month) and a baseline erythropoietin level <200 units/L who have not responded to a trial of erythropoietin alone for six weeks be considered for daily G-CSF therapy, doubling the dose of erythropoietin or both for six more weeks. The G-CSF dose should be doubled weekly (e.g., 75 µg to 150 µg then to 300 µg) to maintain the white blood cell between 6 and $10x10^9$ cells/L. In patients who respond, once the maximum response has been reached, the G-CSF can be reduced to thrice weekly, and the erythropoietin dose can be reduced by one day a week at four weekly intervals (e.g., five days a week to four days then three days) to the lowest dose that retains response. · It is recommended that the combination of erythropoietin and G-CSF be

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	used from the beginning for patients with refractory anemia with excess blasts, symptomatic anemia, baseline erythropoietin levels <500 units/L and a transfusion requirement <2 units/month. · Due to the lack of published data, it is encouraged to continue randomized-controlled trials of erythropoietin±G-CSF to address the issues of quality of life, survival advantage and pharmacoeconomics. Prophylactic management of infection · Prophylactic low-dose G-CSF therapy may be considered in patients who are severely neutropenic in order to maintain a neutrophil count >1X10^{9} cells/L.

Conclusions

Colony-stimulating factors (CSFs) are growth factors which stimulate the production and enhance recovery of neutrophils.[58] There are currently two types of CSFs available in the United States, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Filgrastim, filgrastim-sndz, tbo-filgrastim and pegfilgrastim are the currently available G-CSFs.[1-3,5] Filgratstim-sndz is considered a biosimilar drug to parent molecule filgrastim; however, due to regulatory pathways for biosimilar drugs being available at the time, tbo-filgrastim is not. Tbo-filgrastim was filed with its own Biologic Drug Application and thus does not share the same indications. Since the time the application for filgrastim-sndz was submitted, the parent molecule, filgrastim was granted an additional indication that filgrastim-sndz does not have.[1,2,9] Sargramostim is the only GM-CSF currently available.[4]

G-CSFs are largely used to prevent and reduce the duration of neutropenia in patients receiving chemotherapy.[59] Several clinical trials have demonstrated efficacy of the G-CSFs for this indication. A systematic review published in 2007 reviewed 17 randomized controlled trials comparing primary prophylactic G-CSF to placebo or untreated controls in adult solid tumor and malignant lymphoma patients. The review reported an overall 46% decrease in the risk of febrile neutropenia, a 45% decrease in infection-related mortality and a 40% decrease in all-cause mortality during the chemotherapy period.[60]

Currently the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend CSF prophylaxis in patients whose overall risk of febrile neutropenia is >20%.[9,10,16] Recent retrospective data has reported a potential advantage of pegfilgrastim in reducing the risk of hospitalizations due to febrile neutropenia when compared to filgrastim and sargramostim, while an earlier prospective, randomized trial demonstrated comparable clinical efficacy between filgrastim and pegfilgrastim for the indication of febrile neutropenia.[18-21] The NCCN and the EORTC guidelines currently recommend either G-CSF equally for treatment.[11,13] Moreover, with the lack of clinical studies comparing the efficacy of the G-CSFs and GM-CSF, the ASCO guidelines do not provide recommendations regarding the specific types of products,[12] whereas the NCCN states filgrastim and pegfilgrastim have stronger evidence than sargramostim supporting their use.[11] Additional studies are needed to determine the safety and efficacy differences among the G-CSFs and GM-CSF in febrile neutropenia as well as the other indications.

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New Drug Overview
Diclegis® (doxylamine succinate/pyridoxine hydrochloride)

Overview/Summary: Viberzi® (eluxadoline) is a μ-opioid receptor agonist/δ-opioid receptor antagonist/κ-receptor agonist indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D). It is a locally active visceral analgesic, with low systemic absorption and bioavailability. The μ-opioid agonist activity works by inhibiting gastrointestinal (GI) motility and secretion and the δ-opioid receptor antagonism works by mitigating against the constipating effects of unopposed peripherally acting μ-opioid receptor agonist.[1,2] This agent was assigned a Schedule IV designation due to its documented low potential for abuse and low risk of dependence.[3]

IBS is a functional bowel disorder characterized by chronic abdominal pain and altered bowel habits, in the absence of obvious structural or inflammatory abnormalities. It is thought to affect approximately 5 to 15% of the general population with the majority of cases occurring in individuals between the ages of 15 and 65 years.[4] Although the exact cause of IBS-D is not known, symptoms are thought to result from a disturbance in the way the GI tract and nervous system interact. IBS-D is a subset of irritable bowel syndrome that is defined as the presence of loose or watery stools with ≥ 25 percent of bowel movements and hard or lumpy stools with < 25 percent of bowel movements. This subtype accounts for approximately one-third of all IBS cases in the U.S. Rome III criteria are currently considered the "Gold Standard" for the diagnosis of IBS. These include recurrent abdominal pain or discomfort for at least three days per month in the last three months associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency, onset associated with a change in stool form.[5]

Currently there are a few therapeutic options that exist to manage the symptoms of abdominal pain, bloating, diarrhea and fecal urgency. These include non-pharmacologic options of lifestyle and dietary modifications as well as pharmacologic therapies such as antidiarrheals (e.g., loperamide), bile acid sequestrants (e.g., cholestyramine, colestipol, and colesevelam), antispasmodics for abdominal pain (e.g., hyoscyamine, dicyclomine), tricyclic antidepressants (TCAs) (e.g., amitriptyline) and selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline).[5] The only other FDA-approved treatments for IBS-D currently include Xifaxan® (rifaximin) which received this expanded indication in 2015 and Lotronex® (alosetron) which is restricted to women and requires prescribers to enroll in the Prometheus Prescribing Program due to its black box warning for potentially serious GI adverse reactions such as ischemic colitis and severe constipation.[6]

Table 1. Dosing and Administration[1]

Generic (Trade) Name	Adult Dose	Pediatric Dose	Availability
Eluxadoline (Viberzi®)	Irritable bowel syndrome with diarrhea: Tablet: initial, maintenance, maximum, 100 mg BID with food For individuals with IBS-D who do not have a gallbladder, are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors or have mild or moderate hepatic impairment (Child-Pugh class A or B): Tablet: initial, maintenance and maximum, 75 mg BID with food	Safety and efficacy in children have not been established.	Tablet: 75 mg 100 mg

BID=twice daily

Evidence-based Medicine

- The safety and efficacy of eluxadoline (Viberzi®) in the treatment of IBS-D was established in two identical randomized, multi-center, double-blind, placebo-controlled phase III clinical trials in adults with IBS-D (IBS-3001 and IBS-3002). Both trials were 26 weeks long. Individuals were randomized to receive twice daily placebo, eluxadoline 75 mg or eluxadoline 100 mg. In Study IBS-3001, the double-blinded treatment period was continued for an additional 26 weeks to monitor long-term safety (total of 52 weeks of treatment), followed by a two-week follow-up. Study IBS-3002 included a four-week single-blinded, placebo-withdrawal period upon completion of the 26-week treatment period. Efficacy of eluxadoline was assessed in both trials using an overall composite responder primary endpoint. This was defined by patients meeting the daily response criteria (pain and stool consistency) for ≥ 50% of the days with diary entries for two criteria: daily pain response (improvement in WAP scores in the past 24 hours by ≥ 30% compared to baseline) and daily stool consistency (BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline pain). The primary endpoints for the IBS-3001 trial, showed that the proportion of composite responders for the 75 mg and 100 mg treatment groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.025) and weeks 1 to 26 for the 100 mg treatment group (P<0.001). In the IBS-3002 trial, the proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P=0.001). The onset for response was noted to be within the first week of dosing in both trials.[2,10]

Key Points within the Medication Class

- Due to limited therapeutic options for the treatment of IBS-D, clinical guidelines have consistently provided only moderate or weak recommendations for the use of all agents, new and old.[7-9]
    - All current clinical guidelines suggest rifaximin, alosetron, TCAs, SSRIs, and antispasmodics are effective, but their place in therapy is not well defined and varies by guideline. Loperamide was granted a conditional recommendation by the American Gastrointestinal Association (AGA) due to its usefulness as a potential adjunctive therapy for the management of diarrhea, however the American College of Gastroenterology (ACG) and World Gastroenterology Organization Global Guidelines do not recommend its use due to no relief of the global symptoms of IBS-D.[7-9]
    - Only the World Gastroenterology Organization mentions the use of eluxadoline, but acknowledges that although it has been approved for use in the United States, its position in the management of IBS is difficult to define at this time.[9]

- Other Key Facts:
    - Efficacy of Viberzi® (eluxadoline) beyond 26 weeks has not been established.
    - This agent has shown equal efficacy in men and women, unlike alosetron which is indicated only in women.[2]

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New Drug Review
Viberzi® (eluxadoline)

Overview/Summary

Viberzi® (eluxadoline) is a μ-opioid receptor agonist/δ-opioid receptor antagonist/κ-receptor agonist indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D). It is a locally active visceral analgesic, with low systemic absorption and bioavailability. The μ-opioid agonist activity works by inhibiting gastrointestinal (GI) motility and secretion and the δ-opioid receptor antagonism works by mitigating against the constipating effects of unopposed peripherally acting μ-opioid receptor agonist.[1,2] This agent was assigned a Schedule IV designation due to its documented low potential for abuse and low risk of dependence.[3]

IBS is a functional bowel disorder characterized by chronic abdominal pain and altered bowel habits, in the absence of obvious structural or inflammatory abnormalities. It is thought to affect approximately 5 to 15% of the general population with the majority of cases occurring in individuals between the ages of 15 and 65 years.[4] Although the exact cause of IBS-D is not known, symptoms are thought to result from a disturbance in the way the GI tract and nervous system interact. IBS-D is a subset of irritable bowel syndrome that is defined as the presence of loose or watery stools with ≥ 25 percent of bowel movements and hard or lumpy stools with < 25 percent of bowel movements. This subtype accounts for approximately one-third of all IBS cases in the U.S. Rome III criteria are currently considered the "Gold Standard" for the diagnosis of IBS. These include recurrent abdominal pain or discomfort for at least three days per month in the last three months associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency, onset associated with a change in stool form.[5]

Currently there are a few therapeutic options that exist to manage the symptoms of abdominal pain, bloating, diarrhea and fecal urgency. These include non-pharmacologic options of lifestyle and dietary modifications as well as pharmacologic therapies such as antidiarrheals (e.g., loperamide), bile acid sequestrants (e.g., cholestyramine, colestipol, and colesevelam), antispasmodics for abdominal pain (e.g., hyoscyamine, dicyclomine), tricyclic antidepressants (TCAs) (e.g., amitriptyline) and selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline).[5] The only other FDA-approved treatments for IBS-D currently include Xifaxan® (rifaximin) which received this expanded indication in 2015 and Lotronex® (alosetron) which is restricted to women and requires prescribers to enroll in the Prometheus Prescribing Program due to its black box warning for potentially serious GI adverse reactions such as ischemic colitis and severe constipation.[6]

Due to limited therapeutic options for the treatment of IBS-D, clinical guidelines have consistently provided only moderate or weak recommendations for the use of all agents, new and old. All current clinical guidelines suggest rifaximin, alosetron, TCAs, SSRIs, and antispasmodics are effective, but their place in therapy is not well defined and varies by guideline. Loperamide was granted a conditional recommendation by the American Gastrointestinal Association (AGA) due to its usefulness as a potential adjunctive therapy for the management of diarrhea, however the American College of Gastroenterology (ACG) and World Gastroenterology Organization Global Guidelines do not recommend its use due to no relief of the global symptoms of IBS-D. Only the World Gastroenterology Organization mentions the use of eluxadoline, but acknowledges that although it has been approved for use in the United States, its position in the management of IBS is difficult to define at this time.[7-9]

Indications

Viberzi® is indicated in adults for the treatment of irritable bowel syndrome with diarrhea.

Pharmacokinetics

Table 1. Pharmacokinetics[1,2]

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
Eluxadoline	Not determined	1.5 (range 1 to 8)	<1	Metabolism not well established	3.7 to 6

Clinical Trials

The safety and efficacy of eluxadoline in the treatment of IBS-D was established in two identical randomized, multi-center, double-blind, placebo-controlled phase III clinical trials in adults with IBS-D (IBS-3001 and IBS-3002). Both trials were 26 weeks long. Individuals were randomized to receive twice daily placebo, eluxadoline 75 mg or eluxadoline 100 mg. In Study IBS-3001, the double-blinded treatment period was continued for an additional 26 weeks to monitor long-term safety (total of 52 weeks of treatment), followed by a two-week follow-up. Study IBS-3002 included a four-week single-blinded, placebo-withdrawal period upon completion of the 26-week treatment period. During the double-blind treatment phase and the single-blinded placebo withdrawal phase, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea, but were not allowed to take any other antidiarrheal, antispasmodic agent or rifaximin for their diarrhea.[2,10]

Efficacy of eluxadoline was assessed in both trials using an overall composite responder primary endpoint. This was defined by patients meeting the daily response criteria (pain and stool consistency) for $\geq$ 50% of the days with diary entries for two criteria: daily pain response (improvement in WAP scores in the past 24 hours by $\geq$ 30% compared to baseline) and daily stool consistency (BSS score < five or the absence of a bowel movement if accompanied by $\geq$ 30% improvement in WAP compared to baseline pain). The primary endpoints for the IBS-3001 trial, showed that the proportion of composite responders for the 75 mg and 100 mg treatment groups had a statistically greater response than placebo for weeks 1 to 12 ($P<0.025$) and weeks 1 to 26 for the 100 mg treatment group ($P<0.001$). In the IBS-3002 trial, the proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 ($P<0.001$) and weeks 1 to 26 ($P=0.001$). The onset for response was noted to be within the first week of dosing in both trials.[2,10]

Secondary endpoints in the IBS-3001 trial that were noted to be significant included the proportion of stool consistency responders in the eluxadoline 75 mg group ($P=0.008$) and 100 mg group ($P<0.001$) compared with placebo for weeks 1 to 12 and the eluxadoline 100 mg group only ($P=0.001$) during weeks 1 to 26. The proportion of IBS-D global symptom responders was statistically significant compared with placebo for the eluxadoline 75 mg group ($P=0.048$) from weeks 1 to 12 and from weeks 21 to 24 ($P=0.024$). Lastly, the proportion of patients who reported adequate relief of their IBS symptoms was statistically significant for the eluxadoline 100 mg group ($P\leq 0.005$) compared with placebo over weeks 1 to 12 and weeks 1 to 26 ($P=0.005$). This was also apparent for the eluxadoline 75 mg group ($P=0.008$) compared to placebo over weeks 1 to 12.[2,10]

The IBS-3002 trial also showed significant responses in the eluxadoline groups for several secondary endpoints. The proportion of stool consistency responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically significant compared to placebo over weeks 1 to 12 and weeks 1 to 26 ($P<0.001$). A larger proportion of IBS-D global symptom responders for the 75 mg and 100 mg eluxadoline treatment groups had a statistically greater response than placebo over weeks 1 to 12 ($P<0.001$) and weeks 1 to 26 ($P\leq 0.012$). The proportion of IBS-adequate relief (AR) responders for the eluxadoline 75 mg and 100 mg treatment groups was also greater than placebo ($P\leq 0.013$) over weeks 1 to 12 and weeks 1 to 26.[2,10]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lembo et al[2,10] IBS 3001 Eluxadoline 75 mg BID vs eluxadoline 100 mg BID vs placebo BID	DB, MC, PC, PG, RCT Patients from 18 to 80 years of age with a documented diagnosis of IBS-D (by Rome III criteria), daily average WAP > 3.0 (on a 10-point scale), average BSS score of ≥ 5.5 and at least five days with a BSS score of ≥ 5 on BSS scale (on a 7-point scale), IBS-D global symptom score ≥ 2.0 (on a 4-point scale)	N=1,282 Treatment phase=52 weeks	Primary: Evaluation of composite responders over the initial 12 weeks (for the FDA) and initial 26 weeks (for the EMA) of DB treatment (composite responders were defined as patients meeting the daily response criteria [pain and stool consistency] for ≥ 50% of the days with diary entries on the following two criteria: daily pain response [improvement in WAP scores in the past 24 hours by ≥ 30% compared to baseline] and daily stool consistency response [BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline]) Secondary: Pain response and stool consistency	Primary: The proportion of composite responders for the eluxadoline 75 mg (23.9%; P=0.014) and 100 mg (25.1%; P=0.004) groups had a statistically greater response than placebo (17.1%) over weeks 1 to 12. In addition, the proportion of composite responders for the 100 mg group (29.3%, P<0.001) had a statistically greater response than placebo (19.0%) over weeks 1 to 26. Secondary: The proportion of pain responders was numerically higher in the eluxadoline 75 mg (43.2%; P=0.284) and 100 mg (42.4%; P=0.404) groups compared to placebo (39.6%) over weeks 1 to 12 but not statistically significant. This was the same for weeks 1 to 26. The proportion of stool consistency responders was statistically significant in the eluxadoline 75 mg group (P=0.008) and 100 mg group (P<0.001) compared with placebo for weeks 1 to 12 and the eluxadoline 100 mg group only (P=0.001) during weeks 1 to 26. The proportion of IBS-D global symptom responders was statistically significant compared with placebo for the 75 mg group (P=0.048) from weeks 1 to 12 and from weeks 21 to 24 (P=0.024). The proportion of patients who reported adequate relief of their IBS symptoms was statistically significant for the eluxadoline 100 mg group (P≤ 0.005) compared with placebo over weeks 1 to 12 and weeks 1 to 26. This was also apparent for the eluxadoline 75 mg group (P=0.008) compared to placebo over weeks 1 to 12. The risks for frequency of bowel movements and urgency episodes were noted to be significantly lower for the eluxadoline 75 mg and 100 mg groups throughout week 26 compared to placebo using a longitudinal model. No P values were reported. The proportion of IBS-QOL total score responders for the eluxadoline 100

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			response based on improvement from baseline in daily abdominal pain scores and stool consistency scores, IBS-D global symptom response (i.e., symptom score of 0 [none] or 1 [mild] or a daily IBS-D global symptom score improved by ≥ 2.0 compared to the baseline average), IBS-QOL response (i.e., at least a 14-point improvement in IBS-QOL total score from baseline to the applicable visit), IBS-AR response (i.e., weekly response of 'yes' to adequate relief of their symptoms for ≥ 50% of the total weeks during the interval), abdominal bloating and discomfort, bowel function and QOL response with IBS-QOL	mg group was higher than placebo at most weeks evaluated and significantly higher than placebo (P<0.05) at weeks 4 and 8. The proportion of IBS-QOL total score responders for the eluxadoline 75 mg group was numerically higher or similar to placebo but not significantly different. The overall incidence of AEs was similar across treatment groups with most being mild to moderate in severity. GI symptoms were the most commonly reported AEs and included constipation, nausea, abdominal pain, distension, vomiting, flatulence and diarrhea.
Lembo et al[2,10] IBS 3002 Eluxadoline 75 mg BID	DB, MC, PC, PG, RCT Patients from 18 to 80 years of age with a	N=1,145 Treatment phase=26	Primary: Evaluation of composite responders over the initial 12	Primary: The proportion of composite responders for the eluxadoline 75 mg and 100 mg groups had a statistically greater response than placebo for weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P=0.001). The onset of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs eluxadoline 100 mg BID vs placebo BID	documented diagnosis of IBS-D (by Rome III criteria), daily average WAP > 3.0 (on a 10-point scale), average BSS score of ≥ 5.5 and at least five days with a BSS score of ≥ 5 on BSS scale (on a 7-point scale), IBS-D global symptom score ≥ 2.0 (on a 4-point scale)	weeks	weeks (for the FDA) and initial 26 weeks (for the EMA) of DB treatment (composite responders were defined as patients meeting the daily response criteria [pain and stool consistency] for ≥ 50% of the days with diary entries on the following two criteria: daily pain response [improvement in WAP scores in the past 24 hours by ≥ 30% compared to baseline] and daily stool consistency response [BSS score < five or the absence of a bowel movement if accompanied by ≥ 30% improvement in WAP compared to baseline]) Secondary: Pain response and stool consistency response based on improvement from baseline in daily abdominal pain scores and stool consistency	response for both eluxadoline treatment groups occurred within the first week of dosing. Secondary: The proportion of pain responders for the 75 mg and 100 mg treatment groups was numerically higher than placebo, but not statistically significant, over weeks 1 to12 and weeks 1 to 26. The proportion of stool consistency responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically significant (P<0.001) versus placebo over weeks 1 to 12 and weeks 1 to 26. The proportion of stool consistency responders was significantly higher than placebo for the 75 mg (P<0.05) and 100 mg eluxadoline groups (P<0.001) over each 4-week interval. The proportion of IBS-D global symptom responders for the 75 mg and 100 mg eluxadoline treatment groups was statistically greater than that of placebo over weeks 1 to 12 (P<0.001) and weeks 1 to 26 (P≤0.012). The proportion of IBS-AR responders for the 75 mg and 100 mg treatment groups was statistically greater compared to placebo (P≤ 0.013) over weeks 1 to 12 and weeks 1 to 26. When analyzed over time using a longitudinal model, daily abdominal bloating scores were significantly lower than placebo for the 100 mg treatment group at weeks 16, 20, 24, and 26; daily abdominal discomfort scores were significantly lower than placebo for both eluxadoline treatment groups at each time point evaluated through week 26 (no P values reported). When analyzed over time using a longitudinal model, the risks for frequency of bowel movements and urgency episodes were significantly lower than placebo for both eluxadoline treatment groups at each time point evaluated through week 26 (no P values reported). Patients in both eluxadoline treatment groups had significantly better HRQOL than placebo patients at each time point assessed based on a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			scores, IBS-D global symptom response (i.e., symptom score of 0 [none] or 1 [mild] or a daily IBS-D global symptom score improved by ≥ 2.0 compared to the baseline average), IBS-QOL response (i.e., at least a 14-point improvement in IBS-QOL total score from baseline to the applicable visit), IBS-AR response (i.e., weekly response of 'yes' to adequate relief of their symptoms for ≥ 50% of the total weeks during the interval), abdominal bloating and discomfort, bowel function and QOL response with IBS-QOL	longitudinal analysis of IBS-QOL total scores. GI AEs were the most commonly reported AEs and included constipation, nausea, vomiting, abdominal pain, distension, and flatulence. Constipation occurred in < 10% of patients in each treatment group, with most events being mild or moderate in severity. Pooled data from IBS 3001 and IBS 3002 trials resulted in five cases out of 1,666 patients (0.3%) for pancreatitis and eight cases out of 1,666 patients (0.5%) for spasm of the sphincter of Oddi. No deaths were reported during these studies.

Drug regimen abbreviations: BID=twice daily
Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
AEs=adverse events, BSS= Bristol Stool Scale, CR=clinical response, EQ-5D=Euro-Qol-5dimension, EMA=European Medicines Agency, FDA=Food and Drug Administration, GI=gastrointestinal, HRQOL=health-related quality of life, IBS=irritable bowel syndrome, IBS-AR=IBS-adequate relief, IBS-QOL= IBS-quality of life, IBS-SSS=IBS-Symptom Severity Score, QOL=quality of life, WAP=worst abdominal pain

Special Populations

Table 3. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Eluxadoline	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established	Not studied in renal dysfunction.	Increased concentration in mild or moderate impairment. Reduce dose to 75 mg twice daily in these patients. Contraindicated in severe hepatic impairment.	Not studied in pregnancy	Unknown; use with caution

Adverse Drug Events

Clinical trials data from over 1,700 patients with IBS-D receiving eluxadoline had a resulting sphincter of Oddi spasm in 0.2% (2/807) of patients receiving 75 mg twice daily and in 0.8% (8/1,032) of patients receiving 100 mg twice daily. Common adverse reactions reported in > 2% of IBS-D patients in either eluxadoline treatment group and at an incidence greater than in the placebo group are shown below in Table 4.

Table 4. Common Adverse Reactions in the Placebo-Controlled Studies in IBS-D Patients[1,2]

Adverse Event	Reported Frequency		
	Eluxadoline 100 mg Twice Daily (%), N=1,032	Eluxadoline 75 mg Twice Daily (%), N=807	Placebo (%), N=975
Abdominal distention	3	3	2
Abdominal pain*	7	6	4
Bronchitis	3	3	2
Constipation	8	7	2
Dizziness	3	3	2
Fatigue	2	3	2
Flatulence	3	3	2
Increased ALT	3	2	1
Nasopharyngitis	3	4	3
Nausea	7	8	5
Rash†	3	3	2
Upper respiratory tract infection	5	3	4
Viral gastroenteritis	1	3	2
Vomiting	4	4	1

*Abdominal pain includes: upper and lower abdominal pain
†Rash includes: dermatitis, dermatitis allergic, rash erythematous, rash generalized, rash maculopapular, rash pruritic, urticaria and idiopathic urticaria
ALT=alanine aminotransferase

Contraindications

Table 5. Contraindications[1,2]

Contraindication	Eluxadoline
Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; eluxadoline may place patients at an increased risk of sphincter of Oddi spasm.	a
Alcoholism, alcohol abuse or in those who drink more than three alcoholic beverages per day; patients are at an increased risk of acute pancreatitis.	a
History of pancreatitis or structural disease of the pancreas; patients are at an increased risk for acute pancreatitis.	a
Severe hepatic impairment (Child-Pugh Class C); patients are at risk for a 16 fold increase in plasma concentrations of eluxadoline.	a
History of chronic or severe constipation or known or suspected mechanical gastrointestinal obstruction; patients may be at risk for severe complications of bowel obstruction.	a

Warnings/Precautions

Table 6. Warnings and Precautions[1]

Warning/Precaution	Eluxadoline
Sphincter of Oddi spasm; there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatic or hepatic enzyme elevation associated with acute abdominal pain with eluxadoline. Consider alternative therapies before using this agent in patients without a gallbladder. If decision is made to use in individuals without a gallbladder, use a reduced dosage of 75 mg twice daily. Instruct patients to stop eluxadoline and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain, (e.g. acute epigastric or biliary [i.e., right upper quadrant] pain), that may radiate to the back or shoulder with or without nausea and vomiting, associated with elevations of pancreatic enzymes or liver transaminases. Do not restart this agent in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking eluxadoline.	a
Pancreatitis; there is a potential for increased risk of pancreatitis, not associated with sphincter of Oddi spasm while taking eluxadoline. Instruct patients to avoid chronic or acute excessive alcohol use while taking eluxadoline. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting. Instruct patients to stop this medication and seek medical attention if they experience symptoms suggestive of pancreatitis such as acute abdominal or epigastric pain radiating to the back associated with elevations of pancreatic enzymes.	a

Drug Interactions

Table 6. Drug Interactions[1,6]

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
OATP1B1 Inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals [atazanavir, lopinavir, saquinavir, tipranavir], eltrombopag	Major	Concurrent use may result in increased eluxadoline exposure. Reduce dose of eluxadoline to 75 mg twice daily and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities and for other eluxadoline-

Interacting Medication or Disease	Interaction Severity Rating*	Potential Result
and rifampin)		related adverse reactions.
Strong CYP Inhibitors (e.g., ciprofloxacin [CYP1A2], gemfibrozil [CYP2C8], fluconazole [CYP2C19], clarithromycin [CYP3A4], paroxetine and bupropion [CYP2D6])	Not listed	Concurrent use may result in increased eluxadoline exposure. Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities and for other eluxadoline-related adverse reactions.
Drugs that cause constipation (e.g., alosetron, anticholinergics, opioids, etc.)	Not listed	Avoid use with other drugs that may cause constipation as there is an increased risk for constipation related adverse reactions if given concurrently. Loperamide may be used occasionally for acute management of severe diarrhea but chronic use should be avoided.

*Severity rating per Micromedex

Dosage and Administration

Table 7. Dosing and Administration[1,2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Eluxadoline	Irritable Bowel Syndrome with Diarrhea: Tablet: initial, maintenance, maximum, 100 mg BID with food For individuals with IBS-D who do not have a gallbladder, are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors or have mild or moderate hepatic impairment (Child-Pugh class A or B): Tablet: initial, maintenance and maximum, 75 mg BID with food	Safety and efficacy in children have not been established.	Tablet: 75 mg 100 mg

BID=twice daily

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American Gastroenterological Association (AGA) Institute: **Guideline on the Pharmacological Management of Irritable Bowel Syndrome (2014)**[7]	IBS-C · The use of linaclotide is recommended. (Recommendation: strong; high quality evidence) · The use of lubiprostone (over no drug treatment) is recommended. (Conditional recommendation; moderate-quality evidence) · The use of laxatives (over no drug treatment) is suggested. (Conditional recommendation; low-quality evidence) IBS-D · The use of rifaximin (over no drug treatment) is suggested. (Conditional recommendation; moderate-quality evidence) · The use of alosetron (over no drug treatment) is suggested. (Conditional

Clinical Guideline	Recommendations
	recommendation; moderate evidence) · The use of loperamide (over no drug treatment) is suggested. (Conditional recommendation; very low-quality evidence) IBS · The use of TCAs or SSRIs (over no drug treatment) is suggested. (Conditional recommendation; low-quality evidence) · The use of antispasmodics (over no drug treatment) is suggested in patients with IBS. (Conditional recommendation; low-quality evidence)
American College of Gastroenterology (ACG): **Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation (2014)**[8]	Irritable bowel syndrome (IBS): · Rome III criteria for diagnosing IBS: o Recurrent abdominal pain or discomfort at least three days per month in the past three months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool · Subtypes include IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed-type (IBS-M) and unclassified (IBS-U). · Fiber provides overall symptom relief in IBS. (Recommendation: weak; quality of evidence: moderate) · Probiotics improve global symptoms, bloating and flatulence in IBS. (Recommendation: weak; quality of evidence: low) · Rifaximin has shown modest but consistent efficacy in non-constipated IBS and seems to be well tolerated and safe over the time periods evaluated. · Antispasmodics (hyoscine and dicyclomine) provide symptomatic short-term relief in IBS. (Recommendation: weak; quality of evidence: low). · Peppermint oil is superior to placebo in improving IBS symptoms. (Recommendation: weak; quality of evidence: moderate). · There is insufficient evidence to recommend loperamide for use in IBS. It is an effective antidiarrheal but there is no evidence to support its use for relief of global symptoms in IBS. (Recommendation strong, quality of evidence very low) · Antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) are effective in symptom relief in IBS. (Recommendation: weak; quality of evidence: high) · Alosetron is effective in females with diarrhea-predominant IBS. (Recommendation: weak; quality of evidence: moderate) · The prosecretory agents linaclotide and lubiprostone are effective in constipation-predominant IBS. · There is no evidence that polyethylene glycol (PEG) improves overall symptoms and pain in patients with IBS. (Recommendation: weak; quality of evidence: very low)
World Gastroenterology Organisation Global Guidelines: **Irritable Bowel Syndrome: a Global Perspective (2015)**[9]	Rome III subclassification criteria: · IBS-D: loose stools>25% of time and hard stools< 25% of time, up to 1/3 of cases, more common in men · IBS-C: hard stools > 25% of time and loose stools< 25% of time, up to 1/3 of cases, more common in women · IBS-M: both hard and soft stools > 25% of time, 1/3 to 1/2 of cases · Un-subtyped IBS: insufficient abnormality of stool consistency to meet criteria IBS-C or M. · Patients commonly transition between subtypes.

Clinical Guideline	Recommendations
	Epidemiology: · Prevalence of IBS in Europe and North America is estimated to be 10 to 15%. · IBS mainly occurs between the ages of 15 and 65 years. · Diagnosis is usually suspected on the basis of the patient's history and physical exam, without additional tests. Management: · Specialized diets may improve symptoms in some IBS patients (e.g., fiber-rich diet or bulk-former combine with sufficient fluids, low in fermentable oligo-, di-, and monosaccharides and polyols, wheat-free and gluten-free diets) · Some probiotics give global relief of symptoms in IBS and others alleviate individual symptoms such as bloating and flatulence. The duration of benefits and the nature of the most effective species are not clear. · There is insufficient evidence for a general recommendation of prebiotics or synbiotics in patients with IBS. Overall symptoms- first-line therapy: · Some antispasmodics (hyoscine, dicyclomine, otilonium [unavailable in U.S.], cimetropium [unavailable in U.S.], pinaverium [unavailable in U.S.], and mebeverine [unavailable in U.S.]) provide symptomatic short-term relief in IBS. · Peppermint oil is superior to placebo in improving IBS symptoms. Overall symptoms- second-line therapy: · Laxatives · Antidiarrheals · TCAs and SSRIs are effective for symptom relief in IBS. · SSRIs may be considered in resistant IBS-C, although it is not currently recommended that SSRIs be routinely prescribed for IBS in patients without comorbid psychiatric conditions due to conflicting and limited data on efficacy, safety and long-term outcomes. Overall symptoms- other therapeutic options: · Rifaximin is effective in reducing overall symptoms in IBS-D. It may be considered as second-line therapy but its efficacy and safety has not been established beyond 16 weeks. Older patients and women were found to have higher response rates. · Alosetron is useful for second-line therapy of IBS-D. It has however been associated with an increased risk of ischemic colitis and may cause severe constipation. · Lubiprostone is safe and effective for treatment of IBS-C. · Linaclotide is safe and effective for treatment of IBS-C. · There is insufficient evidence to recommend loperamide for use in IBS. · Mixed 5-HT4 agonists/5-HT3 antagonists are no more effective than placebo at improving symptoms of IBS-C. · Renzapride (unavailable in U.S.) and cisapride have no benefit in IBS. · Evidence is lacking for the use of PEG for overall symptoms of IBS but it may relieve constipation.

Clinical Guideline	Recommendations
	· Ondansetron improves urgency, diarrhea and bloating in IBS-D, but did not help with pain. Ramosetron (unavailable in U.S.) should be considered as second-line therapy in IBS-D. Specific symptoms-pain: · If an analgesic is required, paracetamol (unavailable in U.S.) is preferable to nonsteroidal anti-inflammatory drugs (NSAIDs). Avoid opiates due to potential for dependence, addiction and undesirable side effects on the gastrointestinal tract. · The probiotic strain *Bifidobacterium infantis* 35624 (one capsule per day) has been shown to reduce pain, bloating, and defecatory difficulty and to normalize stool habit in IBS patients, regardless of predominant bowel habit · Antispasmodics, including peppermint oil, are still considered to represent a first-line treatment for abdominal pain in patients with IBS. · TCAs (amitriptyline [starting dose: 10 mg/day, target dose 25 to 50 mg/day at bedtime], desipramine [target dose: 50 mg/day, target dose 100 to 150 mg/day at bedtime]). Avoid use in constipated patients. · SSRIs (paroxetine 10 to 60 mg/day, citalopram 5 to 20 mg/day). · Linaclotide reduces abdominal pain in IBS-C. Specific symptoms- diarrhea: · Loperamide (2 mg every morning or twice daily) is no more effective than placebo in reducing pain, bloating and global symptoms of IBS but it is an effective agent for management of diarrhea, reducing stool frequency and improving stool consistency. However, there is insufficient evidence to recommend loperamide for use in IBS. · Alosetron is indicated for women with severe IBS-D with symptoms > six months and no response to antidiarrheal agents. · Eluxadoline and rifaximin have recently been approved in the U.S. for IBS-D. However, it is difficult to define their position in IBS management at this time.

Conclusions

Viberzi® (eluxadoline) is a first-in-class, oral, locally-acting agent with opioid activity: it is a combination μ-opioid receptor agonist, δ-opioid receptor antagonist and κ-receptor agonist. This agent now offers another option for individuals diagnosed with IBS-D that is not adequately managed by conventional treatment. Current clinical guidelines support the use of less costly alternatives and have not been updated to address the use of eluxadoline and its place in therapy.[7-9] However, in two phase III studies in IBS-D patients, eluxadoline demonstrated statistically significant improvements in abdominal pain and stool consistency, and had beneficial effects on stool frequency, urgency, and global IBS symptom scores.[2] In addition, this agent has shown equal efficacy in men and women, unlike alosetron which is indicated only in women.[2] Of note, efficacy beyond 26 weeks has not been established. While this is currently approved only for use in adults, additional studies in pediatric patients are underway.

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New Drug Overview
Diclegis® (doxylamine succinate/pyridoxine hydrochloride)

- **Overview/Summary:** Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. It should be noted that the agent has not been studied in hyperemesis gravidarum.[1] The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity, although scientific evidence supports the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects.[2]

  Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[1-3]

  Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women.[2,4] Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs infrequently. The treatment goals in patient with NVP are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of nausea and vomiting such as dehydration and to minimize the fetal effects of NVP treatment.[2]

Table 1. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
doxylamine succinate/ pyridoxine hydrochloride	Nausea and Vomiting of Pregnancy: Delayed-release tablet: Initial, two tablets QHS on day one; if symptoms persist into day two increase dose to one tablet QAM and two tablets QHS on day three; if symptoms continue increase to a maximum of four tablets per day with one in the morning, one in the mid-afternoon and two QHS	Safety and efficacy in children have not been established.	Delayed-release tablet: 10 mg/10 mg

NSAID=nonsteroidal anti-inflammatory drug

Evidence-based Medicine

- FDA-approval of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) was based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of the agent in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of doxylamine succinate/pyridoxine hydrochloride.[5] Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 3.9 point decrease in the placebo group. For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to a 1.8 point decrease in the placebo group.[5]

- A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine succinate/pyridoxine hydrochloride. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively). There were no difference between groups for the side effects of sedation or constipation (P=0.707 and P=0.412, respectively).[6]

Key Points within the Medication Class

- According to Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy[4]
  - Mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods.
  - First-line pharmacotherapy with pyridoxine or in combination with doxylamine.
  - If initial therapy with pyridoxine monotherapy fails and if this is inadequate for symptom control then the addition of doxylamine is recommended.
  - For patients who fail this combination, promethazine or dimenhydrinate can be substituted for doxylamine. After this point, if the patient is still experiencing nausea and vomiting, options include metoclopramide, trimethobenzamide, methylprednisolone or ondansetron.

- Other Key Facts:
  - Only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - Initial dosing allows for once daily dosing.

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New Drug Review
Diclegis® (doxylamine succinate/pyridoxine hydrochloride)

Overview/Summary

Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. It should be noted that the agent has not been studied in hyperemesis gravidarum.[1] The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity, although scientific evidence supports the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects.[2]

Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[1-3]

Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women.[2,4] Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs infrequently. The treatment goals in patient with NVP are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of nausea and vomiting such as dehydration and to minimize the fetal effects of NVP treatment.[2] According to the Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy, mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods. For more severe cases, safe and effective treatments are available. The guideline recommends the use of monotherapy with pyridoxine or in combination with doxylamine as safe and effective and that these treatment options should be considered as first-line pharmacotherapy. A treatment algorithm provided in the guideline indicates initial therapy with pyridoxine monotherapy and if this is inadequate for symptom control then the addition of doxylamine is recommended. For patients who fail this combination, promethazine or dimenhydrinate can be substituted for doxylamine. After this point, if the patient is still experiencing nausea and vomiting, options include metoclopramide, trimethobenzamide, methylprednisolone or ondansetron.[4]

Indications

Diclegis® is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Pharmacokinetics

Table 1. Pharmacokinetics[1]

Generic Name	T_{max} (hours)	Excretion	Serum Half-Life (hours)
Doxylamine succinate	7.8	Urine	12.5
Pyridoxine hydrochloride	5.6	Urine	0.5

Clinical Trials

FDA-approval of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) was based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of the agent in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of Diclegis® (doxylamine succinate/pyridoxine hydrochloride).[5]

The primary efficacy endpoint was the change from baseline to day-15 in the symptom domain and the quality of life (QOL) domain of the Pregnancy Unique-Quantification of Emesis (PUQE) score. The symptom domain score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms from 3 (no symptoms) to 15 (most severe). The QOL domain score incorporates patient's report of their present well-being from zero (worst possible) to 10 (best possible). [5]

Treatment with Diclegis® (doxylamine succinate/pyridoxine hydrochloride) resulted in a statistically significant improvement in both the symptom and QOL domains of the PUQE score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to 3.9 point decrease in the placebo group. For QOL, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group compared to a 1.8 point decrease in the placebo group.[5]

Secondary endpoints included the day-by-day area under the curve for change in PUQE from baseline, time loss from employment and the number of women in each arm who continued with blinded compassionate use of their medication. The number of patients who reported concurrent use of alternate therapy for nausea and vomiting were also recorded. Finally safety was examined. [5]

The mean area under the curve of the change in PUQE from baseline was significantly larger with Diclegis® (doxylamine succinate/pyridoxine hydrochloride) than with placebo. There was also a trend toward more time lost from employment in the placebo group (2.37 days) compared to the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (0.92); however, this difference was not statistically significant.[5]

At the end of the 15 day trial, a significantly higher percentage of patients in the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (48.9%) compared to in the placebo group (32.8%) requested to continue compassionate use of their medication. Significantly more patients receiving placebo (36%) requested alternate therapies for nausea and vomiting compared to the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group (23.7%).[5]

For the Diclegis® (doxylamine succinate/pyridoxine hydrochloride) group and placebo group, respectively, the most common treatment emergent adverse events included somnolence (14.5% vs 2%), dry mouth (3.0% vs 0.8%), hypersensitivity (0.8% vs 0%), dizziness (6.0% vs 6.4%), headache (13.0% vs 16.0%), and loss of consciousness (0% vs 0.8%).[5]

A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine/pyridoxine. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively). There were no difference between groups for the side effects of sedation or constipation (P=0.707 and P=0.412, respectively).[6]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Koren et al[5] Doxylamine succinate/pyridoxine hydrochloride, two tablets QHS, up to a maximum dose of four tablets per day vs placebo	DB, MC, PC, RCT Pregnant women ≥ 18 years of age in the gestational age range of 7 to 14 weeks with NVP and a PUQE score ≥ 6 and had not responded to conservative management consisting of dietary/lifestyle advice	N=298 15 days	Primary: Change from baseline to day-15 in symptom and QOL domain PUQE scores Secondary: Day-by-day area under the curve for change in PUQE from baseline, time loss from employment, number of women in each arm who continued with blinded compassionate use of their medication, number of patients who reported concurrent use of alternate therapy for NVP, safety	Primary: There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day-15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 3.9 point decrease in the placebo group (P=0.006). There was a 2.8 point mean increase from baseline in QOL domain PUQE score at day 15 in the doxylamine succinate/pyridoxine hydrochloride group compared to 1.8 point decrease in the placebo group (P=0.005). Secondary: The mean area under the curve of the change in PUQE from baseline as measured day-by-day was significantly larger in the doxylamine succinate/pyridoxine hydrochloride combination group compared (61.5) to placebo (53.5) with the difference being statistically significant ((P<0.001). There was a trend toward more time lost from employment in the placebo group (2.37 days) compared to the doxylamine succinate/pyridoxine hydrochloride combination group compared (0.92); however, it should be noted that this difference was no statistically significant (P=0.06). At the end of the 15-day trial, 48.9% of patients in the doxylamine succinate/pyridoxine hydrochloride combination group compared to 32.8% in the placebo group requested to continue compassionate use of their medication (P=0.009). Significantly more women receiving placebo (36%), requested alternate therapies for NVP compared to the doxylamine succinate/pyridoxine hydrochloride combination group (23.7%). The difference was statistically significant (P=0.04). For the doxylamine succinate/pyridoxine hydrochloride combination group and placebo group respectively the most common treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				emergent adverse events included somnolence (14.5% vs 2%; P=0.54), dry mouth (3.0% vs 0.8%; P=0.37), hypersensitivity (0.8% vs 0%; P>0.99), dizziness (6.0% vs 6.4%; P=0.94), headache (13.0% vs 16.0%; P=0.51), and loss of consciousness (0% vs 0.8%; P=0.49).
Oliveira et al[6] Ondansetron 4 mg every eight hours for five days vs pyridoxine/doxylamine 25/12.5 mg every eight hours for five days	AC, DB,DD, PC, RCT Women 18 years of age or older with nausea with or without vomiting and less than 16 weeks of gestation	N=36 5 days	Primary: Reduction in nausea on the VAS Secondary: Reduction in vomiting and the proportion of patients reporting sedation or constipation while using either study regimen.	Primary: There was a statistically significant difference for reduction in nausea in the ondansetron group compared with the pyridoxine/doxylamine group (median 51 mm [interquartile range 37 to 64] compared with 20 mm [interquartile range 8 to 51]; P=0.019). In the ondansetron group, 12 out of the 13 patients had a clinically significant reduction in nausea from baseline (defined as a 25-mm or greater reduction in nausea on the VAS); however, in the pyridoxine/doxylamine group, only 7 out of 17 patients had a clinically significant reduction from baseline. There was a statically significant difference in the reduction of nausea from baseline in favor of ondansetron (P=0.007). Secondary: The ondansetron group reported less vomiting on the VAS as compared with the pyridoxine/doxylamine group (median 41 [interquartile range 17 to 57] compared with 17 [interquartile range -4 to 38]; P=0.049). In the ondansetron group, 10 out of the 13 patients had a reduction in emesis on the VAS; however, in the pyridoxine/doxylamine group, only 6 out of 17 patients had a reduction in emesis (P=0.033). There was no difference between groups for sedation or constipation (P=0.707 and P=0.412, respectively).

Drug regimen abbreviations:, QHS=every night at bedtime
Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PUQE= Pregnancy Unique-Quantification of Emesis, RCT=randomized controlled trial, QOL=quality of life, VAS=visual analog scales

Special Populations

Table 3. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Doxylamine succinate/pyridoxine hydrochloride	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	No dosage adjustment required..	A	Yes (Women should not breastfeed while using the agent)

Adverse Drug Events

Table 4. Adverse Drug Events[1]

Adverse Event	doxylamine succinate/ pyridoxine hydrochloride	
	doxylamine succinate/ pyridoxine hydrochloride N (%), N=133	placebo N (%), N=128
Somnolence	19 (14.3)	15 (11.7)

Contraindications

Table 5. Contraindications[1]

Contraindication	doxylamine succinate/ pyridoxine hydrochloride
Concurrent use of a monoamine oxidase inhibitor as they intensify and prolong the adverse effects of the agent.	a
Known hypersensitivity to doxylamine succinate other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredients in the formulation.	a

CNS=central nervous system

Warnings/Precautions

Table 6. Warnings and Precautions[3,5]

Contraindication	doxylamine succinate/ pyridoxine hydrochloride
Activities Requiring Mental Alertness; avoid activities that require mental alertness unless cleared by a healthcare provider. Avoid use with other CNS depressants or alcohol.	a
Concomitant Medical Conditions; due to anticholinergic effects, use caution in patients with: asthma, increased intraocular pressure, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.	a

CNS=central nervous system

Drug Interactions

Table 7. Drug Interactions[3,5]

Generic Name	Interacting Medication or Disease	Potential Result
doxylamine succinate/ pyridoxine hydrochloride	Monoamine oxidase inhibitors (MAOIs)	Concurrent use is contraindicated as MAOIs can prolong and intensify the anticholinergic effects of the doxylamine succinate component.

Dosage and Administration

Table 8. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
doxylamine succinate/ pyridoxine hydrochloride	Nausea and Vomiting of Pregnancy: Delayed-release tablet: Initial, two tablets QHS on day one; if symptoms persist into day two increase dose to one tablet QAM and two tablets QHS on day three; if symptoms continue increase to a maximum of four tablets per day with one in the morning, one in the mid-afternoon and two QHS	Safety and efficacy in children have not been established.	Delayed-release tablet: 10 mg/10 mg

QAM=every morning, QHS= every night at bedtime

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Clinical Management Guidelines For Obstetrician-Gynecologists **ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy (2004)**[4]	· Nausea and vomiting of pregnancy (NVP) is a common condition that affects 70 to 85% of pregnant women. · The incidence of hyperemesis gravidarum is 0.5% to 2% of pregnancies. · Mild cases of NVP may be resolved with lifestyle and dietary changes and sage and effective treatments are available for more severe cases. · Symptoms of NVP manifest before week 9 of gestation in virtually all women. Non-Pharmacological Therapies: · It is reasonable for women with NVP in a previous pregnancy to take a multivitamin at the time of the next conception. · Common recommendation to alleviate initial signs and symptoms of NVP include rest and avoidance of sensory stimuli that may provoke symptoms. · Frequent, small meals, avoiding spicy or fatty foods, eliminating pills containing iron, and eating dry bland or dry foods are also recommended. · It should be noted however that there is little published evidence regarding the efficacy of dietary changes for prevention or treatment of NVP. Pharmacological Therapies: · Despite the fact that the combination of doxylamine and pyridoxine is no longer commercially available in the US it remains among first-line therapies. · Treatment with either pyridoxine or combination pyridoxine plus doxylamine are both recommended as first-line treatment options based on good and consistent scientific evidence (Level A). · The treatment algorithm indicates that initial pharmacologic therapy consists of monotherapy pyridoxine followed by the addition of doxylamine

Clinical Guideline	Recommendations
	if systems persist. · In patients with consistent symptoms promethazine or dimenhydrinate should be added. · After this if symptoms still persist options include the addition of any of the following: o Metoclopramide o Promethazine o Trimethobenzamide · For patients who continue to be refractory options include: o Methylprednisolone o Ondansetron

Conclusions

Diclegis® (doxylamine succinate/pyridoxine hydrochloride) is a fixed dose combination drug product of doxylamine succinate, and pyridoxine hydrochloride, a vitamin B6 analog. The agent is indicated for the treatment of nausea and vomiting of pregnancy in women who do not responds to conservative management.[1] The combination of these agents was previous available in the United States under the name brand Bendectin®.[2]

In the clinical study that evaluated the use of Diclegis® (doxylamine succinate/pyridoxine hydrochloride) compared to placebo the agent was found to be effective and well tolerated in relieving the symptoms of NVP.[5] Doxylamine/pyridoxine was shown to be less effective at reducing nausea and vomiting in pregnancy when compared with ondansetron; however, only the low doses were study for a short duration of time.[6]

The clinical consensus guideline on nausea and vomiting of pregnancy from the American College of Obstetricians and Gynecologists recommend pyridoxine alone or in combination with doxylamine as first line pharmacologic therapy.[4]

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Therapeutic Class Overview
Neurokinin-1 (NK1) Receptor Antagonists and Combinations

Therapeutic Class Overview/Summary:
This review will focus on neurokin-1 (NK_1) receptor antagonist anti-emetics and their combinations. All of these agents are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). Single-entity products include: aprepitant (Emend®) and its prodrug fosaprepitant dimeglumine (Emend®) along with rolapitant hydrochloride (Varubi®). There is a single NK_1 antagonist combination product currently available, netupitant/palonosetron (Akynzeo®). With this combination, netupitant, the NK_1 antagonist is co-formulated with palonosetron, a serotonin type-3 (5-HT_3) receptor antagonist. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4] Differences in anti-emetic effect for the acute and delayed phases of CINV exist between agents and are summarized in Table 1. As the pathophysiology of CINV is not completely understood, the exact mechanisms by which NK_1 antagonists exert there antiemetic effects are not known. NK_1 is a broadly distributed receptor located in both the central and peripheral nervous systems. One proposed mechanism of NK_1 antagonists is by depressing the substance P mediated response in the central nevous system by blocking activation of NK_1 in areas of the brain responsible for chemoreception. Decreased activation of NK_1 by substance P reduces the emetic reflex. A second proposed mechanism is the blockade of peripheral NK_1 receptors located on the vagal terminals of the gut. It is hypothesized that peripheral blockade may decrease the intensity of the signal transmitted to the central nervous system, thus decreasing the overall emetic reflex.[1-6]

Table 1. Current Medications Available in the Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Aprepitant (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of CINV associated with initial and repeat courses of MEC, Prevention of PONV	Capsule: 40 mg 80 mg 125 mg Capsule Dose Pack: 125 and 80 mg	-
Fosaprepitant dimeglumine (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC	Vial: 150 mg	-
Rolapitant hydrochloride (Varubi®)	Prevention of delayed CINV associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC and prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide	Tablet: 90 mg	-
Netupitant/palonosetron (Akynzeo®)	Prevention of acute and delayed CINV associated with initial and	Capsule: 300/0.5 mg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	repeat courses of HEC, Prevention of acute and delayed CINV associated with initial and repeat courses of cancer chemotherapy not considered highly emetogenic		

Other abbreviations: CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomiting

Evidence-based Medicine

- The safety and efficacy of the NK_1 antagonists have been evaluated in several clinical trials for their FDA-approved indications.[11-45] Aprepitant, being an older, more established agent has had more extensive review. Results of these trials are similar to those used by the FDA for approval.[15-32] There are currently no clinical trials that compare NK_1 antagonists to one-another.
- The approval of rolapitant (Varubi®) was based on the efficacy and safety in preventing CINV in patients receiving anthracycline combination therapy, MEC, or HEC with a cisplatin-based regimen in three clinical trials. The primary endpoint in both HEC studies was complete response (CR) in the delayed phase (defined as 25 to 120 hours post administration of chemotherapy) of CINV. Results of the showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group in HEC-1: (192 [73%] compared to 153 [58%]; P=0.0006). However, in HEC-2, this was statistically significant: (rolapitant [70%] compared to placebo control group [62%]; P=0.0426).[35,36] In the third trial, the antiemetic effect of rolapitant was evaluated in MEC. The primary endpoint of CR in the delayed phase of CINV showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group: (475 [71%] compared to 410 [62%]; P=0.0002).[35,37]
- The approval of netupitant/palonosetron (Akynzeo®) was based on the efficacy and safety in preventing CINV in patients receiving MEC or HEC. Both trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone. CR in the delayed phase was statically significant in HEC and MEC for patients who received netupitant/palonosetron (P=0.032 and P=0.01, respectively).[38,39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[7]
  - For the prevention of CINV post-HEC, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[7-8]
  - The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[7]
  - For the prevention of CINV post-MEC, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[7-9]
  - Guidelines generally recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention CINV associated with MEC. Adjunctive therapies include with lorazepam, an H_2 receptor antagonist or a proton pump inhibitor.[7-9]
  - The Pediatric Oncology Group of Ontario in 2012 recommend aprepitant in combination with granisetron and dexamethasone in children 12 years of age or older who will be receiving HEC and in which the antineoplastics are not known to or suspected of interacting with

aprepitant. Dual therapy with ondansetron or granisetron and dexamethasone is recommended if the antineoplastic agents interact with aprepitant.[10]
- Several guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[8-10]

· Other Key Facts:
- All agents are formulated as oral capsules or tablets, with the exception of fosaprepitant, which is an intravenous injection.
- For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days.
- All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4]
- Aprepitant capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients.
- Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age.[1,10]
- Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

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Therapeutic Class Review
Neurokinin-1 (NK1) Receptor Antagonists and Combinations

Overview/Summary

This review will focus on neurokin-1 (NK_1) receptor antagonist anti-emetics and their combinations. All of these agents are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). Single-entity products include: aprepitant (Emend®) and its prodrug fosaprepitant dimeglumine (Emend®) along with rolapitant hydrochloride (Varubi®). There is a single NK_1 antagonist combination product currently available, netupitant/palonosetron (Akynzeo®). With this combination, netupitant, the NK_1 antagonist is co-formulated with palonosetron, a serotonin type-3 (5-HT_3) receptor antagonist. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4] Differences in anti-emetic effect for the acute and delayed phases of CINV exist between agents and are summarized in Table 2. As the pathophysiology of CINV is not completely understood, the exact mechanisms by which NK_1 antagonists exert there antiemetic effects are not known. NK_1 is a broadly distributed receptor located in both the central and peripheral nervous systems. One proposed mechanism of NK_1 antagonists is by depressing the substance P mediated response in the central nevous system by blocking activation of NK_1 in areas of the brain responsible for chemoreception. Decreased activation of NK_1 by substance P reduces the emetic reflex. A second proposed mechanism is the blockade of peripheral NK_1 receptors located on the vagal terminals of the gut. It is hypothesized that peripheral blockade may decrease the intensity of the signal transmitted to the central nervous system, thus decreasing the overall emetic reflex.[1-6]

It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[7] For the prevention of CINV post-HEC, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[7-8] The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[7] For the prevention of CINV post-MEC, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[7-9] Guidelines generally recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention CINV associated with MEC. Adjunctive therapies include with lorazepam, an H_2 receptor antagonist or a proton pump inhibitor.[7-9] The Pediatric Oncology Group of Ontario in 2012 recommend aprepitant in combination with granisetron and dexamethasone in children 12 years of age or older who will be receiving HEC and in which the antineoplastics are not known to or suspected of interacting with aprepitant. Dual therapy with ondansetron or granisetron and dexamethasone is recommended if the antineoplastic agents interact with aprepitant.[10] Several guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[8-10] Complete guideline summaries can be found in Table 11.

All agents are formulated as oral capsules or tablets, with the exception of fosaprepitant, which is an intravenous injection. For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days. All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4] Aprepitant capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients. Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age.[1,10] Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Aprepitant (Emend®)	Neurokinin1 (NK_1) Receptor Antagonist	-
Fosaprepitant dimeglumine (Emend®)	Neurokinin1 (NK_1) Receptor Antagonist	-
Rolapitant hydrochloride (Varubi®)	Neurokinin1 (NK_1) Receptor Antagonist	-
Combination Products		
Netupitant/palonosetron (Akynzeo®)	Neurokinin1 (NK_1) Receptor Antagonist/ Serotonin (5-HT_3) receptor antagonist	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-4]

Indication	Aprepitant	Fosaprepitant	Rolapitant	Netupitant/ palonosetron
Prevention of acute and delayed CINV associated with initial and repeat courses of HEC	a *	a *		a
Prevention of CINV associated with initial and repeat courses of MEC	a *			a
Prevention of delayed CINV associated with initial and repeat courses of HEC			a	
Prevention of delayed CINV associated with initial and repeat courses of MEC		a *	a	
Prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide			a	a
Prevention of PONV in adults	a			

CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomitting
*FDA-approved in pediatric patients ≥ 12 years of age

Pharmacokinetics

Table 3. Pharmacokinetics[1-4]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Hepatic Metabolism	Active Metabolites	Serum Half-Life (hours)
Single Entity Products					
Aprepitant	60 to 65	Not renally excreted	Primary (CYP3A4), Minor (CYP1A2/2C19)	Yes*	9 to 13
Fosaprepitant dimeglumine	Not reported	Not renally excreted	Hepatic/extrahepatic (kidney, lung, ileum)	Yes (aprepitant)	9 to 13
Rolapitant hydrochloride	Not reported	14.2	Hepatic (Primary: CYP3A4)	Yes	169 to 183
Combination Products					
Netupitant/ palonosetron	N: Not reported P: 97	N: 4.7 P: 85 to 93	N: Extensive (CYP3A4) P: Partial	Yes	80/48

N=Netupitant, P=Palonosetron
*Seven metabolites have been identified; each is weakly active.
†Active metabolite is aprepitant

Clinical Trials

The safety and efficacy of the NK_1 antagonists have been evaluated in several clinical trials for their FDA-approved indications.[11-45] Aprepitant, being an older, more established agent has had more extensive review. Results of these trials are similar to those used by the FDA for approval.[15-32] There are currently no clinical trials that compare NK_1 antagonists to one-another.

The safety and efficacy of aprepitant (Emend®) was established in a number of clinical trials.[11-14] FDA-approval for the prevention of CINV associated with HEC and MEC was based on the results of two clinical trials each. For approval of HEC, aprepitant for three days in combination with standard therapy (dexamethasone on days 1, 2, and three plus ondansetron on day 1) was compared to standard therapy plus placebo. The antiemetic activity of aprepitant was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. The primary endpoint for both studies was complete response (CR), defined as no emetic episodes and no use of rescue therapy as recorded in patient diaries. Both studies showed a statistically significant difference in CR favoring the aprepitant group (P<0.001).[11,12] For the treatment of MEC, aprepitant was given for three days (in combination with dexamethasone and ondansetron on day 1) and was compared to standard therapy (dexamethasone on day 1 plus ondansetron on days 1, 2, and 3).[13,14] The use of aprepitant was also evaluated in two clinical trials for the treatment of post-operative nausea and vomiting (PONV).[41-42] Here aprepitant 40 mg as a single dose was compare to ondansetron. The primary end-point in the first study was the percentage of patients with no vomiting over 0 to 24 hours. The aprepitant group had 84% of patients with no vomiting, while the ondansetron group had only 71% (P<0.001).[41] The primary end-point of the second study was CR, defined as no vomiting and no use of rescue medication during 0 to 24 hours. There was no statistically significant difference between groups for CR (difference, 2.5%; P=0.61), however, there was a statistically significant difference in the secondary end-point of no vomiting from 0 to 24 hours (difference, 16.3%; P<0.001).[42]

The approval of rolapitant (Varubi®) was based on the efficacy and safety in preventing CINV in patients receiving anthracycline combination therapy, MEC, or HEC with a cisplatin-based regimen in three clinical trials. All of these phase III trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of rolapitant given as a single oral dose 60 to 120 minutes before administration of chemotherapy in combination with dexamethasone and granisetron.[35] The first two trials HEC-1 (N=532) and HEC-2 (N=555) enrolled patients with cancer who were 18 years of age or older. These individuals received either a single oral dose of rolapitant (180 mg) in addition to intravenous (IV) granisetron and oral dexamethasone or placebo plus IV granisetron and oral dexamethasone. The primary endpoint in both studies was CR in the delayed phase (defined as 25 to 120 hours post administration of chemotherapy) of CINV. Results of the showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group in HEC-1: (192 [73%] compared to 153 [58%]; P=0.0006). However, in HEC-2, this was statistically significant: (rolapitant [70%] compared to placebo control group [62%]; P=0.0426).[35,36] In the third trial, 1,369 patients with cancer who were 18 years of age or older who had a Karnofsky performance score of 60 or higher, a predicted life expectancy of four months or longer and who were scheduled to receive a first course of MEC including anthracycline were randomized in a 1:1 ratio to receive either a single oral dose of rolapitant (180 mg) in addition to oral granisetron (2 mg) and oral dexamethasone or placebo plus oral granisetron and oral dexamethasone. The primary endpoint of CR in the delayed phase of CINV showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group: (475 [71%] compared to 410 [62%]; P=0.0002).[35,37]

The approval of netupitant/palonosetron (Akynzeo®) was based on the efficacy and safety in preventing CINV in patients receiving MEC or HEC. Both trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone. CR in the delayed phase was statically significant in HEC and MEC for patients who received netupitant/palonosetron (P=0.032 and P=0.01, respectively).[38,39]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Gralla et al[11] Aprepitant 125 mg plus ondansetron 32 mg and dexamethasone 12 mg on day one; aprepitant 80 mg and dexamethasone 8 mg on days two to three; and dexamethasone 8 mg on day four vs ondansetron 32 mg IV and dexamethasone 20 mg orally on day one; dexamethasone 8 mg twice daily on days two to four	DB, PG, RCT (pooled analysis) Patients >18 years of age receiving their first cisplatin-based chemotherapy	N=1,043 120 hours	Primary: Complete response (defined as no vomiting and no rescue therapy) on days one to five Secondary: Not reported	Primary: In the total combined study population, regardless of treatment group or use of concomitant chemotherapy, complete response was achieved in 58% of patients. Analysis by treatment group showed a 20% greater efficacy with the aprepitant regimen (68 vs 48%; P<0.001). Among 13% of patients who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33% improvement in the complete response rate compared to the control regimen (P<0.001). Secondary: Not reported
Warr et al[12] Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs	DB, PG, RCT Patients with breast cancer who were naïve to emetogenic chemotherapy and who were treated with a regimen of cyclophosphamide alone, cyclophosphamide plus	N=857 120 hours	Primary: Proportion of patients with complete response (defined as no vomiting and no use of rescue therapy) 120 hours after initiation of chemotherapy in cycle one	Primary: Overall complete response was greater with the aprepitant regimen than with the control regimen (50.8 vs 42.5%; P=0.015). Secondary: More patients in the aprepitant group reported minimal or no impact of CINV on daily life (63.5 vs 55.6%; P=0.019). Both treatments were generally well tolerated. The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	doxorubicin, or cyclophosphamide plus epirubicin		Secondary: Proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	
Herrstedt et al[13] Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	DB, MC, PG, RCT Patients with breast carcinoma who were naïve to emetogenic chemotherapy and treated with cyclophosphamide alone or in combination with doxorubicin or epirubicin	N=866 3 days of treatment during cycles 1 to 4 of chemotherapy	Primary: Proportion of patients with a complete response (no emesis or use of rescue therapy) in cycle one, efficacy end points for the multiple-cycle extension were the probabilities of a complete response in cycles two to four and a sustained complete response rate across multiple cycles Secondary: Not reported	Primary: Overall, the complete response was greater with the aprepitant regimen over the four cycles: 50.8 vs 42.5% for cycle one, 53.8 vs 39.4% for cycle two, 54.1 vs 39.3% for cycle three, and 55.0 vs 38.4% for cycle four. The cumulative percentage of patients with a sustained complete response over all four cycles was greater with the aprepitant regimen (P=0.017). The aprepitant regimen was more effective than a control regimen for the prevention of nausea and emesis induced by moderately emetogenic chemotherapy over multiple chemotherapy cycles. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kang et al[14] Aprepitant (125 mg for ages 12 to 17 years; 3.0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day one, followed by aprepitant (80 mg for ages 12 to 17 years; 2.0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3 vs placebo plus ondansetron on day one followed by placebo on days two and three (addition of dexamethasone was permitted)	AC, DB, PG, RCT Patients 6 months to 17 years of age with documented malignancy scheduled to receive at least moderately emetic chemotherapy	N=302 Up to 5 cycles	Primary: Complete response (defined as no vomiting, no retching, and no use of rescue medication) during the delayed phase Secondary: Complete response during the acute and overall phases, safety	Primary: Seventy-seven (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase (P<0.0001). Secondary: Complete response during the acute and overall phases was also more common in patients in the aprepitant group than in those who were in the control group (P=0.0135 and P=0.0002). Median time to first vomiting episode was 96.3 hours (95% CI, 68.8 to not estimable) in the aprepitant group and 27.5 hours (95% CI, 19.3 to 35.6) in the control group (log-rank P<0.0001). Similarly, time to first rescue medication use was significantly longer for patients in the aprepitant group than in the control group (log-rank P=0.0024). Adverse events were reported by 120 (79%) of 152 patients in the aprepitant group and 116 (77%) of 150 in the control group. In addition to vomiting, the most commonly reported all-grade adverse events were anaemia, febrile neutropenia, and neutropenia.
Rapoport et al[15] Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12	DB, MC, PG, RCT Adult patients who were naïve to moderate or highly emetogenic chemotherapy and were	N=848 120 hours	Primary: Proportion of patients reporting no vomiting Secondary: Overall complete response (no emesis and no	Primary: Significantly more patients in the aprepitant (triple therapy) group reported no vomiting (76.2%) compared to patients receiving dual therapy (62.1%) during the 120 hour study period (P<0.001). Secondary: Significantly more patients in the aprepitant (triple therapy) group reported complete response (68.7%) compared to patients receiving dual therapy (56.3%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	scheduled to receive treatment with one or more moderately emetogenic agents		use of rescue therapy)	There were no significant differences in adverse events between the two groups; however, the overall incidence of adverse events in the entire study population was 65%.
Yeo et al[16] Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, plus dexamethasone 12 mg prior to chemotherapy vs ondansetron 8 mg prior to chemotherapy followed by 8 mg eight hours later, then 8 mg twice daily (days two to three), plus dexamethasone 20 mg prior to chemotherapy	DB, PC, RCT Breast cancer patients ≥18 years of age who were naïve to chemotherapy and were receiving a moderately emetogenic regimen (doxorubicin and cyclophosphamide)	N=127 120 hours	Primary: Complete response (no vomiting and no rescue therapy used) during the overall period (0 to 120 hours) Secondary: Proportion of patients with no vomiting, no nausea, no significant nausea, no rescue therapy, complete protection, and total control during the acute (0 to 24 hour), delayed (24 to 120 hours), and	Primary: There was no significant difference in the complete response rates for patients receiving aprepitant (triple therapy) compared to patients receiving dual therapy during the overall period (46.8 vs 41.9%, respectively; P=0.58). Secondary: During the overall period, there was no significant difference among the treatment groups in the proportion of patients reporting complete protection (P=0.71), total control (P=0.55), no vomiting (P=0.58), no significant nausea (P=0.71) and no nausea (P=0.57). Rescue medication use was lower in the aprepitant group than the control group (11 vs 20%; P=0.06). There was no significant difference between the two groups with respect to all the parameters of emesis control in the acute and delayed time frames. The median time to first vomiting after the initiation of chemotherapy was 64.4 hours for the aprepitant arm and 52.6 hours in the control arm (P=0.78).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			overall periods	
De Wit et al[17] Aprepitant 125 mg, ondansetron 32 mg IV, dexamethasone 12 mg on day one, aprepitant 80 mg and dexamethasone 8 mg on days two to three, dexamethasone 8 mg on day four vs ondansetron 32 mg IV and dexamethasone 20 mg on day one, dexamethasone 8 mg twice daily on days two to four	DB, MC, RCT Patients with cancer who were receiving their first cycle of cisplatin-based chemotherapy	N=1,038 120 hours	Primary: No emesis and no significant nausea over the five days following cisplatin, for up to six cycles of chemotherapy Secondary: Not reported	Primary: In every cycle, the estimated probabilities (rates) of no emesis and no significant nausea were significantly higher (P<0.006) in the aprepitant group. In the first cycle, rates were 61% in the aprepitant group and 46% in the standard therapy group. Thereafter, rates for the aprepitant regimen remained higher throughout (59 vs 40% for the standard therapy by cycle six). Repeated dosing with aprepitant over multiple cycles was generally well tolerated. Those who received aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy. Secondary: Not reported
Poli-Bigelli et al[18] Aprepitant 125 mg, ondansetron 32 mg IV, and dexamethasone 12 mg orally on day one; aprepitant 80 mg and dexamethasone 8 mg orally on days two to three; and dexamethasone 8 mg orally on day four vs ondansetron 32 mg IV and dexamethasone 20 mg	DB, MC, PG, RCT Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy	N=1,091 120 hours	Primary: Complete response (no emesis and no rescue therapy) during the five-day period post cisplatin therapy Secondary: Not reported	Primary: During the five days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group compared to 43.3% in the standard therapy group (P<0.001). For day one, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group (P<0.001); for days two to five, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group (P<0.001). The overall incidence of adverse events was similar between the two treatment groups (72.8% in the aprepitant group and 72.6% in the standard therapy group) as were rates of serious adverse events, discontinuations due to adverse events, and deaths. In patients with cancer who were receiving high-dose cisplatin-based chemotherapy, therapy consisting of aprepitant (125 mg on day one

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
orally on day one, followed by dexamethasone 8 mg orally twice daily on days two to four				and 80 mg on days two to three) plus a standard regimen of ondansetron and dexamethasone provided greater antiemetic protection compared to standard therapy alone and was generally well tolerated. Secondary: Not reported
Hesketh et al[19] Aprepitant plus ondansetron and dexamethasone on day one; aprepitant and dexamethasone on days two to three; dexamethasone on day four vs ondansetron and dexamethasone on day one; dexamethasone on days two to four	DB, MC, PG, RCT Patients with cancer who were receiving cisplatin for the first time	N=530 120 hours	Primary: Complete response (no emesis and no rescue therapy) on days one to five post cisplatin therapy Secondary: Not reported	Primary: The percentage of patients with complete response was significantly higher in the aprepitant group (72.7 vs 52.3% in the standard therapy group), as were the percentages on day one, and especially on days two to five (P<0.001 for all three comparisons). Compared to standard dual therapy, addition of aprepitant was generally well tolerated and provided consistent protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy. Secondary: Not reported
Martin et al[20] Aprepitant and dexamethasone plus ondansetron on day one, followed by aprepitant and dexamethasone on days two to five vs	DB, RCT Patients with cancer who were receiving cisplatin	N=381 5 days	Primary: Complete response, the Functional Living Index-Emesis Secondary: Not reported	Primary: Compared to standard therapy, significantly more patients treated with the high-dose aprepitant regimen achieved a complete response (71 vs 44%; P<0.001) and also reported no impact on daily life as indicated by the Functional Living Index-Emesis total score (84 vs 66%; P<0.01). Use of the Functional Living Index-Emesis demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily activities.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dexamethasone and ondansetron on day one, followed by dexamethasone on days two to five				Secondary: Not reported
Gore et al[21] Aprepitant 125 mg one hour prior to chemotherapy followed by 80 mg on days two to three, plus ondansetron 0.15 mg/kg for three doses on days one to two, plus dexamethasone 8 mg on day one followed by 4 mg on days two to four vs ondansetron 0.15 mg/kg for three doses on days one to two, plus dexamethasone 16 mg on day one followed by 8 mg on days two to four	DB, MC, RCT Patients 11 to 19 years of age who were receiving emetogenic chemotherapy or who had experienced intolerable CINV with previous chemotherapy	N=46 120 hours	Primary: Complete response (no vomiting and no rescue therapy used), as well as the proportion of patients with no vomiting and/or no rescue therapy during the overall period (0 to 120 hours), acute period (0 to 24 hour), and delayed (24 to 120 hours) period Secondary: Not reported	Primary: There was no significant difference among the treatment groups with regards to the complete response rates, proportion of patients reporting no vomiting, or the proportion of patients reporting no nausea during the overall period, acute period, or delayed period. There were no significant differences in adverse event rates between the two groups. Secondary: Not reported
Schmitt et al[22] Aprepitant (125 mg orally on day one and 80 mg orally on days two to four), granisetron (2 mg orally on	DB, PC, PG, RCT Patients ≥18 years of age with multiple	N=362 7 days	Primary: Complete response (no emesis and no rescue therapy for 120 hours)	Primary: Significantly more patients receiving aprepitant reported complete response within 120 hours of melphalan administration compared with placebo (58 vs 41%; OR, 1.92; 95% CI, 1.23 to 3.00; P=0.0042). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days one to four), and dexamethasone (4 mg orally on day one and 2 mg orally on days two to three) vs matching placebo, granisetron (2 mg orally on days one to four), and dexamethasone (8 mg orally on day one and 4 mg orally on days two to three)	myeloma undergoing autologous transplantation after high-dose melphalan		Secondary: Complete response in acute (0 to 24 hours) or delayed phase (25 to 120 hours), rates of emesis, nausea and significant nausea, number of adverse events, and impact on quality of daily life, as assessed by FLIE score	No emesis or additional antiemetic treatment in the acute phase was reported by 97 and 90% of patients receiving aprepitant and placebo, respectively (OR, 3.11; 95% CI, 1.23 to 8.92; P=0.022). During the delayed phase this was achieved in 60 and 46% of patients, respectively (OR, 1.80; 95% CI, 1.15 to 2.85; P=0.011), suggesting a lasting benefit after 24 hours. Major nausea was prevented in 94 and 88% of patients in the aprepitant and placebo arms, respectively (P=0.026). 74% of those receiving aprepitant, compared with 59% of patients receiving placebo, had an FLIE score indicating no impact on daily life (P=0.004). Rates of adverse events did not significantly differ between the two treatment arms.
Nishimura et al[23] SENRI Two-drug combination treatment (5-HT3 receptor antagonist plus dexamethasone) vs three-drug combination treatment (5-HT3 receptor antagonist plus dexamethasone plus aprepitant or fosaprepitant) All patients received the	MC, OL, RCT Patients 20 years of age and older with colorectal cancer who underwent oxaliplatin-based chemotherapy	N=413 6 days	Primary: Proportion of patients with no emesis Secondary: Proportion of patients with no nausea, complete response and complete protection in the overall phase	Primary: The aprepitant group had significantly higher rates of no vomiting overall (95.7 vs 83.6%; RR, 1.1449; 95% CI, 1.07 to 1.23; P<0.0001), as well as in the separate analyses of both the acute phase (100 vs 96.7%; P=0.013) and the delayed phase (95.7 vs 84.7%; P=0.0003) compared with the control group. Secondary: The aprepitant group also had statistically significantly higher percentages of no significant nausea, complete response and complete protection than the control group overall.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
three drug treatment in the second course of chemotherapy				
Jordan et al[24] Aprepitant 125 mg prior to chemotherapy, then 80 mg on days two to three, plus granisetron 1 mg on day one, plus dexamethasone 8 mg on days one to three	PRO Adult patients undergoing multiple-day chemotherapy of moderate or high emetogenic potential	N=78 Variable duration	Primary: Complete response (no vomiting or use of rescue therapy) at the end of the treatment cycle Secondary: Complete response in the acute and delayed phase of the treatment cycle	Primary: The percentage of patients with a complete response was 57.9% in those who were receiving highly emetogenic chemotherapy and 72.5% in those who were receiving moderately emetogenic chemotherapy. Secondary: During the acute and delayed phases, the complete response in patients receiving highly emetogenic chemotherapy was 65.8 and 68.5%, respectively. During the acute and delayed phases, the complete response in patients receiving moderately emetogenic chemotherapy was 72.5 and 82.5%, respectively. The most common adverse events were related to chemotherapy, not antiemetic therapy.
Grunberg et al[25] Aprepitant 285 mg plus dexamethasone 20 mg plus palonosetron 0.25 mg prior to chemotherapy (single dose therapy)	MC, PRO Adult patients with documented solid tumor who were naïve to chemotherapy and were receiving a moderately emetogenic regimen	N=41 120 hours	Primary: Complete response (no vomiting or use of rescue therapy) during the overall period (0 to 120 hours) during the first chemotherapy cycle Secondary: Proportion of patients with no	Primary: Complete response was seen in 51% of patients during the overall period. A total of 76% of patients experienced a complete response during the acute period and 66% of patients experienced a complete response during the delayed period. Secondary: No emesis was seen in 95% of patients during the overall period. No emesis was reported for 100% of patients during the acute period and for 95% of patients during the delayed period. No nausea was seen in 32% of patients during the overall period and 56% of patients had no significant nausea. During the acute period, 59% of patients had no nausea and 79% of patients had no significant nausea. During the delayed period, 41% of patients had no nausea and 59% of patients had no significant nausea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			vomiting, no nausea, and no significant nausea during the acute (0 to 24 hour), delayed (24 to 120 hours), and overall periods	There were no major adverse events seen during the study period that were attributed to the antiemetic regimen.
Gao et al[26] Aprepitant 125 mg 1 hour before chemotherapy on day 1, and 80 mg once daily on the following 2 days, palonosetron 0.5 mg IV once daily on the days 1 and 3, and dexamethasone 5 mg IV once daily from day 1 to day 3	OS, PRO Patients were consecutively included if they received 3-day cisplatin-based (25 mg/m^2/day) chemotherapy and had never treated with aprepitant before	N=41 8 days	Primary: Complete response in the overall phase of CINV Secondary: Complete response in the acute and delayed phases, safety and the severity of nausea	Primary and Secondary: Seven (17.1%) patients had no nausea, 22 (53.7%) experienced grade 1 nausea and 12 (29.2%) experienced grade 2 nausea. With regard to acute and delayed phase, 24.4 and 36.6% of patients were prevented from nausea. The complete response rate in the acute, delayed and overall phases was achieved in 63.4, 78.0 and 58.5% of patients respectively. Regarding single days of the acute phase, the complete response rate decreased from 85.4% on day one to 65.8% on day three. In 23 patients (56.1%) who received the study treatment more than one cycle, the cumulative emetic protection rate after five cycles was 0.82. Regardless of cause, the most common side effects were hiccups (31.7%), fatigue (17.1%), headache (14.6%) and constipation (12.2%).
Hesketh et al[27] All patients received the following antiemetics: day 1: aprepitant 125 mg 1 hours before chemotherapy; dexamethasone 8 to 10 mg IV or orally 30 minutes	OS, PRO Patients were required to have pathologically documented breast cancer and be ≥18 years of age,	N=36 5 days	Primary: Proportion of patients achieving complete response during the 120-hour study period	Primary: Complete response for the 120-hour study period was achieved in 18 (50%) patients. Secondary: Acute and delayed complete response rates were 81 (27/36) and 61% (22/36), respectively. No emesis rates for the acute, delayed, and overall study periods were 97 (35/36), 94 (34/36), and 92% (33/36), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before chemotherapy; palonosetron 0.25 mg IV 30 minutes before chemotherapy; on days 2 to 3, dexamethasone 4 mg orally and aprepitant 80 mg orally each morning	chemotherapy naïve, have a Karnofsky performance status of ≥60, and scheduled to receive their first course of chemotherapy with cyclophosphamide (≥500 mg/m^2) and doxorubicin (60 mg/m^2)		Secondary: Acute complete response (no emesis, no rescue antiemetics during the 24 hours following chemotherapy); acute complete control (no emesis, no nausea, no rescue antiemetics during the 24 hours following chemotherapy); delayed complete response (no emesis, no rescue antiemetics during hours 24–120 following chemotherapy); delayed complete control (no emesis, no nausea, no rescue antiemetics during hours 24–120 following	Complete control rates for the acute, delayed, and overall study periods were 53 (19/36), 36 (13/36), and 31% (11/36), respectively. No nausea rates for the acute, delayed, and overall study periods were 53 (19/36), 42 (15/36), and 36% (13/36), respectively. Overall 22 patients (61%) experienced some degree of nausea. Six patients (17%) noted moderate nausea. Antiemetic therapy was well tolerated overall. The most common treatment-related adverse events were headache in five patients (15%) and fatigue in four patients (10%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			chemotherapy); and safety	
Longo et al[28] Palonosetron 0.25 mg IV, dexamethasone IV 20 mg, and aprepitant 125 mg 1 hour before chemotherapy on day 1; aprepitant 80 mg and dexamethasone on day 2; aprepitant 80 mg and dexamethasone 4 mg on day 3	MC, PRO Chemotherapy-naïve patients with histologically or cytologically proven solid or blood tumors	N=not reported 5 days	Primary: Proportion of patients who achieved a complete response (defined as no emetic episodes and no use of rescue therapy), during the overall phase Secondary: Complete control (defined as no emesis, no rescue therapy, and no more than mild nausea), complete response, and proportion of patients with no emesis, during the acute, delayed, and overall phases, proportion of patients with no nausea, nausea severity, no use	Primary: 70.3% of patients had complete response during the overall phase. An analysis of each component of the primary end point showed that 92.8% of patients did not experience any vomiting, while 70.3% of patients did not use rescue medication throughout the entire observation period. Secondary: The majority of patients (59.9%) did not experience any nausea; 31.1% of patients experienced mild nausea, 8.1% moderate nausea, and 0.9% severe nausea. Nausea experience was the main reason for use of rescue medication: 53 patients (23.9%) due to nausea and 13 (5.9%) due to vomiting. None of the patients with complete response experienced more than mild nausea and then complete control rates coincided with the complete response rates. No major adverse events were recorded due to antiemetic therapy. The most commonly reported side effects were constipation (39% of patients) and headache (5%). Laxative therapy was allowed in patients who reported constipation. 41% of patients reported fatigue, 23% reported some grade of pain, and 33% reported a reduction in their social activity.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			of rescue medication, and causes for the use of rescue therapy were assessed during the overall phase, quality of life during the whole study observation period, safety	
Herrington et al[29] Aprepitant 125 mg orally on day 1, then 80 mg orally days 2 to 3 (Arm A) vs aprepitant 125 mg orally day 1, then placebo days 2 to 3 (Arm B) All patients received dexamethasone 12 mg orally and palonosetron 0.25 mg IV before chemotherapy.	DB, PC, RCT Patients ≥18 years of age with malignant disease and an Eastern Cooperative Oncology Group performance status of 0 to 2	N=75 5 days	Primary: Proportion of patients without emesis in the acute (day one) and delayed (days two to five) phases after chemotherapy Secondary: Assessment of prevention of acute and delayed nausea and the use of breakthrough antiemetics	Primary: The proportion of patients without emesis during the acute phase was similar between Arm A and Arm B (96.4 vs 100%, respectively; P=1.00). The proportion of patients without emesis during the delayed phase was similar between Arm A and Arm B (92.9 vs 92.6%, respectively; P=1.00). Secondary: The overall incidence of nausea and severity of nausea was not different among the treatment groups (P=NS). The frequency of rescue Antiemetics was similar among the treatment groups (P=NS).
Jin et al[30] Aprepitant vs	MA RCTs comparing the antiemetic efficacy of	N=4,798 (15 trials) Duration varied	Primary: Complete response during the acute, delayed, and	Primary: The cumulative incidence of emesis was significantly reduced in the aprepitant containing group on the first day (RR, 1.13; 95% CI, 1.10 to 1.16). Similar results were also obtained for delayed nausea and vomiting induced by highly or moderately emetogenic chemotherapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or no intervention	aprepitant with a placebo or no intervention for the prophylaxis of CINV		overall time intervals after initiation of qualifying chemotherapy, safety Secondary: Not reported	(from days two to five: RR, 1.35; 95% CI, 1.22 to 1.48; overall five days: RR, 1.30; 95% CI, 1.22 to 1.39). Aprepitant and ondansetron or granisetron was more efficacious than the non-aprepitant regimen, however, aprepitant and palonosetron was not more efficacious in the acute phase (RR, 1.19; 95% CI, 0.71 to 1.97) or in the delayed phase (RR, 2.02; 95% CI, 0.92 to 4.41) when compared to non-aprepitant regimen. There were no significant differences regarding the occurrence of adverse effects in aprepitant-containing groups and control groups in the pooled analysis. Secondary: Not reported
Roila et al[31] Aprepitant 80 mg once per day on days two and three vs dexamethasone 4 mg twice per day on days two and three All patients were treated with intravenous palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg before chemotherapy.	DB, RCT Chemotherapy-naïve patients with breast cancer treated with anthracyclines plus cyclophosphamide	N=551 5 days	Primary: Rate of complete response (no vomiting or rescue treatment) on days two through five Secondary: Complete protection (no vomiting, no rescue treatment, no significant nausea; visual analogue scale <25 mm), total control (no	Primary: Complete response was the same with both antiemetic prophylaxes (79.5%); therefore, dexamethasone was not superior to aprepitant. Secondary: Results related to all secondary end points were not significantly different between the two groups. On days two to five, day by day, the percentages of patients with no vomiting (from 92 to 97%) and no nausea (from 52 to 67%) were not significantly different between the two groups (data not shown).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			vomiting, no rescue treatment, no nausea; visual analogue scale <5 mm), no vomiting and no nausea (visual analogue scale <5 mm), no significant nausea, mean number of emetic episodes in patients who vomited, mean maximum severity of nausea, and mean duration of nausea	
Moon et al[32] Aprepitant 40 mg by mouth vs palonosetron 0.075 mg IV	DB, RCT Patients 20 to 60 years of age who were scheduled to undergo laparoscopic gynecologic surgery under general anaesthesia	N=93 48 hours	Primary: Complete response (visual analogue scale nausea score <4 and no use of rescue therapy) 0 to 48 h after surgery Secondary: Effect of aprepitant quantified using	Primary: Aprepitant was non-inferior to palonosetron in terms of complete response 0 to 48 hours after surgery (74 vs 77%). The nausea intensity in the recovery room and two hours after surgery assessed using the 10-point visual analogue scale was significantly lower in the aprepitant group (11.2 ± 2.1 and 9.7 ± 2.1, respectively) than in the palonosetron group (19.0 ± 2.2 and 19.4 ± 3.5, respectively; $P < 0.05$). However, the results at 6, 24, and 48 h after surgery did not differ significantly. Secondary: The pain intensity was also not significantly different throughout the study period. Fentanyl consumption via automated intravenous patient-controlled analgesia was significantly lower in the aprepitant group than in the palonosetron group at two and six hours after surgery. No

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			a 10-point visual analogue scale for pain, consumption of intravenous patient-controlled analgesia, and use of rescue analgesics	significant differences were observed in the incidence and number of additional fentanyl administrations between the two groups.
Saito et al[33] Granisetron 40 µg/kg IV and dexamethasone (20 mg) on day 1 and dexamethasone (8 mg) on days 2 and 3 vs fosaprepitant (150 mg), granisetron (40 µg/kg), and dexamethasone (10 mg) on day 1, dexamethasone (4 mg) on day 2, and dexamethasone (8 mg) on day 3	DB, MC, PC, RCT Patients ≥20 years of age who received cancer chemotherapy containing cisplatin (≥70 mg/m^2)	N=347 3 days	Primary: Percentage of patients who achieved a complete response (no emesis and no rescue therapy) in the overall phase Secondary: In the acute and delayed phases, the percentages of patients with a complete response, the percentages of patients with complete protection (no emesis, no rescue therapy, and no	Primary: The percentage of patients who achieved a complete response (no emesis and no rescue therapy) in the overall phase (0–120 h) was significantly higher in the fosaprepitant group (64%; 95% CI, 16 to 46 vs 47%; 95% CI, 10 to 36; P=0.0015. Secondary: In the acute and delayed phases, the percentages of patients with a complete response were significantly higher in the fosaprepitant group (acute phase, 94 vs 81%; P=0.0006, delayed phase, 65 vs 49%; P=0.0025). Among the patients who had previously been treated with cisplatin and experienced vomiting, the complete response rates in the overall phase were higher in the fosaprepitant group (60.0 vs 30.3%). The percentages of patients with complete protection (no emesis, no rescue therapy, and no significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase were significantly higher in the fosaprepitant group. The percentages of patients with no rescue therapy in the overall phase also did not differ significantly.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			significant nausea) in the overall, acute, and delayed phases, with no emesis in the overall, acute, and delayed phases, and with no rescue therapy in the acute phase, percentages of patients with no rescue therapy in the overall phase	
Grunberg et al[34] Aprepitant 125 mg prior to chemotherapy followed by 80 mg daily on days two to three, plus ondansetron and dexamethasone vs fosaprepitant 150 mg on day 1) plus ondansetron and dexamethasone	AC, DB, RCT Male and female patients >18 years of age with histologically confirmed malignancies, Karnofsky scores 60, and predicted life expectancy 3 months, naive to cisplatin-containing chemotherapy and scheduled for a first course	N=2,322 Single dose or 3 day regimen	Primary: Complete response in the overall phase, defined as no vomiting or retching episodes with no use of rescue medication Secondary: Efficacy end points were the proportion of patients with complete response in the	Primary: In the overall phase, 71.9% (95% CI, 69.1 to 74.5) of patients in the fosaprepitant group reported Complete response compared to 72.3% (95% CI, 69.6 to 74.9) in the aprepitant group, a between-group difference of 0.4 percentage points (95% CI, 4.1 to 3.3). Secondary: In the delayed phase, 74.3% (95% CI, 71.6 to 76.9) of patients in the fosaprepitant group reported complete response compared to 74.2% (95% CI, 71.6 to 76.8) in the aprepitant group, a between-group difference of 0.1 percentage point (95% CI, 3.5 to 3.7). 72.9% (95% CI, 70.2 to 75.5) of patients in the fosaprepitant group reported no vomiting compared to 74.6% (95% CI, 71.9 to 77.1) in the aprepitant group, a between group difference of 1.7 percentage points (95% CI, 5.3 to 2.0).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of cisplatin		delayed phase and the proportion of patients with no vomiting in the overall phase	
Rapoport et al[35,36] HEC-1 Day 1: Rolapitant 180 mg once plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO vs Day 1: placebo plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO Both groups received dexamethasone 8 mg PO BID on days two to four	AC, DB, MC, PG, RCT Patients ≥ 18 years of age with KPS ≥60, life expectancy ≥ 4 months, scheduled to receive a first course of cisplatin-based chemotherapy (≥ 60 mg/m^2)	N=532 One cycle	Primary: CR in the delayed phase of CINV Secondary: CR in the acute and overall phases, no emesis, no significant nausea, time to first emesis or to use of rescue medications	Primary: Complete response in the delayed phase of CINV was observed in 73% of the individuals who received rolapitant compared to 58% who received placebo (P=0.006). Secondary: Rolapitant significantly improved the outcome of CR in the overall phase (P=0.001) and showed some improvement in CR during the acute phase (P=0.0051). For the endpoint of no emesis, there was observed to be a significant response in the rolapitant group for the delayed and overall phase (P<0.001) and an improved response in this same group for the acute phase (P<0.002). No significant difference was observed between the groups when evaluating the endpoint of no significant nausea.
Rapoport et al[35,36] HEC -2 Day 1: Rolapitant 180 mg once plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO vs	AC, DB, MC, PG, RCT Patients ≥ 18 years of age with KPS ≥60, life expectancy ≥ 4 months, scheduled to receive a first	N=555 One cycle	Primary: CR in the delayed phase of CINV Secondary: CR in the acute and overall phases, no emesis, no	Primary: Complete response in the delayed phase of CINV was observed in 70% of the individuals who received rolapitant compared to 62% who received placebo (P=0.042). Secondary: No significant differences were observed for the secondary endpoints in the rolapitant group for the acute, overall and delayed phases.

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>Day 1:
placebo plus granisetron 10 µg/kg IV plus dexamethasone 20 mg PO

Both groups received dexamethasone 8 mg PO BID on days two to four</td><td>course of cisplatin-based chemotherapy (≥ 60 mg/m^2)</td><td></td><td>significant nausea, time to first emesis or to use of rescue medications</td><td></td></tr>
<tr><td>Schwartzberg et al[35,37]

Day 1:
Rolapitant 180 mg once plus granisetron 2 mg PO plus dexamethasone 20 mg PO

vs

Day 1:
placebo plus granisetron 2 mg PO plus dexamethasone 20 mg PO

Both groups received granisetron 2 mg PO QD on days two and three</td><td>AC, DB, MC, PG, RCT

Patients ≥ 18 years of age, naïve to HEC/MEC, with KPS ≥60, life expectancy ≥ 4 months, scheduled to receive a first course of MEC including anthracycline</td><td>N=1,369
One cycle</td><td>Primary:
CR in the delayed phase of CINV

Secondary:
CR in the acute and overall phases, no emesis, no significant nausea, time to first emesis or to use of rescue medications</td><td>Primary:
Complete response in the delayed phase of CINV was observed in 71% of the individuals who received rolapitant compared to 62% who received placebo when evaluating the total population (P=0.0002). For the population that received an anthracycline, a CR in the delayed phase of CINV was seen in 67% of the individuals who received rolapitant compared to 62% who received placebo (P=0.0465). When evaluating those that received a non-anthracycline MEC regimen, 76% of the rolapitant group had a CR in the delayed phase of CINV compared to 64% in the placebo group (P=0.0008).

Secondary:
The rolapitant group had a significant improvement in CR in the overall phase and in emesis rates in both the delayed and overall CINV phases. There were no significant differences in the other end points
<table>
<tr><th>Outcome, population</th><th>Phase</th><th>Rolapitant (%)</th><th>Placebo (%)</th><th>P-value</th></tr>
<tr><td>CR, total population</td><td>Acute</td><td>83</td><td>80</td><td>0.1425</td></tr>
<tr><td>CR, ANC</td><td>Acute</td><td>77</td><td>77</td><td>0.9659</td></tr>
<tr><td>CR, non-AC MEC</td><td>Acute</td><td>91</td><td>84</td><td>0.0163</td></tr>
<tr><td>CR, total population</td><td>Overall</td><td>69</td><td>58</td><td><0.0001</td></tr>
<tr><td>CR, ANC</td><td>Overall</td><td>63</td><td>55</td><td>0.0332</td></tr>
<tr><td>CR, non-ANC, MEC</td><td>Overall</td><td>75</td><td>61</td><td>0.0003</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>No emesis</td><td>Delayed</td><td>80</td><td>70</td><td><0.001</td></tr>
<tr><td>No emesis</td><td>Acute</td><td>88</td><td>85</td><td>0.085</td></tr>
<tr><td>No emesis</td><td>Overall</td><td>79</td><td>65</td><td><0.001</td></tr>
<tr><td>No significant nausea</td><td>Delayed</td><td>73</td><td>69</td><td>0.194</td></tr>
<tr><td>No significant nausea</td><td>Acute</td><td>82</td><td>85</td><td>0.192</td></tr>
<tr><td>No significant nausea</td><td>Overall</td><td>71</td><td>67</td><td>0.118</td></tr>
</table>
</td></tr>
<tr><td>Hesketh et al[38]
NEPA 07-07

Netupitant-palonosetron 100 mg-0.5 mg for one dose

vs

netupitant-palonosetron (200 mg-0.5 mg) for one dose

vs

netupitant-palonosetron (300 mg-0.5 mg) for one dose

vs

palonosetron 0.5 mg for one dose

vs</td><td>DB, DD, PG, MC, RCT

Patients ≥18 years of age with histologically or cytologically confirmed malignant disease featuring solid tumor(s), chemotherapy naïve, Karnofsky index ≥ 70%; scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents</td><td>N=694

Multiple cycles</td><td>Primary:
Complete response during the overall phase period

Secondary:
Complete response during the acute and delayed phases; complete protection during the acute, delayed, and overall phases; no emesis during the acute, delayed, and overall phases; no significant nausea during the acute, delayed, and overall phases</td><td>Primary:
During the overall phase, 87.4% of patients in the netupitant-palonosetron 100 mg-0.5 mg group achieved complete response (P=0.018); 87.6% in the netupitant-palonosetron 200 mg-0.5 mg group (P=0.017); 89.6%; in the netupitant-palonosetron 300 mg-0.5 mg group (P=0.004); 76.5% in the palonosetron alone group (P value not reported) and 86.6% in the aprepitant plus ondansetron group (P=0.027).

Secondary:
Complete response during the acute phase was seen in 98.5% of patients in the netupitant 300 mg-palonosetron 0.5mg group compared to 89.7% in the palonosetron alone group (P≤0.01).

Complete response during the delayed phase was seen in 90.4% of patients in the netupitant 100 mg-palonosetron 0.5 mg group (P≤0.05), 91.2% in the netupitant 200 mg-palonosetron 0.5 mg group (P≤0.01) and 90.4 % of the netupitant 300 mg-palonosetron 0.5 mg group (P≤0.05) compared to 80.1% in the palonosetron group (no P value reported) and 88.8% in the aprepitant plus ondansetron group (P≤0.05).

Complete protection was reported by more individuals in the netupitant-palonosetron 300 mg-0.5 mg group compared to palonosetron alone in the acute, delayed and overall phases (P≤0.01, P≤0.05, and P≤0.01, respectively). Significantly more patients in the netupitant-palonosetron</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aprepitant 125 mg plus ondansetron 32 mg IV (exploratory arm) for one dose (All groups received dexamethasone therapy-varying doses based on study drug assigned)				300 mg-0.5 mg group reported no emesis during the acute, delayed and overall phases compared to the palonosetron alone group (all P values ≤0.01). For the endpoint of no significant nausea, the netupitant-palonosetron 300 mg-0.5 mg group reported higher rates of 98.5% (P≤0.05) for the acute phase, 90.4% (P≤0.01) for the delayed phase, and 89.6% (P≤0.05) for overall phase compared to palonosetron alone (93.4, 80.9, and 79.4%, respectively; no P values reported). The exploratory arm of aprepitant plus ondansetron reported rates 94.0% for acute phase, 88.1% for delayed phase, and 85.8% for overall phase (P values not reported).
Aapro et al[39] NEPA 08-18 Netupitant-palonosetron (300 mg-0.5 mg) plus dexamethasone 12 mg for one dose vs palonosetron 0.5 mg plus dexamethasone 20 mg for one dose	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG performance status of 0,1, or 2 and scheduled to receive an anthracycline/ cyclophosphamide regimen on Day 1 for treatment of a solid malignant tumor	N=1,455 One cycle	Primary: Complete response (no emetic episode and no rescue medication) in preventing nausea and vomiting during the delayed phase Secondary: Complete response during the acute phase, the overall phase; Complete protection during the acute, delayed and overall phases; no emesis during	Primary: Complete response during the delayed phase was seen in 76.9% of the netupitant-palonosetron group compared to 69.5% of the palonosetron group (P=0.001). Secondary: Complete response during the acute phase was seen in 88.4% of the netupitant-palonosetron group compared to 85.0% of the palonosetron group (P=0.047). Complete response during the overall phase was seen in 74.3% of the netupitant-palonosetron group compared to 66.6% of the palonosetron group (P=0.001). Significantly more patients in the netupitant-palonosetron group reported no emesis during the acute, delayed and overall phases compared with the palonosetron group (P=0.025, P=0.004, and P<0.001, respectively). Significantly more patients in the netupitant-palonosetron group reported no significant nausea during the delayed and overall phases, but not the acute phase, compared with the palonosetron group (delayed, P=0.014; overall, P=0.020; acute, P=0.747).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases; proportion of patients with scores reflecting "no impact on daily life" on daily life using the FLIE questionnaire	Complete protection was achieved by more patients who received netupitant-palonosetron compared to palonosetron during the delayed (67.3 vs 60.3%; P=0.005) and overall phases (63.8 vs 57.9%; P=0.020). FLIE questionnaire results showed that a greater proportion of patients receiving netupitant-palonosetron vs patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, P=0.015; vomiting domain, P=0.001; combined domain, P=0.005).
Gralla et al[40] NEPA 10-29 Netupitant-palonosetron (300 mg-0.5 mg) plus dexamethasone for one dose (dose based on the emetogenic potential of the chemotherapy regimen) vs palonosetron 0.5 mg on Day one plus aprepitant (125 mg Day one and 80 mg Days two to three) plus dexamethasone (dose based on the emetogenic potential of the	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG performance status of 0 to 2 and scheduled to receive repeated consecutive courses of chemotherapy with either highly or moderately emetogenic	N=413 Multiple cycles (total of 1961)	Primary: Safety (adverse events, vital sign measurements, laboratory tests including cardiac troponin I, physical examination ECG recordings including left ventricular ejection fraction) Secondary: Complete response during the acute, delayed and	Primary: The most common treatment-emergent, drug-related adverse events reported in the treatment groups were constipation (netupitant-palonosetron, 3.6%; palonosetron-aprepitant, 1.0%) and headache (netupitant-palonosetron and palonosetron-aprepitant, both 1.0%). Adverse events did not increase over multiple cycles, and the incidence, type and frequency of treatment-emergent adverse events was similar for both groups throughout the study. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities. Secondary: Complete response rates during the overall phase were high in both treatment groups over all six cycles of chemotherapy, ranging from 81 to 92% in the netupitant-palonosetron group and from 76 to 88% in the palonosetron-aprepitant group. Complete response rates were numerically greater for patients receiving netupitant-palonosetron during the overall phase and the delayed phase. Complete response

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
chemotherapy regimen)	agents for treatment of a malignant tumor		overall phases; no significant nausea during the acute, delayed and overall phases	rates were similar for the treatment groups during the acute phase (P values not reported).
Postoperative Nausea and Vomiting (PONV)				
Diemunsch et al[41] Aprepitant 40 mg by mouth vs aprepitant 125 mg mouth vs ondansetron 4 mg IV	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) undergoing open abdominal surgery requiring at least one overnight hospital stay and receiving volatile-agent-based general anesthesia including nitrous oxide	N=922 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy) over 0 to 24 hours after surgery; no vomiting over 0 to 24 hours after surgery Secondary: No vomiting in the first 48 hours after surgery	Primary: Complete response was achieved in 64% of patients in the aprepitant 40 mg group, 63% in the aprepitant 125 mg group, and 55% in the ondansetron group, indicating non-inferiority of the aprepitant treatment compared to ondansetron treatment. The percentage of patients with no vomiting over 0 to 24 hours was 84% with aprepitant 40 mg, 86% with aprepitant 125 mg, and 71% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron). Secondary: The percentage of patients with no vomiting over 0 to 48 hours was 82% with aprepitant 40 mg, 85% with aprepitant 125 mg, and 66% with ondansetron 4 mg (P<0.001 for both doses of aprepitant vs ondansetron).
Gan et al[42] Ondansetron 4 mg IV vs aprepitant 40 mg by mouth vs	DB, MC, PC, RCT Patients ≥18 years of age (ASA I or III status) who were scheduled to undergo open	N=805 48 hours	Primary: Complete response (no vomiting and no use of rescue therapy in the 24 hours after surgery)	Primary: Complete response was achieved in 45% of patients in the aprepitant 40 mg group, 43% in the aprepitant 125 mg group, and 42% in the ondansetron group, indicating non inferiority of the aprepitant treatment compared to ondansetron treatment (P>0.5 for both doses of aprepitant vs ondansetron). Secondary: Over 0 to 24 hours, the treatments did not differ significantly in the use

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aprepitant 125 mg by mouth	abdominal surgery requiring an overnight hospital stay and were scheduled to receive general anesthesia including nitrous oxide with volatile anesthetics		Secondary: No rescue therapy 0 to 24 hours; no vomiting 0 to 48 hours	of rescue therapy (45, 44, and 46% for aprepitant 40 mg, 125 mg, and ondansetron, respectively). More patients in both aprepitant groups reported no vomiting for the 0 to 48 hour time interval compared to the ondansetron group (OR, 2.7 for aprepitant 40 mg vs ondansetron and 6.9 for aprepitant 125 mg vs ondansetron; P<0.001 for both ratios).
Green et al[43] Aprepitant 40 mg vs aprepitant 40 mg and scopolamine transdermal patch	DB, RCT Patients >18 years of age, ASA I–III, two or more Apfel four-point risk factors, undergoing an elective surgical procedure with a high risk of PONV expected to last at least 60 minutes	N=120 24 hours	Primary: Complete response Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication	Primary: The aprepitant alone and aprepitant with scopolamine did not differ in complete responses (63 vs 57%; P=0.57). Secondary: Incidences of nausea, vomiting, their composite, and the need for rescue medication, all showed no statistical difference.
Hartrick et al[44] Aprepitant 40 mg by mouth vs ondansetron 4 mg and dexamethasone (4 to 6 mg) plus either	OL, PRO Patients undergoing total knee arthroplasty receiving extended-release	N=24 48 hours	Primary: Presence or absence of PONV during the postoperative period Secondary: Not reported	Primary: The percentage of patients experiencing PONV was significantly lower with aprepitant (25%) compared to the multimodal analgesia group (75%; P=0.039). There were no significant differences in pain scores, need for rescue therapy, or adverse events among the treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metoclopramide 10 mg, diphenhydramine 25 mg, or prochlorperazine 5 mg	morphine for postoperative pain management			Not reported
Sinha et al[45] Aprepitant 80 mg vs placebo All patients received intravenous ondansetron (4 mg) intraoperatively.	DB, PC, RCT Morbidly obese adult patients undergoing laparoscopic bariatric surgery considered at high risk for PONV	N=124 3 days	Primary: Incidence of vomiting Secondary: Nausea verbal rating scale, complete response (no nausea or vomiting), rescue treatment use	Primary: The cumulative incidence of vomiting at 72 hours was 3.1% (2/64) the aprepitant group and 15.0% (9/60) in the placebo group (P=0.021). Secondary: Complete response to treatment was seen in 42.18 and 36.67% patients in the aprepitant and placebo groups, respectively (P=0.510). Verbal rating scale scores failed to show any statistically significant difference between the groups at all the recorded time points (P=0.675). There were no statistical differences with respect to rescue treatments for nausea and vomiting, as 42.18% in the aprepitant group vs 42.33% in the placebo group required additional antiemetics.

Drug regimen abbreviations: BID=twice daily, IV=intravenously, PO=by mouth, QD=once daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NS=non-significant, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Other abbreviations: 5-HT3=serotonin type-3, ASA=American Society of Anesthesiologists, CINV=chemotherapy-induced nausea and vomiting, CR=complete response, ECG=echocardiogram, FILE=Functional Living Index-Emesis, PONV=post-operative nausea and vomiting

Special Populations

Table 5. Special Populations[1-4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Aprepitant	Clinical experience has not identified differences in responses between elderly and younger patients. FDA-approved for CINV in pediatric patients ≥12 years of age. Safety and efficacy in pediatric patients has not been established for PONV.	No dose adjustment is required for any degree of renal dysfunction, including end-stage renal disease.	No dosage adjustment required for mild to moderate (Child-Pugh score 5 to 9) hepatic dysfunction. Not studied in patients with severe (Child-Pugh score >9) hepatic dysfunction.	Insufficient data to inform of a drug-associated risk.	Unknown; use with caution.
Fosaprepitant dimeglumine	Clinical experience has not identified differences in responses between elderly and younger patients. Safety and efficacy in pediatric patients has not been established.	No dose adjustment is required for any degree of renal dysfunction, including end-stage renal disease.	No dosage adjustment required for mild to moderate (Child-Pugh score 5 to 9) hepatic dysfunction. Not studied in patients with severe (Child-Pugh score >9) hepatic dysfunction.	Insufficient data to inform of a drug-associated risk.	Unknown; use with caution.
Rolapitant hydrochloride	No overall differences in safety or efficacy were reported between the elderly subjects and younger subjects. Safety and efficacy in pediatric patients has not been established.	Not reported.	No dosage adjustment required for mild to moderate (Child-Pugh class A or B) hepatic dysfunction. Use is not recommended in patients with severe (Child-Pugh	Insufficient data to inform of a drug-associated risk.	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
			class C) hepatic dysfunction.		
Combination Products					
Netupitant/ palonosetron	Controlled clinical studies did not include sufficient numbers of elderly patients to determine whether they respond defiantly than younger adult patients. Safety and efficacy in pediatric patients have not been established.	Renal dose adjustment not required for mild or moderate dysfunction (CrCl≥30). Not studied in severe dysfunction (CrCl<30).	No dose adjustment required for mild to moderate dysfunction (Child-Pugh score 5 to 8). Data is limited for severe hepatic dysfunction (Child-Pugh score >8).	C Insufficient data to inform of a drug-associated risk.	Unknown; use with caution.

CINV=chemotherapy-induced nausea and vomiting, CrCl=creatinine clearance, PONV=post-operative nausea and vomiting

Adverse Drug Events

Table 6. Adverse Drug Events[1-4]

Adverse Events	Aprepitant*	Fosaprepitant*	Rolapitant†	Netupitant/ palonosetron‡
Abdominal pain	6	-	3	-
Anemia	-	3	3	-
Asthenia	7	4	-	8
Constipation	-	-	-	3
Decreased appetite	-	-	9	-
Dehydration	3	-	-	-
Diarrhea	9	13	-	-
Dizziness	-	-	6	-
Dyspepsia	7	2	4	4
Erythema	-	-	-	3
Extremity Pain	-	2	-	-
Fatigue	13	13	-	4 to 7
Headache	-	-	-	9
Hiccups	5	-	5	-
Leukopenia	-	2	-	-
Neutropenia	4	8	7 to 9	-
Peripheral Neuropathy	-	3	-	-
Stomatitis	-	-	4	-
Urinary Tract Infection	-	2	4	-

-Event not reported or <1%
*In combination with ondansetron and dexamethasone
†In combination with a 5-HT3 receptor antagonist and dexamethasone
‡In combination with dexamethasone

Contraindications

Table 7. Contraindications[1-4]

Contraindication	Aprepitant	Fosaprepitant	Rolapitant hydrochloride	Netupitant/ palonosetron
Hypersensitivity to the active drug or any component	a	a	a	a
Concurrent use of pimozide	a	a		
Concurrent use of thioridazine			a	

Warnings/Precautions

Table 8. Warnings and Precautions[1-3]

Warning/Precaution	Aprepitant	Fosaprepitant	Rolapitant hydrochloride	Netupitant/ palonosetron
Clinically significant CYP3A4 drug interactions; aprepitant is a substrate, a weak-to moderate inhibitor and inducer of CYP3A4; use with strong CYP3A4 inhibitors or inducers may result in an increased risk of adverse events.	a	a		
Clinically significant CYP2D6 substrate drug interactions with a narrow therapeutic index; inhibitory effect may last for up to seven days.			a	
Concurrent use of warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time.	a	a		
Risk of reduced efficacy of hormonal contraceptives; recommend back-up method of contraception during treatment and for one month following the last dose	a	a		
Hypersensitivity reactions, including anaphylaxis have been reported with or without known hypersensitivity to other 5-HT3 receptor antagonists.				a
Serotonin syndrome has been reported in patients treated with 5-HT3 receptor antagonists, most of which have been associated with concomitant use of serotonergic drugs; discontinue use if symptoms of serotonin syndrome develop.				a

Drug Interactions

Table 9. Drug Interactions[1-4]

Generic Name	Interacting Medication or Disease	Potential Result
Aprepitant, fosaprepitant	CYP3A4 substrates (Pimozide)	Increased pimozide exposure; aprepitant use is contraindicated
Aprepitant, fosaprepitant	CYP3A4 substrates (benzodiazepines)	Increased exposure to benzodiazepines metabolized via CYP3A4 (midazolam, alprazolam, triazolam); increased risk for adverse events; monitoring for benzodiazepine-related adverse events is

Generic Name	Interacting Medication or Disease	Potential Result
		recommended.
Aprepitant, fosaprepitant	CYP3A4 substrates (dexamethasone)	Increased exposure to dexamethasone; increased risk for adverse events; dexamethasone dose adjustment may be required.
Aprepitant, fosaprepitant	CYP3A4 substrates (methylprednisolone)	Increased exposure to methylprednisolone; increased risk for adverse events; methylprednisolone dose adjustment may be required.
Aprepitant, fosaprepitant	CYP3A4 substrates (chemotherapy agents)	Increased exposure to the chemotherapeutic agent metabolized by CYP3A4; increased risk of adverse events; additional monitoring for adverse events is recommended.
Aprepitant, fosaprepitant	CYP3A4 substrates (hormonal contraceptives)	Concurrent use may reduce the effectiveness of hormonal contraceptives; use of an effective back-up method is recommended during treatment with aprepitant and for one month after the last dose.
Aprepitant, fosaprepitant	CYP2C9 substrates (warfarin)	Decreased warfarin exposure and prolongation of prothrombin time; increased monitoring of warfarin prothrombin time is recommended when aprepitant is used.
Aprepitant, fosaprepitant	Moderate (e.g. diltiazem) to Strong (e.g. ketoconazole, clarithromycin, ritonavir) CYP3A4 Inhibitors	Significantly increased exposure of aprepitant; increased risk of adverse events; use of aprepitant in combination with a moderate or strong CYP3A4 inhibitor is not recommended.
Aprepitant, fosaprepitant	Strong CYP3A4 Inducers (e.g. rifampin, carbamazepine, phenytoin)	Substantially decreased exposure of aprepitant in patients with chronically taking a strong CYP3A4 inducer may decrease the efficacy of aprepitant; concurrent use of aprepitant and a strong CYP3A4 inducer is not recommended
Rolapitant	CYP2D6 substrates with a narrow therapeutic index (thioridazine, pimozide)	Increased exposure to thioridazine and pimozide; may result in QT prolongation and torsades de pointes; concurrent use is contraindicated; effect of rolapitant on CYP2D6 has been observed for 7 days, and may last longer.
Rolapitant	BCRP Substrates with a narrow therapeutic index (e.g. methotrexate, topotecan)	Increased plasma concentrations of BCRP substrates may result in potential adverse events; monitoring for adverse events is recommended if concurrent use cannot be avoided; use the lowest effective dose
Rolapitant	P-gp substrates with a narrow therapeutic index (e.g. digoxin)	Increased plasma concentrations of digoxin or other P-gp substrates; increased risk for adverse events; monitoring for digoxin toxicity is recommended if concurrent use cannot be avoided.
Rolapitant	Strong CYP3A4 Inducers (e.g. rifampin)	Significantly reduced plasma concentrations of rolapitant; decreased efficacy of rolapitant may result; avoid use of rolapitant in patients who require chronic administration of a strong CYP3A4 inducer
Netupitant/ palonosetron	CYP3A4 substrates (e.g. dexamethasone, midazolam, certain chemotherapy agents)	Increased systemic exposure to CYP3A4 substrates; may result in increased risk of adverse events.
Netupitant/	CYP3A4 inducers	Avoid use of netupitant/palonosetron in patients who

Generic Name	Interacting Medication or Disease	Potential Result
palonosetron	(e.g. rifampin)	are chronically using a strong CPY3A4 inducer due to reduced efficacy of the netupitant component.
Netupitant/ palonosetron	CYP3A4 inhibitors (e.g. ketoconazole)	Concomitant use of netupitant/palonosetron in patients using a strong CYP3A4 inhibitor can significantly increase systemic exposure of netupitant. However, no change is needed for a single dose.
Netupitant/ palonosetron	Serotonergic drugs (e.g. 5-HT3 antagonists, SSRIs, SNRIs)	Increased risk of serotonin syndrome (including altered mental status, autonomic instability, neuromuscular symptoms) have been observed; monitor for symptoms of serotonin syndrome; if symptoms are present, discontinue netupitant/palonosetron and begin supportive treatment.

BCRP=Breast-Cancer-Resistance Protein, SSRI=selective serotonin reuptake inhibitor, SNRI=serotonin-norepinephrine reuptake inhibitor

Dosage and Administration

Table 10. Dosing and Administration[1-4]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Aprepitant	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC: Capsule: **Day 1**: aprepitant 125 mg (one hour prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist **Day 2 and 3**: aprepitant 80 mg + dexamethasone 8 mg once daily in the morning **Day 4**: dexamethasone 8 mg once daily in the morning Prevention of CINV associated with initial and repeat courses of MEC: Capsule: **Day 1**: aprepitant 125 mg (one hour prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist **Day 2 and 3**: aprepitant 80 mg once daily in the morning Prevention of PONV: Capsule: 40 mg within three hours prior to induction of anesthesia	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC (≥12 years of age): Capsule: refer to adult dosing; if a corticosteroid such as dexamethasone is co-administered, use 50% of the recommended corticosteroid dose on days 1 through 4 Safety and efficacy for CINV has not been established in pediatric patients <12 years of age. Safety and efficacy for PONV has not been established in pediatric patients.	Capsule: 40 mg 80 mg 125 mg Capsule Dose Pack: 125 and 80 mg
Fosaprepitant	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC:	Safety and efficacy in pediatric patients has not	Vial: 150 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Vial: **Day 1**: aprepitant 150 mg via IV infusion over 20 to 30 minutes (30 minutes prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist **Day 2**: dexamethasone 8 mg once daily in the morning **Day 3 and 4**: dexamethasone 8 mg twice daily Prevention of delayed CINV associated with initial and repeat courses of MEC: Vial: **Day 1**: aprepitant 150 mg via IV infusion over 20 to 30 minutes (30 minutes prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist	been established.	
Rolapitant	Prevention of delayed CINV associated with initial and repeat courses of HEC: Tablet: **Day 1**: rolapitant 180 mg (two tablets; one to two hours prior to chemo) + dexamethasone 20 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist **Day 2, 3, 4**: dexamethasone 8 mg twice daily Prevention of delayed CINV associated with initial and repeat courses of MEC and prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide: Tablet: **Day 1**: rolapitant 180 mg (two tablets; one to two hours prior to chemo) + dexamethasone 20 mg (30 minutes prior to chemo) + a 5-HT_3 antagonist	Safety and efficacy in pediatric patients has not been established.	Tablet: 90 mg
Combination Products			
Netupitant/ palonosetron	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC: Capsule: **Day 1**: netupitant/palonosetron 300/0.5 mg (one hour prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo) **Day 2, 3, 4**: dexamethasone 8 mg	Safety and efficacy in pediatric patients has not been established.	Capsule: 300/0.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	once daily Prevention of acute and delayed CINV associated with initial and repeat courses of cancer chemotherapy not considered highly emetogenic: Capsule: **Day 1**: netupitant/palonosetron 300/0.5 mg (one hour prior to chemo) + dexamethasone 12 mg (30 minutes prior to chemo)		

Other abbreviations: CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomiting

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network (NCCN) **Clinical Practice Guidelines in Oncology: Antiemesis (2015)**[7]	For high emetic risk intravenous (IV) chemotherapy the following is recommended: *Day 1:* · The combination of a neurokinin 1 (NK_1) receptor antagonist (aprepitant 125 mg PO once, fosaprepitant 150 mg IV once or rolapitant 180 mg PO once) plus dexamethasone and any serotonin ($5\text{-}HT_3$) antagonist (dolasetron 100 mg PO once, granisetron [2 mg PO once or 1 mg PO BID, or 0.01 mg/kg (max 1 mg) IV once, 3.1 mg/24h TD patch applied 24 to 48 hours prior to first does of chemo], ondansetron 16 to 24 mg PO once or 8 to 16 mg IV once, or palonosetron 0.25 mg IV once) *Day 2:* · If aprepitant PO is given on day 1, give aprepitant 80 mg PO daily on days 2,3 plus dexamethasone daily days 2, 3, 4 · If fosaprepitant IV given on day 1, give dexamethasone days 2, 3, 4 · If rolapitant is given on day1, give dexamethasone days 2, 3, 4 **OR** *Day 1:* · Netupitant 300 mg/palonosetron 0.5 mg PO once plus dexamethasone *Day 2:* · Dexamethasone days 2, 3, 4 **OR** *Day 1:* · The combination of olanzapine 10 mg PO once, palonosetron 0.25 mg IV once and dexamethasone may be given *Day 2:* · Olanzapine 10 mg PO days 2, 3, 4 May be given with or without lorazepam, an H_2 receptor blocker or a PPI. For moderate emetic risk IV chemotherapy the following is recommended:

Clinical Guideline	Recommendations
	Day 1: · The combination of dexamethasone and a 5-HT_3 antagonist (palonosetron preferred) with or without a NK_{-1} receptor antagonist. *Day 2:* · 5-HT_3 antagonist monotherapy days 2, 3 (unless palonosetron IV had been given on day 1) OR · Steroid monotherapy days 2, 3 OR · NK_{-1} antagonist ± steroid **OR** *Day 1:* · Netupitant 300 mg/palonosetron 0.5 mg PO once plus dexamethasone *Day 2:* · Dexamethasone days 2, 3, 4 ***OR*** *Day 1:* · The combination of olanzapine 10 mg PO once, palonosetron 0.25 mg IV once and dexamethasone may be given Day 2: · Olanzapine 10 mg PO days 2, 3 May be given with or without lorazepam, an H_2 receptor blocker or a PPI. For low emetic risk IV chemotherapy the following is recommended*:* · Dexamethasone; OR · Metoclopramide PRN; OR · Prochlorperazine PRN (maximum 40 mg/day); OR · Dolasetron, granisetron or ondansetron; OR · Lorazepam PRN; OR · H_2 blocker or PPI For oral chemotherapy with moderate to high emetic risk the following is recommended: · A 5-HT_3 antagonist (dolasetron, granisetron or ondansetron) · Lorazepam may be given. · An H_2 receptor blocker or PPI may be given.
American Society of Clinical Oncology Clinical Practice: **Guideline Update-Emesis (2015)**[8]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk the following is recommended: · A three-drug combination of a NK_{-1} receptor antagonist (Days 1 through 3 for aprepitant; Day 1 only for fosaprepitant), a 5-HT_3 receptor antagonist (Day 1 only) and dexamethasone (Days 1 through 3 or Days 1 through 4). The oral combination of netupitant and palonosetron plus dexamethasone is an additional treatment option. For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended: · A two-drug combination of palonosetron (Day 1 only) and dexamethasone (Days 1 through 3). If palonosetron is not available, may substitute a first-generation 5-HT_3 receptor antagonist (preferably

Clinical Guideline	Recommendations
	granisetron or ondansetron). · There is limited evidence that supports adding aprepitant to the combination. For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended: · A single 8 mg dose of dexamethasone before chemotherapy. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended: · No antiemetic should be administered routinely to individuals before or after chemotherapy.
Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO): **Antiemetic Guideline (2013)**[9]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk or a regimen of anthracycline plus cyclophosphamide the following is recommended*:* · A three-drug regimen of single doses of a 5-HT_3 receptor antagonist, dexamethasone and oral aprepitant 125 mg (or fosaprepitant 150 mg IV). · For delayed emesis, it is recommended to give aprepitant 80 mg once daily for two days after chemotherapy (or none if fosaprepitant is used on Day 1). For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended*:* · Palonosetron plus a single IV dose of dexamethasone 8 mg. For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended*:* · A single antiemetic such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended*:* · No antiemetic should be routinely administered to individuals without a history of nausea and vomiting. *F*or patients receiving multiple-day cisplatin the following is recommended*:* · A 5-HT_3 receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. · The addition of an NK_1 receptor antagonist (aprepitant or fosaprepitant) could be considered starting no later than day three (optimal administration schedule not defined).
Pediatric Oncology Group of Ontario: **Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients (2012)**[10]	Acute antineoplastic-induced (high emetic risk) nausea and vomiting · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone + aprepitant. · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone. · Children <12 years old and receiving antineoplastic agents of high emetic risk receive: ondansetron or granisetron + dexamethasone. Acute antineoplastic-induced (moderate emetic risk) nausea and vomiting

Clinical Guideline	Recommendations
	· Ondansetron or granisetron + dexamethasone is recommended Acute antineoplastic-induced (low emetic risk) nausea and vomiting · Ondansetron or granisetron is recommended Acute antineoplastic-induced (minimal emetic risk) nausea and vomiting · No routine prophylaxis is recommended Role of aprepitant in children receiving antineoplastic therapy: · Use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. · There is no evidence to support the safe and effective use of aprepitant in younger children.

Conclusions

The NK_1 antagonists are mostly utilized for the prevention CINV. Aprepitant (Emend®) and its prodrug fosaprepitant dimeglumine (Emend®) have been available for some time with newer agents such as rolapitant (Varubi®) and neutipitant/palonosetron (Akynzeo®) recently receiving FDA approval. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4]

It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[7] For the prevention of CINV post-HEC, triple therapy with a $5\text{-}HT_3$ receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[7-8] The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[7] For the prevention of CINV post-MEC, a $5\text{-}HT_3$ receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[7-9] Most guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[8-10]

The safety and efficacy of the NK1 antagonists have been evaluated in several clinical trials for their FDA-approved indications.[11-45] There are currently no clinical trials that compare two different NK_1 antagonist to each other. All agents are formulated as oral capsules or tablets, with the exception of fosaprepitant, which is an intravenous injection. For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days. All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4] Aprepitant capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients. Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age.[1,10] Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

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Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
This review will focus on the partial opioid agonists and opioid antagonists. These agents are used alone or in combination in the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-9] Buprenorphine (Subutex®) buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Naloxone solution and naloxone auto-injector (Evzio®) are used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-9] Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection. Naloxone is available as a vial for injection, prefilled syringe for injection and auto-injector solution (Evzio®)[1-9] Products which contain buprenorphine are classified as Schedule III controlled substances.[10] The transdermal and injectable formulations of buprenorphine, Butrans® and Buprenex®, respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.[11,12] Buprenorphine and buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone vials and prefilled syringes are currently available generically.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria). Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Buprenorphine is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists [1,4-7] Naloxone and naltrexone are antagonists at the μ-opioid receptor.[2-9] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[10] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-9] Evzio® (naloxone injection) is a prefilled autoinjector designed to deliver 0.4 mg of naloxone per injection. The injection can be given intramuscularly or subcutaneously into the outer thigh and may be given through clothing, if necessary. In addition, the device has a retractable needle system that is designed to prevent needlesticks. Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. The autoinjector device gives electronic voice instructions to the caregiver, including instruction to seek emergency medical assistance after a dose is administered.[9]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[13] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[16,17]

Table 1. Current Medications Available in Therapeutic Class[1-9]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	a
Naltrexone (ReVia®, Vivitrol®)	Alcohol dependence; opioid dependence‡ (ReVia®); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol®)	Suspension for injection, extended-release (Vivitrol®): 380 mg Tablet (ReVia®): 50 mg	-
Naloxone (Evzio®)	Opioid overdose§	Auto-injector solution (Evzio®): 0.4 mg/0.4 mL Prefilled syringe, solution: 0.4 mg/mL 2 mg/2 mL Vial, solution 0.4 mg/mL	a
Combination Product			
Buprenorphine/naloxone (Bunavail®, Suboxone®‖, Zubsolv®)	Opioid dependence, treatment induction† (Suboxone®); opioid dependence, treatment maintenance†	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg	a

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§As manifested by respiratory and/or central nervous system depression.
‖Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Buprenorphine and buprenorphine/naloxone significantly improve many different outcomes for patients with opioid dependence compared to placebo and no treatment, but are generally found to not be significantly different from one another.[20-30, 41-48]

- FDA-approval of buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) was via the 505(b)(2) pathway. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.[5,7]
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.[22, 31-38]
- A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes.
    - Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).[58]
- The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[59]
- FDA-approval of Evzio® (naloxone injection) was based upon data from a bioavailability trial that compared Evzio® (naloxone injection) to naloxone given through a standard syringe. Subjects were randomized to receive Evzio® (naloxone injection) or standard naloxone injection on day one. On day two, the subjects received the opposite treatment in order to evaluate the comparative bioavailability. The mean peak plasma concentration (C_{max}), median times to peak plasma concentrations (T_{max}), mean elimination half-life ($T_{1/2}$) and mean area under-the-curve (AUC) mere similar when Evizio® (naloxone injection) was compared to standard naloxone injections (P values not reported).[60]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients.[13]
    - This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[13]
    - Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[15]
- Other Key Facts:
    - According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[18]
    - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.[3]

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Therapeutic Class Review
Opioid Dependence Agents

Overview/Summary

This review will focus on the partial opioid agonists and opioid antagonists. These agents are used alone or in combination in the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-9] Buprenorphine (Subutex®) buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Naloxone solution and naloxone auto-injector (Evzio®) are used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-9] Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection. Naloxone is available as a vial for injection, prefilled syringe for injection and auto-injector solution (Evzio®)[1-9] Products which contain buprenorphine are classified as Schedule III controlled substances.[10] The transdermal and injectable formulations of buprenorphine, Butrans® and Buprenex®, respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.[11,12] Buprenorphine and buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone vials and prefilled syringes are currently available generically.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria).[1,4-7] Compared to full opioid agonists, partial agonists bind to the μ-opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.[13] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[4-7]

Naloxone and naltrexone are antagonists at the μ-opioid receptor.[2-9] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[10] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-9] Evzio® (naloxone injection) is a prefilled autoinjector designed to deliver 0.4 mg of naloxone per injection. The injection can be given intramuscularly or subcutaneously into the outer thigh. Evzio® (naloxone injection) may be given through clothing, if necessary, and the device has a retractable needle system that is designed to prevent needlesticks. Each carton of Evzio® (naloxone injection) contains two autoinjector devices and a trainer that may be reused for repeat training purposes.[9] Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. The autoinjector device gives electronic voice instructions to the caregiver, including instruction to seek emergency medical assistance after a dose is administered. The electronic voice instructions also instruct caregivers to take the Evzio® (naloxone injection) to the patient's physician for proper disposal and a refill of the medication after a dose is used. Should the electronic voice instructions fail to work, each autoinjector has printed instructions on the label of the device. If used according to the printed instructions on the device label, the Evzio® (naloxone injection) autoinjector will still deliver the necessary dose of naloxone, even if the electronic voice instructions fail to properly function.[9]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[13] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[13] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[14-15] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[15] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[14] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[16,17]

According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[18]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine	Partial opioid agonist	a
Naltrexone (ReVia®, Vivitrol®)	Opioid antagonist	-
Naloxone (Evzio®)	Opioid antagonist	a
Combination Product		
Buprenorphine/naloxone (Bunavail®, Suboxone®*, Zubsolv®)	Partial opioid agonist/ opioid antagonist	a †

*Generic available in one dosage form or strengths.
† Buprenorphine/naloxone 2/0.5 mg and 8/2 mg sublingual tablets only.

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications[1-9]

Indication	Single Entity			Combination
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/ Naloxone
Alcohol dependence		a		
Opioid dependence, treatment induction†	a *			a ¶
Opioid dependence, treatment maintenance†	a *			a
Opioid dependence‡		a §		
Opioid dependence, prevention of relapse following opioid detoxification		a ‖		
Opioid overdose#			a	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§Indication is for ReVia® only.
‖Indiction is for Vivitrol® only.
¶Indication is for Suboxone® only.
#As manifested by respiratory and/or central nervous system depression.

Pharmacokinetics

The inter-patient variability in the sublingual absorption of buprenorphine and naloxone is wide; however, the variability within subjects is low.[4-7] Pharmacokinetic parameters for the combination products are similar to that observed for the individual components. The median time to peak plasma concentration of naloxone injection is 0.25 hours.[8-9]

Table 3. Pharmacokinetics[1-9]

Generic Name	Bioavailability (%)	Metabolism	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Buprenorphine	15 to 31	Cytochrome P450 3A4	96	Urine:30 Feces:69	24 to 42
Naloxone	3†	Glucuronidation, N-dealkylation, and reduction	45†	Primarily in the urine	2 to 12 (oral)† 0.5 to 1.36 (inj)‡
Naltrexone	5 to 40	Not specified (>98% metabolized)	21	Primarily in the urine	4(13)*

*The half-life of parent molecule, naltrexone, is four hours; the half-life of the active metabolite 6-ß-naltrexol is 13 hours.
†Sublingual and buccal formulations only; not reported for naloxone injection.
‡Half-life of naloxone auto-injector reported as 1.36 hours, half-life of other naloxone formulations reported as 0.5 to 1.35 hours.

Clinical Trials

The safety and efficacy of buprenorphine, buprenorphine/naloxone and naltrexone in the treatment of opioid dependence were demonstrated in several clinical trials outlined in Table 4.[19-59] FDA-approval of Evzio® (naloxone injection) was based upon data from a bioavailability trial that compared Evzio® (naloxone injection) to naloxone 0.4 mg given through a standard syringe. Additionally, an ease of use study was conducted for Evzio® (naloxone injection).[60]

In the study in which approval of Evzio® (naloxone injection) was based upon, bioavailability of Evzio® (naloxone injection) was compared to naloxone 0.4 mg given through a standard syringe in 30 healthy subjects. Subjects were randomized to receive Evzio® (naloxone injection) or standard naloxone injection on day one. On day two, the subjects received the opposite treatment in order to evaluate the comparative bioavailability. The mean peak plasma concentration (C_{max}) for Evzio® (naloxone injection) was 1,240 pg/mL, versus a C_{max} of 1,070 pg/mL for standard naloxone injection. Median times to peak plasma concentrations for Evzio® (naloxone injection) and standard naloxone injection were 0.25 hour and 0.33 hour, respectively. The mean elimination half-life ($T_{1/2}$) for Evzio® (naloxone injection) was 1.28 hours, versus a mean $T_{1/2}$ of 1.36 hours for standard naloxone injection. The mean area under-the-curve (AUC) for Evzio® (naloxone injection) was 1,930 pg•hr/mL, and the mean AUC for standard naloxone injection was 1,980 pg•hr/mL.[60]

In addition to the bioavailability study, an ease of use study was conducted for Evzio® (naloxone injection) in order to evaluate the ability of laypersons to administer a successful injection. The study evaluated the ability of 20 English-speaking participants aged 12 to 19 years and 20 English-speaking participants aged 20 to 65 years to administer a simulated dose of Evzio® (naloxone injection). The participants were not previously trained to use the Evzio® (naloxone injection) system, and relied upon the voice commands for use instructions. Of the 40 participants, 36 participants (90%) were able to successfully deliver an effective dose of naloxone from the Evzio® (naloxone injection) device. Of the four participants that failed to deliver the dose, two did not press the base of injector firmly enough to activate the autoinjector. One participant did not hold the autoinjector in place for a full second, and the other participant that failed to deliver an effective naloxone dose used the Evzio® (naloxone injection) training unit, rather than the unit with active medication. The average time to give the injection was 64.0 seconds for the adult cohort and 57.6 seconds for the juvenile (12 to 29 years of age) cohort.[60]

Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine 16 mg daily and buprenorphine/naloxone 16/4 mg daily compared to placebo, while no significant difference was seen between the two active treatment

groups.[20-21] A smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.[22]

FDA-approval of buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) was via the 505(b)(2) pathway, which allows a manufacturer to compare a new product to a previously-approved drug (or drugs) and utilize data from studies that were performed on the reference drug. These medications have not been specifically studied in clinical trials evaluating their efficacy. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.[5,7]

Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or lower self-reported drug use with longer treatment duration compared to detoxification; however, one of the studies (Woody et al) showed no significant difference in the percentage of positive urine tests between the two treatment groups at 12 weeks.[23-25] A cost-effectiveness analysis showed that compared to two-week detoxification, a 12-week outpatient treatment program with buprenorphine/naloxone was associated with an incremental first-year direct medical cost of $1,376 per quality-adjusted life year and had an 86% chance of being accepted as cost-effective for a threshold of $100,000 per quality-adjusted life year.[26]

In a meta-analysis of 21 randomized controlled trials, buprenorphine at doses ≥16 mg/day was demonstrated to be more likely to retain in treatment compared to doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high and low dose groups.[27] Studies that compared different dosing regimens of buprenorphine showed no differences in rate of treatment retention, percentage of urine tests positive for opioids or withdrawal symptoms.[28-31]

Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.[22, 231-38] However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious.[29, 39-41]

A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18.[58]

The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[59]

Table 4. Clinical Trials

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mattick et al[19] Buprenorphine maintenance therapy vs methadone maintenance therapy (17 studies) or placebo (seven studies)	MA (24 RCTs) Patients with opioid dependence	N=4,497 2 to 52 weeks	Primary: Treatment retention, use of opioids, use of other substances, criminal activity and mortality; physical health, psychological health and adverse events Secondary: Not reported	Primary: Buprenorphine at low, medium and high doses was significantly more effective than placebo in retaining patients in treatment but was not as effective as methadone when delivered at adequate doses. *Flexible dose buprenorphine vs flexible dose methadone* Results from eight studies (N=1,068) showed lower retention rate with buprenorphine compared to methadone (RR, 0.85; 95% CI, 0.73 to 0.98). No significant differences were seen in the percentage of opioid positive urine tests (SMD, -0.12; 95% CI, -0.26 to 0.02), self-reported opioid use (SMD, -0.12; 95% CI, -0.31 to 0.07), cocaine use (SMD, 0.11; 95% CI, -0.03 to 0.25), benzodiazepine use (SMD, 0.11; 95% CI, -0.04 to 0.26) or criminal activity (SMD, -0.14; 95% CI, -0.41 to 0.14). *Low dose buprenorphine vs low dose methadone* Results from three studies (N=253) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.52 to 0.87). No significant differences were seen in percentage of opioid positive urine tests (SMD, -0.35; 95% CI, -0.87 to 0.16), self-reported opioid use (SMD, -0.29; 95% CI, -0.38 to 0.96) or cocaine use (SMD, 0.08; 95% CI, -0.43 to 0.59). *Low dose buprenorphine vs medium dose methadone* Results from three studies (N=305) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.55 to 0.81). More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.88; 95% CI, 0.33 to 1.42). One study showed no significant difference in self-reported opioid use (SMD, -0.10; 95% CI, -0.48 to 0.68) while a second study showed significantly fewer reports with methadone. No significant difference was seen in cocaine use (SMD, -0.08; 95% CI, -0.60 to 0.44). *Medium dose buprenorphine vs low dose methadone* One study showed lower retention rate with buprenorphine compared to methadone while three studies showed no statistically significant

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. Fewer patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, -0.23; 95% CI, -0.45 to -0.01). No significant difference was seen in cocaine use (SMD, 0.38; 95% CI, -0.14 to 0.89). *Medium dose buprenorphine vs medium dose methadone* Two studies (N=312) showed lower retention rate with buprenorphine compared to methadone while four studies (N=335) showed no statistically significant difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.27; 95% CI, 0.05 to 0.50). No significant difference was seen in self-reported opioid use (SMD, -0.27; 95% CI, -0.90 to 0.35) or cocaine use (SMD, 0.22; 95% CI, -0.30 to 0.74). *Low dose buprenorphine vs placebo* Results from five studies (N=1,131) showed higher retention rate with buprenorphine compared to placebo (RR, 1.50; 95% CI, 1.19 to 1.88). No significant differences were seen in percentage of opioid positive urine tests (SMD, 0.10; 95% CI, -0.80 to 1.01), cocaine use (SMD, 0.26; 95% CI, -0.10 to 0.62) or benzodiazepine use (SMD, 0.03; 95% CI, -0.33 to 0.38). *Medium dose buprenorphine vs placebo* Results from four studies (N=887) showed higher retention rate with buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.06 to 2.87). Fewer patients had opioid positive urine tests (SMD, -0.28; 95% CI, -0.47 to -0.10) and benzodiazepine use (SMD, -0.81; 95% CI, -1.27 to -0.36) with buprenorphine compared to placebo. One study showed more cocaine use with buprenorphine compared to placebo (SMD, 0.50; 95% CI, 0.05 to 0.94). *High dose buprenorphine vs placebo* Results from four studies (N=728) showed higher retention rate with

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.02 to 2.96). Fewer patients had opioid positive urine tests with buprenorphine compared to placebo (SMD, -1.23; 95% CI, -0.95 to -0.51). No significant difference was seen in cocaine use (SMD, 0.08; 95% CI, -0.20 to 0.36) or benzodiazepine use (SMD, -0.25; 95% CI, -0.52 to 0.02). Secondary: Not reported
Fudala et al[20] Phase 1 Buprenorphine 16 mg daily vs buprenorphine/naloxone 16/4 mg daily vs placebo Phase 2 Buprenorphine 8 to12 mg for two days, then buprenorphine/naloxone 24/6 mg daily	MC, PC, RCT with OL phase Patients 18 to 59 years of age who met the DMS-IV criteria for opioid dependence and who were seeking opioid-substitution pharmacotherapy	Phase 1 N=326 Phase 2 N=472 52 weeks	Primary: Efficacy measured by percentage of urine samples negative for opioids and the patients' self-reported craving for opioids Secondary: Patients' and clinicians' impressions of overall status and adverse events	Primary: The percentages of urine tests that were opioid-negative were 17.8% in the combined-treatment group and 20.7% in the buprenorphine group, as compared to 5.8% in the placebo group (P<0.001 for both comparisons). For each of the four study weeks, the mean scores for opioid craving in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group (P<0.001 for both comparisons each week). Secondary: Each week scores for patients' and clinicians' global impression were significantly higher in both the combined treatment group and buprenorphine alone group than those in the placebo group (P<0.001 for both comparisons each week). The overall rate of adverse events did not differ significantly among the groups (78% in the combined treatment group, 85% in the buprenorphine only group and 80% in the placebo group). The only adverse events that showed a significant difference in occurrences between treatment groups and placebo were withdrawal syndrome, constipation and diarrhea. (P=0.008, P=0.03 and P=005 respectively), with the withdrawal syndrome and diarrhea occurring more frequently in the placebo group and constipation occurring more frequently in the treatment groups.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daulouede et al[21] Buprenorphine at patient's current dosage SL vs buprenorphine/naloxone at the same buprenorphine dose SL	MC, OL, PRO, XO Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months	N=53 5 days	Primary: Patient-rated global satisfaction with study medication Secondary: Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events	Primary: Daily mean VAS score for global satisfaction was similar between buprenorphine (6.83 to 7.04) and buprenorphine/naloxone (6.89 to 7.38; P=0.781). Secondary: Daily mean VAS score for well-being in the past 24 hours were similar between buprenorphine (7.17) and buprenorphine/naloxone (6.33 to 7.04; P=0.824). Patients preferred buprenorphine/naloxone over buprenorphine with regard to tablet size (6.83 to 7.02 vs 5.29 to 5.76; P=0.151), tablet taste (6.83 to 6.98 vs 2.45 to 2.74; P=0.57) and SL dissolution time (6.62 to 6.84 vs 3.73 to 3.92; P=0.751), though no statistical significance was reached. On day five, 54 and 31% of patients indicated preference to buprenorphine/naloxone and buprenorphine, respectively. Fifteen percent of patients indicated that they had no preference (P value not reported). Seventy-one percent of patients also indicated that they would like to continue treatment with buprenorphine/naloxone. Patients were more likely to want to continue treatment with buprenorphine/naloxone if they had a history of injecting buprenorphine. Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache.
Strain et al[22] Buprenorphine soluble film 16 mg SL daily vs buprenorphine/naloxone soluble film 16 mg SL daily	RCT Patients 25 to 56 years of age with opioid dependence	N=34 5 days	Primary: Change in COWS scores Secondary: Pupillometry, VAS and subjective adjective rating scales and adverse	Primary: No significant differences were observed between buprenorphine and buprenorphine/naloxone with respect to baseline COWS scores (9.1 and 10.1, respectively) and peak post-administration COWS scores (4.2 and 5.7, respectively). COWS scores improved significantly at one hour after dose administration in both treatment groups compared to baseline (P values not reported). Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			events	In both treatment groups, pupil diameter decreased, rating on good effects were elevated, and ratings on bad effects and high feeling remained relatively low after dose administration (data not reported). The most common adverse events were those consistent with opioid withdrawal. Four patients reported mild non-ulcerous irritation of oral mucosa, and one patient with a history of hepatitis C had clinically significant elevation of liver function tests.
Kakko et al[23] Buprenorphine 16 mg SL daily vs buprenorphine SL six-day taper (8 mg for two days, 4 mg for two days, 2 mg for two days) followed by placebo	PC, RCT Patients >20 years of age with opioid dependence who were seeking admission for medically-assisted heroin withdrawal and who had a history of heroin dependence (as defined by the DSM-IV criteria) for at least one year	N=40 1 year	Primary: One-year retention in treatment Secondary: ASI	Primary: One-year retention was significantly higher in the buprenorphine daily group compared to the taper/placebo group (RR, 58.7; 95% CI, 7.4 to 467.4; P=0.001). Secondary: The buprenorphine daily group had a significant reduction in ASI scores over time from baseline (P<0.0001).
Woody et al[24] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by day 14 (detoxification) vs buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12	MC, RCT Patients 14 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment	N=152 12 weeks	Primary: Opioid-positive urine test results at weeks four, eight and 12 Secondary: Treatment retention rate, self-reported use, injecting, enrollment in addiction treatment outside of the study, other drug use and	Primary: General estimating equation models were used for longitudinal data analysis. When missing data were inputted as positive urine test results, patients in the two-week group were more likely to provide opioid positive urine tests than those in the 12-week group at weeks four (61 vs 26%; OR, 7.05; 95% CI, 2.87 to 17.29; P<0.001) and eight (54 vs 23%; OR, 5.07; 95% CI, 2.02 to 12.79; P=0.001) but not at week 12 (51 vs 43%; OR, 1.84; 95% CI, 0.75 to 4.49; P=0.18). Secondary: At week 12, fewer patients in the two-week group were remained in the study compared to the 12-week group (20.5 vs 70.0%; OR, 0.13; 95% CI, 0.07 to 0.26; P<0.001). The most common reason for study drop-out was

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.			adverse events	missing counseling sessions for at least two weeks. More patients in the two-week group reported use of opioid (OR, 4.30; 95% CI, 2.25 to 8.22; P<0.001), marijuana (OR, 6.15; 95% CI, 2.10 to 18.01; P=0.001), cocaine (OR, 16.39; 95% CI, 3.07 to 87.47; P<0.001) and injection (OR, 3.54; 95% CI, 1.27 to 9.87; P=0.01). Alcohol use was similar between the two groups (OR, 1.35; 95% CI, 0.66 to 2.77; P=0.42). Patients in the two-week group were also more likely to be receiving other addiction treatments (OR, 13.09; 95% CI, 3.73 to 45.89; P<0.001). The most commonly reported adverse events were headaches, nausea, insomnia, stomachache, vomiting and anxiety in both groups.
Weiss et al[25] Phase 1 Buprenorphine/naloxone induction and two-week stabilization at 8 to 32 mg/day of buprenorphine, followed by two-week taper and eight-week post medication follow-up Phase 2 buprenorphine/naloxone at 8 to 32 mg/day of buprenorphine for 12 weeks followed by four-week taper and eight-week follow-up (Phase 2) Patients who did not have successful outcome at week 12 proceeded to Phase 2.	MC, RCT Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment	Phase 1 N=653 12 weeks Phase 2 N=360 24 weeks	Primary: Percentage of patients achieving successful outcome Secondary: Adverse events	Primary: In Phase 1, successful outcome was defined by self-reported opioid use on no more than four days in a month, absence of two consecutive opioid-positive urine test results, no additional substance use disorder treatment and no more than one missing urine sample during the past 12 weeks. Overall, 43 of 653 patients (6.6%) had successful outcome with brief buprenorphine/naloxone treatment. In Phase 2, successful outcome was defined by abstinence from opioids during week 12 and at least two of the previous three weeks (during weeks nine to 11). One hundred and seventy-seven of 360 patients (49.2%) achieved successful outcome in the extended buprenorphine/naloxone treatment. However, the success rate at week 24 dropped to 8.6% (P<0.001 compared to week 12). No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling. Secondary: The most common adverse events were headache, constipation, insomnia, nasopharyngitis and nausea. Twelve and 24 serious adverse events were reported in Phase 1 and 2, respectively. Psychiatric

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients were randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.				symptoms, particularly depression leading to hospitalization (N=5), were the most common serious adverse events, all of which occurred soon after completion of treatment taper.
Polsky et al[26] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by week 2 (detoxification) vs buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.	MC, RCT Patients 15 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment	N=152 12 weeks	Primary: Treatment cost, opioid-free years, QALY, one-year direct medical cost per QALY and one-year direct medical cost per opioid-free years Secondary: Net social cost	Primary: The cost of the 12-week outpatient treatment program was $1,514 higher in the 12-week group compared to the two-week group (P<0.001). The point estimate for the incremental direct medical costs during the first year was $83 higher with the 12-week treatment (P=0.97). During the first year since the start of treatment, patients who received 12-weeks of treatment had an increase in opioid-free years by 0.27 year (P<0.001) and an increase in QALY by 0.06 year (P=0.08) compared to those who received two-week detoxification. The incremental one-year direct medical cost per QALY was $1,376 for the 12-week treatment program. The outpatient treatment program cost per QALY was $25,049. The incremental one-year direct medical cost per opioid-free year was $308, and the outpatient treatment program cost per opioid-free year was $5,610. The acceptability curve suggested that the cost-effectiveness ratio of 12-week treatment relative to two-week treatment has an 86% chance of being accepted as cost-effective for a threshold of $100,000 per QALY. Secondary: During the first year, total net social cost, which included total direct medical costs, were lower by $31,264 for the 12-week group compared to the two-week group (P=0.2).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fareed et al[27] Buprenorphine ≥16 mg/day vs buprenorphine <16 mg/day	MA (21 RCTs) Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=2,703 3 to 48 weeks	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Patients receiving the higher doses of buprenorphine had a higher treatment retention rate compared to those receiving the lower doses (69±12 vs 51±14%; P=0.006). The incidence of positive urine drug screen for opioids and cocaine was similar between the higher and lower dose groups (41±16 vs 47±13%; P=0.35, 44±13 vs 49±20%; P=0.64, respectively). Secondary: Not reported
Bickel et al[28] Buprenorphine maintenance dose (range from 4 to 8 mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours Maintenance dose was administered to patients for 13 consecutive days prior to the initiation of the above dosing schedules.	DB, PC Patients ≥18 years of age who were in good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment	N=16 Approximately 80 days	Primary: Self-report measures (i.e., VAS and adjective rating scales) and observer measures Secondary: Not reported	Primary: Overall, there were no statistically significant differences among the different dosing schedules in any of the outcome measures, including opioid agonist and withdrawal effects observed during the study (P values not reported). Significant differences were observed in some of the measures (i.e., percent identifications as placebo, percent identification as greater than maintenance dose, ARCI subscales) when comparing the daily maintenance dosing to those measures obtained 24, 48 and 72 hours following dosing schedules. Secondary: Not reported
Petry et al[29] Buprenorphine maintenance dose (ranged from 4 to 8	DB, PC, XO Patients ≥18 years of age who were in	N=14 Approximately 43 days	Primary: Subjective opioid agonist and withdrawal effects	Primary: There were no statistically significant differences among the different dosing schedules in any of the outcome measures, including subjective opioid agonist and withdrawal effects (P values not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours vs quadruple maintenance dose SL every 96 hours Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization.	good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment		Secondary: Not reported	When patients received quadrupled doses, there were no significant increases observed in opioid agonist effects compared to their usual maintenance dose (P values not reported). Subjects did report some differences in withdrawal effects (i.e., VAS, ARCI subscales) as the time between buprenorphine doses increased, but the clinical significance of these differences may be limited. Secondary: Not reported
Schottenfeld et al[30] Buprenorphine 16 mg/70 kg SL daily vs buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg SL on Tuesdays There was a three-day buprenorphine induction phase prior to randomization.	DB, RCT Patients who met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids and met the DMS-IV criteria for opioid dependence	N=92 12 weeks	Primary: Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use Secondary: Not reported	Primary: There was no difference in percentage of patients who completed the 12 weeks of treatment between the daily and thrice-weekly groups (76.6 vs 71.1%; P value not reported). There was also no statistical difference observed between the two treatment groups in the average number of weeks in treatment (11.0±4.0 and 11.2±3.7 weeks, respectively; P=0.64). A significant decline in the proportion of opioid-positive urine tests was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (57% in the daily group vs 58% in the thrice-weekly group; P=0.84). A significant decline in the number of self-reported days per week of heroin use was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (1.30±0.23 in the

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				daily group vs 1.70±0.22 in the thrice-weekly group; P=0.27). Secondary: Not reported
Gibson et al[31] Buprenorphine (dosing not specified) vs methadone (dosing not specified)	DB, MC, RCT Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic	N=405 91 day treatment period followed by a 10 year longitudinal follow-up	Primary: Effects of opioid maintenance treatment on mortality rate Secondary: Difference between two treatment groups in exposure to opioid maintenance treatment episodes greater than seven and 14 days, causes of death and effects of race, level of heroin dependence and age on mortality rate	Primary: There were 30 deaths in the follow-up period (16 in the buprenorphine group vs 14 in the methadone group). Each additional treatment episode of methadone or buprenorphine treatment lasting longer than seven days reduced the risk of death on average by 28% (95% CI, 7 to 44). Secondary: There was no significant difference over the follow-up period in percentage time exposure to opioid maintenance treatment episodes greater than seven days between the buprenorphine and methadone groups (P=0.52). The methadone group was significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days (P<0.0001).The buprenorphine group was also significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days (P<0.0001). Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths). Aboriginal or Torres Strait Islander patients had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants (95% CI, 1.89 to 14.95). The risk of death among participants using more heroin at baseline during follow-up was 12% lower (95% CI, 5 to 18; P value not reported) than less frequent heroin users at baseline. The risk of death during the follow-up period was 11% lower for older patients (95% CI, 2 to 19) than younger participants who were randomized to methadone.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Farré et al[32] Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8 mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-acetylmethadol	MA Patients seeking treatment for opioid dependence	N=1,944 (13 trials) Variable duration	Primary: Retention rate and reduction of opioid use Secondary: Not reported	Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day). Patients treated with levo-acetylmethadol had more risk of failure of retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78). Secondary: Not reported
Gowing et al[33] Buprenorphine vs methadone (five studies), α_2-adrenergic agonists (12 studies) or different buprenorphine-based regimens (five studies)	MA (22 RCTs) Patients who were withdrawing from heroin and/or methadone	N=1,736 5 to 90 days	Primary: Intensity of withdrawal, duration of withdrawal treatment, adverse events and completion of treatment, number of treatment following completion of withdrawal intervention	Primary: Overall, buprenorphine and methadone appeared to be similarly effective in the management of opioid withdrawal. Buprenorphine was shown to be more effective than clonidine in reducing withdrawal symptoms and retaining patients in withdrawal treatment. No significant differences in adverse events were found between buprenorphine and other treatments. *Buprenorphine vs methadone* Studies comparing buprenorphine to methadone reported no significant difference in withdrawal severity between the two groups. Results from two studies showed that duration of withdrawal treatment was 1.38 days shorter with buprenorphine than methadone, but this

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	difference did not reach statistical significance (95% CI, -4.27 to 1.51; P=0.35). Four studies showed no significant difference in completion of treatment between buprenorphine and methadone (RR, 1.18; 95% CI, 0.93 to 1.49; P=0.18). *Buprenorphine vs α_2-adrenergic agonists* Intensity of withdrawal was significantly lower with buprenorphine compared to clonidine in terms of both mean peak withdrawal score (SMD, -0.45; 95% CI, -0.64 to -0.25; P<0.001) and mean overall withdrawal score (SMD, -0.59; 95% CI, -0.79 to -0.39; P<0.001). In four studies, duration of withdrawal treatment was significantly shorter with buprenorphine by 0.92 day compared to clonidine (95% CI, 0.57 to 1.27; P<0.001). Completion of treatment was shown to be more likely with buprenorphine compared to clonidine in eight studies (RR, 1.64; 95% CI, 1.31 to 2.06; P<0.001; NNT, 4). *Comparison of different rates of buprenorphine taper* Two studies showed no significant difference in withdrawal severity between groups of different rates of buprenorphine dose reduction. One study showed greater patient-rated severity with the rapid taper group but no difference in observers' assessment. Another study showed that patients in the rapid taper group but not the gradual taper group reported muscle aches and insomnia. A third study showed that peak withdrawal occurred earlier with the rapid taper group. Duration of treatment was shown to be shorter with the rapid taper group than the gradual taper group (9 vs 28 days; P value not reported) but not significantly different in the other study (9.5±1.8 vs 9.8±0.9 days; P>0.05). Data were conflicting on the completion of treatment.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Johnson et al[34] Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	DB, PG, RCT Adults seeking treatment for opioid dependence	N=162 17-week maintenance phase, followed by a 8-week detoxification phase	Primary: Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04). During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%). Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03). During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids. During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%). All treatments were well tolerated, with similar profiles of self-reported adverse effects. The percentages of patients who received counseling did not differ between groups. Secondary: Not reported
Kamien et al[35] Buprenorphine/ naloxone 8 mg/2 mg daily	DB, DD, RCT Patients ≥18 years of age who met criteria for opioid	N=268 17 weeks	Primary: Amount of opioid abstinence achieved over time	Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46). Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs buprenorphine/ naloxone 16 mg/4 mg daily vs methadone 45 to 90 mg daily	dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment		Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication compliance, non-opioid illicit drug use, and treatment retention	The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine/naloxone 8 mg/2 mg) 17% (buprenorphine/naloxone 16 mg/4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine/naloxone; P<0.001, 45 vs 90 mg methadone; P=0.02), but not by drug (8 mg buprenorphine/naloxone vs 45 mg methadone; P=0.18, 16 mg buprenorphine/naloxone vs 90 mg methadone; P=0.22). Those receiving higher doses of methadone or buprenorphine/naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses. Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine/naloxone 8 mg/2 mg, buprenorphine/naloxone 16 mg/4 mg, methadone 45 and 90 mg, respectively. There were no significant differences among the treatment groups (P=0.22 to P=0.98). Medication compliance did not differ significantly among the treatment groups (P=0.41). Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83). Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28).
Meader et al[36] Buprenorphine vs methadone (three studies), clonidine (eight studies) or lofexidine* (one study)	MA (23 RCTs) Patients with opioid dependence who were undergoing opioid detoxification	N=2,112 3 to 30 days	Primary: Completion of treatment Secondary: Not reported	Primary: Buprenorphine had the highest probability (85.00%) of being the most effective treatment for opioid detoxification, followed by methadone (12.10%), lofexidine (2.60%) and clonidine (0.01%). There was no significant difference between buprenorphine and methadone (OR, 1.64; 95% CI, 0.68 to 3.79). Based on the mixed treatment comparisons, buprenorphine was more effective than clonidine (OR, 3.95; 95% CI, 2.01 to 7.46) and lofexidine (OR, 2.64; 95% CI, 0.90 to 7.50), though the latter comparison did not

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
In addition, studies involving the following comparisons were included: methadone vs clonidine (five studies), methadone vs lofexidine* (two studies) and clonidine vs lofexidine* (four studies)				reach statistical significance. Methadone was more effective than clonidine (OR, 2.42; 95% CI, 1.07 to 5.37) and lofexidine (OR, 1.62; 95% CI, 0.58 to 4.57), though the latter comparison did not reach statistical significance. Secondary: Not reported
Petitijean et al[37] Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance use Secondary: Not reported	Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001). There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001). The proportion of cocaine-positive toxicology results did not differ between groups. At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone. Secondary: Not reported
Soyka et al[38] Buprenorphine (mean daily dose 9 to 12 mg) vs methadone (mean daily dose 44 to 50 mg)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome Secondary: Not reported	Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Secondary: Not reported
Ling et al[39] Buprenorphine 8 mg daily vs methadone 30 mg daily vs methadone 80 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group and the buprenorphine group. Secondary: Not reported
Schottenfeld et al[40] Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported
Ling et al[41] Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30%	DB, MC Patients with a mean age of 36	N=736 16 weeks	Primary: Safety and efficacy as measured by retention in	Primary: Fifty-one percent of the patients completed the 16 week study. Completion rates varied by dosage group as follows: 40% for the 1 mg

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ethyl alcohol	who met the DSM-III criteria for opioid dependence and had used opioids daily during the previous six months		treatment, illicit opioid use and opioid craving Secondary: Not reported	group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group. The 16 mg group had significantly more patients with 13 consecutive negative urines than both the 1 mg group (P<0.001) and the 4 mg group (P<0.006). Significantly higher craving scores were observed for the 1 mg group compared to the 8 mg group at week four (P<0.01), eight (P<0.01) and 12 (P=0.04), but not at week 16 (P=0.15). Secondary: Not reported
Lintzeris et al[42] Buprenorphine SL tablets titrated to achieve comfortable withdrawal at the following total daily dose range: 4 to 8 mg on day 1, 0 to 16 mg on days 2 to 4, 0 to 8 mg on day 5 and 0 mg on days 6 to 8	OL Patients ≥18 years of age with opioid dependent and an opioid positive urine screen on assessment	N=18 8 days	Primary: Severity of withdrawal experience as measured by VAS Secondary: Measure of patient satisfaction with buprenorphine treatment, satisfaction with dosing regimen by Likert scale, drug use during the withdrawal episode, positive urine drug screen and adverse events	Primary: The mean expected withdrawal severity as measured by VAS was 28 at intake. The mean experienced withdrawal severity was significantly lower compared to baseline (16±12; 95% CI, -26 to -2; P<0.05). Secondary: When asked to identify positive and negative aspects of treatment, 79% of patients reported no, minimal or mild withdrawal symptoms; 57% of patients reported feeling normal and being able to perform daily activities; 36% of patients reported reduced or no cravings for heroin use; 29% of patients reported being psychologically comfortable during withdrawal; 7% of patients reported dissatisfaction with inconvenience of daily dosing; 7% of patients reported that the dosing interval was too short; 7% of patients identified sleep disturbance; 57% of patients reported side effects and 36% did not report any negative aspects of treatment. The majority of patients rated the adequacy of their doses as “about right” on the Likert scale (11 of 14 patients). Three subjects rated their doses as “too low” (P value not reported). Over the eight days of treatment, five patients (28%) reported no drug use, five patients (28%) reported drug use on one day, two patients (11%) reported drug use on two days, three patients (17%) reported drug use on

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				three or more days, and data was unavailable for the remaining three patients (P values not reported). On day five, nine patients (50% of total sample and 60% of patients in treatment) had a negative urine screen for opioids. Five patients had positive urine test results while results for one patient were missing. On days seven and eight, there were an equal number of patients with positive and negative opioid urine screens (four patients, 22% of the sample, 29% of patients in treatment). Four patients were no longer in treatment, and six reported heroin use (P values not reported). Sixteen patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation and anxiety (21%).
Kornor et al[43] Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	OL Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program	N=75 9 months	Primary: Self reported opioid abstinence in program completers and non-completers Secondary: Difference in number of days within 30 days prior to follow up interview in which the following occurred: heavy drinking, street opioid use, sedative, amphetamine, cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric	Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a difference that was not significant (7 vs 2; P=0.16). Secondary: Completers were employed for a higher number of days than non-completers at follow up (9 vs 2 days, respectively; P=0.012). There were no statistically significant differences between the two groups with regard to other psychosocial variables and substance use (P values not reported). At follow-up, 37 patients received agonist replacement therapy in the past 30 days while 31 patients did not. There was a higher rate of abstinence from street opioids in the patients who received agonist therapy (24 of 37) compared to those who did not (9 of 31; P=0.003). Patients who received agonist therapy within 30 days prior to follow-up had spent fewer days using street opioids (P<0.001), using two or more substances (P<0.038), injecting substances (P<0.007) and engaging in illegal activities (P<0.001) compared to those who did not. Patients who

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			problems and medical problems	received agonist therapy had also been employed for a higher number of days (P=0.046). There was no difference between the two groups in health problems, heavy drinking and use of sedatives, amphetamine and cannabis (P values not reported).
Fareed et al[44] Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg) vs buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg)	OS Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=77 ≥1 month	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; P=0.67). The percentage of the first four urine drug screens that were positive for opioids was higher in the high-dose group compared to the moderate-dose group (45, 14, 9 and 5 vs 29, 5, 10 and 5%, respectively; P<0.00001). No significant differences were seen between the two groups in the percentage of the first four urine drug screens positive for cocaine (P=0.74) or the last four urine drug screens positive for opioids or cocaine (P=0.21 and P=0.47, respectively). Secondary: Not reported
Assadi et al[45] Experimental protocol: Buprenorphine 12 mg IM in 24 hours vs Conventional protocol: buprenorphine taper IM over five days (3 mg for two days, 2.7 mg for one day, 1.2 mg for one day and 0.6 mg for 1 day) Authors reported that buprenorphine SL is two thirds as potent as IM, so 32	DB, PG, RCT Patients 18 to 60 years of age who met the DSM-IV criteria for opioid dependence	N=40 10 days	Primary: Days of retention in treatment and rates of successful detoxification Secondary: SOWS and OOWS	Primary: There were no significant differences among the treatment protocols in the average number of days the patients stayed in the study (experimental group, 9.5±1.8 days vs the conventional group, 9.8±0.9 days; P=0.52). There were no significant differences in the rates of successful detoxification among the treatment protocols; 18 patients (90%) in each group were detoxified successfully (P value not reported). Secondary: There was no significant difference demonstrated in mean overall SOWS scores between the two treatment protocols (experimental group, 9.0±6.6 vs the conventional group, 9.3±5.2; P=0.86). There were no significant differences found between the treatment protocols with regard to OOWS scores of the main effect of treatment (P=0.81), main effect of time (P=0.60) or treatment-time interactions

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg SL is equivalent to 18 mg IM.				(P=0.56).
Minozzi et al[46] Buprenorphine vs buprenorphine-based treatment (one study) or clonidine (one study)	SR (2 RCTs) Patients 13 to 18 years of age with opioid dependence	N=190 2 to 12 weeks	Primary: Drop-out rate, opioid-positive urine test results or self-reported drug use, tolerability and rate of relapse Secondary: Enrollment in other treatment, use of other substances of abuse, overdose, criminal activity and social functioning	Primary: The authors stated that more clinical trials, especially ones involving methadone, were needed to draw a conclusion in the detoxification treatment for opioid dependent adolescents. *Buprenorphine vs clonidine* There were no significant differences between buprenorphine and clonidine in drop-out rate (RR, 0.45; 95% CI, 0.20 to 1.04) or duration and severity of withdrawal symptoms (WMD, 3.97; 95% CI, -1.38 to 9.32). *Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* Drop-out rate and relapse rate were significantly higher with detoxification compared to maintenance treatment (RR, 2.67; 95% CI, 1.85 to 3.86; RR, 1.36; 95% CI, 1.05 to 1.76, respectively). No significant differences were seen in opioid positive urine test results (RR, 1.03; 95% CI, 0.82 to 1.28). Self-reported drug use was higher with detoxification compared to maintenance treatment (RR, 1.36; 95% CI, 1.05 to 1.76). Secondary: *Buprenorphine vs clonidine* Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55). *Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* Self-reported alcohol and marijuana use were similar between the two groups (RR, 1.13; 95% CI, 0.63 to 2.02; RR, 1.58; 95% CI, 0.83 to 3.00, respectively). More patients in the detoxification group reported use of cocaine (RR, 8.54; 95% CI, 1.11 to 65.75).
Amass et al[47] Buprenorphine/naloxone SL tablets for a total of 4/1 mg	DB, MC, OL, RCT Patients ≥15 years of age with opioid	N=234 13 days	Primary: Treatment compliance and retention	Primary: Of the 234 patients on buprenorphine/naloxone, all of the patients took the first dose, and most patients received the second dose on day one (82.9%), the doses on days two and three (90.1%) and the majority of

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
on day 1 followed by another 4/1 mg on day 1 unless the patient displayed agonist effects; escalated to 16/4 mg on day 3 and tapered by 2 mg buprenorphine/day to 2/0.5 mg by day 13	dependence who were experiencing withdrawal symptoms and who requested medical treatment for the symptoms		Secondary: Ancillary medications administration rate and adverse effects	doses over the entire treatment course (10.5±3.8 of the 13 possible doses; 80.7%). Sixty-eight percent of patients completed the entire detoxification program (P values not reported). Secondary: The majority of patients (80.3%) were treated with ancillary medications for an average of 2.3 withdrawal medications. The most commonly treated symptoms were insomnia (61.5%), anxiety and restlessness (52.1%) and bone pain and arthralgias (53.8%). Sixty-one percent of adverse events were expected events associated with drug relapse; however, the specific adverse events were not reported.
Correia et al[48] Buprenorphine/naloxone 8/2 mg SL daily vs buprenorphine/naloxone 16 mg/4 mg SL daily vs buprenorphine/naloxone 32/8 mg SL daily After two weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone.	DB, RCT Patients with active opioid dependence as confirmed through self-report, urinalysis and observation and who met DSM-IV criteria of current opioid (heroin) dependence	N=8 11 weeks	Primary: Opioid blockade and withdrawal effects Secondary: Not reported	Primary: Although substantial, all three buprenorphine doses provided incomplete blockade against opioid agonist effects for 98 hours based on the number of subjective (i.e., drug effects) and physiologic (i.e., blood pressure, heart rate) effects measured (P values for most measures were >0.05 with the exception of pupil diameter and oxygen saturation). The 32/8 mg dose produced less constricted pupils compared to the 8/2 mg dose (P≤0.05). The 8/2 mg dose produced lower oxygen saturation as compared to the 16/4 mg dose (P≤0.05). There were no significant differences regarding symptoms of withdrawal among the study doses (P>0.05). As time since the last dose increased, so did the number of mild effects reported (P value not reported). Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Maremmani et al[49] Buprenorphine vs methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life Secondary: Not reported	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients. Secondary: Not reported
Jones et al[50] Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary: Not reported	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091). The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Pinto et al[51] Buprenorphine vs methadone	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient selected substitution therapy Secondary:	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the primary factor in favorable outcomes at six months.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification. A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Fiellin et al[52] Buprenorphine/naloxone	OS Patients meeting criteria for opioid dependence	N=166 2 to 5 years	Primary: Retention in treatment; percentage of opioid-negative urine specimens Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events	Primary: During the follow-up period, 40 patients left treatment. A total of 91% of urine specimens had no evidence of illicit opioids. Secondary: Overall, 96% had no evidence of cocaine; 98% of tested urines had no evidence of benzodiazepines; 99% of tested urines had no evidence of methadone. The mean dose of buprenorphine/naloxone was 17 mg. The mean score on the patient satisfaction instruments was 86 out of a possible 95. No patients developed elevations in their aspartate aminotransferase or alanine aminotransferase values that required changes in buprenorphine/naloxone dose or discontinuation. No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the two to five-year follow-up period.
Kakko et al[53] Buprenorphine/naloxone (stepped treatment) vs	RCT Patients >20 years of age with heroin dependence for >1 year	N=96 24-day induction phase, followed by a 6 month	Primary: Retention in treatment Secondary: Completer analyses of problem severity	Primary: The 6-month retention was 78% with buprenorphine/naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60). The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
methadone (maintenance treatment)		follow-up phase	(Addiction Severity Index); proportion of urine samples free of illicit drugs	study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Strain et al[54] Buprenorphine SL tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate¸ medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively. Secondary: Not reported
Cornish et al[55] Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased 8 to 9-fold in the month immediately after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine. Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.
Strain et al[56] Buprenorphine 4 mg to 16 mg per day vs buprenorphine/naloxone SL tablets 1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg per day vs hydromorphone 2 and 4 mg intramuscular vs placebo	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine/naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine/naloxone 8/2 and 16/4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo ($P<0.05$ and $P<0.01$, respectively). The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine/naloxone doses were not statistically significant for these or any other measures. None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate. There were no significant differences in psychomotor effects among the treatments. Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bell et al[57] Buprenorphine/naloxone	RCT Heroin users seeking maintenance treatment	N=119 3 months	Primary: Retention in treatment and heroin use at three months Secondary: Not reported	Primary: At three months, 57% randomized to unobserved treatment, and 61% randomized to observed treatment were retained in the heroin treatment program (P=0.84). On an intention-to-treat analysis, reductions in days of heroin use in the preceding month, from baseline to three months, did not differ significantly; 18.5 days (95% CI, 21.8 to 15.3) and 22 days (95% CI, 24.3 to 19.7), respectively (P=0.13). Secondary: Not reported
Minozzi et al[58] Naltrexone maintenance treatment vs placebo maintenance treatment or no pharmacologic treatment or psychotherapy or benzodiazepines	MA (13 RCTs) Patients with a diagnosis of opioid dependence	N=1,158 varies	Primary: Retention in treatment, use of the primary substance of abuse, side effects and/or Secondary: Re-incarcerations	Primary: Naltrexone maintenance therapy was not statistically different for all the primary outcomes considered when compared to no pharmacological treatment. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (RR, 2.93; 95% CI, 1.66 to 5.18). There was no statically significant difference in the two outcomes considered between naltrexone and psychotherapy (one study). Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects (one study). Secondary: There was a significant difference in re-incarceration between the naltrexone maintenance group and no pharmacological treatment, RR 0.47 (95% CI, 0.26 to 0.84).
Krupitsky et al[59] Naltrexone extended-release	DB, MC, PC, RCT Patients 18 years	N=250 24 weeks	Primary: Response profile for confirmed	Primary: The median proportion of weeks of confirmed abstinence was 90.0% (95% CI, 69.9 to 92.4) in the naltrexone extended-release group

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
injection once monthly vs placebo	of age or older with a diagnosis of opioid dependence disorder		abstinence during weeks 5 to 24 Secondary: Self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence	compared with 35.0% (11.4 to 63.8) in the placebo group (P=0.0002). Secondary: Patients in the naltrexone extended-release group self-reported a median of 99.2% (range 89.1 to 99.4) opioid-free days compared with 60.4% (46.2 to 94.0) for the placebo group (P=0.0004). The mean change in craving was –10.1 (95% CI, –12.3 to –7.8) in the naltrexone extended-release group compared with 0.7 (95% CI, –3.1 to 4.4) in the placebo group (P<0.0001). Median retention was over 168 days in the naltrexone extended-release group compared with 96 days (95% CI, 63 to 165) in the placebo group (P=0.0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the naltrexone extended-release group (P<0.0001). Naltrexone extended-release was well tolerated. Two patients in each group discontinued owing to adverse events. No naltrexone extended-release-treated patients died, overdosed, or discontinued owing to severe adverse events.

*Agent not available in the United States.
Drug regimen abbreviations: IM=intramuscular, SL=sublingual
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multi-center, NNT=number needed to treat, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SMD=standard mean difference, SR=systematic review, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: ARCI=Addiction Research Center Inventory, ASI=addiction severity index, COWS=Clinical Opiate Withdrawal Scale, DSM=Diagnostic and Statistical Manual of Mental Disorders, FDA=Food and Drug Administration, OOWS=Objective Opiate Withdrawal Scale, QALY=quality-adjusted life year, SOWS=Subjective Opiate Withdrawal Scale, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1-9]

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	No difference is response was identified between elderly and younger patients; use with caution in elderly patients. Safety and efficacy in pediatric patients <16 years of age have not been established.	No dosage adjustment required.	Hepatic dose adjustment may be required; effects of hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment	C	Yes (% unknown).
Naltrexone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly patients in order to determine whether they respond differently than younger subjects; no elderly subjects were included in clinical trials for the treatment of opioid dependence; use with caution in elderly patients. Safety and efficacy in pediatric patients <18 years of age have not been established.	Dose adjustment is not required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Use in moderate or severe renal impairment or those on hemodialysis has not been evaluated; use caution as the primary mode of excretion is via the urine.	Dose adjustment is not required in patients with mild to moderate hepatic impairment (Child-Pugh groups A and B). Use in severe hepatic impairment has not been evaluated.	C	Yes (% unknown).
Naloxone	Reported clinical experience has not indicated differences in response to naloxone; however, clinical studies of	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown.

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	naloxone have not included sufficient amounts of patients aged 65 years and older to determine whether clinical response in geriatric patients is different from younger patients. FDA-approved for use in children <18 years of age.				
Combination Product					
Buprenorphine/naloxone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly patients in order to determine whether they respond differently than younger subjects; use with caution in elderly patients. Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required for buprenorphine. Naloxone is not studied in renal dysfunction.	Hepatic dose adjustment may be required; effects of hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment	C	Yes (% unknown).

Adverse Drug Events

The adverse events of buprenorphine, buprenorphine/naloxone (tablets, film), naloxone and naltrexone are summarized in Table 6. Adverse effects for naloxone have generally been voluntarily reported. As such, there is no accurate method to provide their frequency, or to determine if naloxone can be implicated as a causative agent for the events reported. Adverse reactions that have been reported in the post-operative setting are listed below. Additionally, excessive doses of naloxone have been reported to cause agitation, nausea and vomiting.[61,62]

Table 6. Adverse Drug Events[1-7]

Adverse Event (%)	Single Entity Agents			Combination Product	
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Body as a Whole					
Agitation	-	-	a	-	-
Anxiety	-	>10%		-	-
Appetite loss	-	<10%		-	-
Asthenia	4.9	-		6.5	-
Attention disturbances	-	-	-	-	a
Chills	7.8	<10%		7.5	-
Coma	-	-	a	-	-
Death	-	-	a	-	-
Delayed ejaculation	-	<10%		-	-
Energy decreased	-	>10%		-	-
Energy increased	-	<10%		-	-
Depression	-	<10%		-	-
Headache	29.1	>10%		36.4	-
Infection	11.7	-		5.6	-
Intoxication	-	-		-	a
Irritability	-	<10%		-	-
Pain	18.4	-		22.4	-
Pain, abdomen	11.7	>10%		11.2	-
Pain, back	7.8	-		3.7	-
Pain, joint	-	>10%		-	-
Pain, muscle	-	>10%		-	-
Thirst increased	-	<10%		-	-
Withdrawal syndrome	18.4	a		25.2	a
Cardiovascular System					
Cardiac arrest	-	-	a	-	-
Hypertension	-	-	a	-	-
Hypotension	-	-	a	-	-
Palpitation	-	-		-	a
Vasodilation	3.9	-		9.3	-
Ventricular fibrillation	-	-	a	-	-
Ventricular tachycardia	-	-	a	-	-
Digestive System					
Constipation	7.8	<10%		12.1	a
Diarrhea	4.9	<10%		3.7	-
Nausea	13.6	a	a	15	-
Vomiting	7.8	>10%	a	7.5	a
Local Administration Site					
Glossodynia	-	-		-	a
Oral hypoesthesia	-	-		-	≥1
Oral mucosal erythema	-	-		-	a
Nervous System					
Blurry vision	-	-		-	a
Encephalopathy	-	-	a	-	-
Insomnia	21.4	>10%		14	a
Seizure	-	-	a	-	-

Adverse Event (%)	Single Entity Agents			Combination Product	
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Respiratory System					
Dyspnea	-	-	a	-	-
Rhinitis	9.7	-		4.7	-
Pulmonary edema	-	-	a	-	-
Skin & Appendages					
Skin rash	-	<10%		-	-
Sweating	12.6	-		14	a

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-9]

Contraindication	Single Entity Agents			Combination Product
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/ Naloxone
Hypersensitivity to the active ingredient or to any component.	a	a	a	a
Patients currently dependent on opioids (physiologic), including patients who are receiving maintenance therapy with opiate agonists or partial agonists		a		
Patients that has failed the naloxone challenge test		a		
Patients that has a positive urine drug screen for opioids		a		
Patients in acute opioid withdrawal		a		
Patients receiving opioid analgesics		a		

Warnings/Precautions

Table 8. Warnings and Precautions[1-9]

Warning or Precaution	Single Entity Agents			Combination Product
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/Naloxone
Abdominal conditions, acute; diagnosis or clinical course of acute abdominal conditions may be obscured with use.	a	a (Vivitrol®)		a
Abuse potential; can be abused similar to opioids, use precautions to minimize risk of misuse, abuse or diversion; do not prescribe multiple refills during early treatment.	a			a
Alcohol withdrawal symptoms are not eliminated or diminished with use.		a (Vivitrol®)		
Allergic reactions; bronchospasm, angioneurotic edema, and aphylactic shock has been associated with use.	a			a
Central nervous system depression;	a			a

Warning or Precaution	Single Entity Agents			Combination Product
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/Naloxone
concurrent use other central nervous system depressants may exhibit increased central nervous system depression; consider dose reduction of one or both in situations of concomitant prescription.				
Cerebrospinal fluid pressure elevated; use caution in patients with head injury, intracranial lesions or when cerebrospinal pressure may be elevated.	a			a
Dependence; chronic administration produces physical dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper.	a			a
Depression and suicide has been reported when used for opioid dependence.		a		
Duration of action of most opioids is likely to exceed that of naloxone resulting in a return of respiratory and/or central nervous system depression after initial improvement.			a	
Eosinophilic pneumonia has been associated with use; consider when processive dyspnea and hypoxemia develop.		a (Vivitrol®)		
Hepatitis, hepatic events; cases of cytolytic hepatitis with jaundice have been reported; baseline and periodic monitoring of liver function during treatment is recommended.	a	a		a
Impairment of ability to drive or operate machinery; use caution in driving or operating hazardous machinery until stabilized.	a			a
Injection site reactions (mild to very severe); accidental subcutaneous injection may increase the risk for severe reactions.		a (Vivitrol®)		
Intracholedochal pressure increased; use with caution with biliary tract dysfunction.	a			a
Limited efficacy with reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as; reversal may be incomplete.			a	
Neonatal withdrawal has been reported in infants of women treated during pregnancy, often occurs from day one to eight of life.	a			a
Opioid detoxification (ultra-rapid);		a		

Warning or Precaution	Single Entity Agents			Combination Product
	Buprenorphine	Naltrexone	Naloxone	Buprenorphine/Naloxone
safety has not been established.				
Opioid naïve patients; deaths have been reported when used for analgesia; do not use as an analgesic.	a			a
Opioid overdose vulnerability; use likely to have reduced tolerance to opioids after use and thus respond to lower doses then previously; use caution if restarting opioid therapy.		a		
Opioid withdrawal; may occur in individuals physically dependent on full opioid agonists before the effects of the full opioid agonist has subsided.	a	a	a	a
Orthostatic hypotension may occur.	a			a
Pediatric exposure; accidental exposure can cause severe, life-threatening respiratory depression.	a			a
Respiratory depression and death has been associated with use when used with central nervous system depressants; use caution in patients with compromised respiratory function.	a			a
Special populations; administer with caution in debilitated patients, patients with myxedema or hypothyroidism, adrenal cortical insufficiency, central nervous system depression or coma, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens or kyphoscoliosis	a			a
Surmountable effect of antagonistic effects when a large dose of opioids are administered.		a		
Use with caution in patients with thrombocytopenia or any coagulation disorder (due to intramuscular injection).		a		

Drug Interactions

Table 9. Drug Interactions[1-9]

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	Barbiturate anesthetics (methohexital, thiamylal, thiopental)	The dose of anesthetic required to induce anesthesia may be reduced, increasing the likelihood of apnea.
Buprenorphine	Benzodiazepines	Concomitant administration results in an increased risk of sedation and life-threatening respiratory depression, especially with over dosage.
Buprenorphine	CYP3A4 Inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)	Increased effects of buprenorphine

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	CYP3A4 Inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin)	Decreased effects of buprenorphine
Buprenorphine	Non-nucleotide reverse transcriptase inhibitors	Significant reactions involving CYP3A4 inducers (efavirenz, nevirapine, etravirine) and CYP3A4 inhibitors (delavirdine) have been shown, however there was no significant pharmacodynamic effect.
Naltrexone	Opioid-continuing products (analgesics, antidiarrheals, cough and cold remedies)	Antagonistic effect decreases effectiveness of opioid containing products.
Naloxone	Clonidine	Hypotensive and bradycardic effects of clonidine may be reduced; monitor for hypertension.
Naloxone	Yohimbine	An increase in adverse effects such as anxiety, hot and cold flashes, increased plasma cortisol levels, nausea, nervousness, and palpitations may result.

Dosage and Administration

Table 10. Dosing and Administration[1-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction†: Sublingual tablet: initial, 8 mg on day one followed by 16 mg on day two Opioid dependence, treatment maintenance†: Sublingual tablet: maintenance progressive dose adjustment of 2 to 4 mg, general range of 4 to 24 mg per day	Safety and efficacy in children <16 years of age have not been established.	Sublingual tablet: 2 mg 8 mg
Naltrexone	Alcohol dependence: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider Tablet: 50 mg once daily for up to 12 weeks Opioid dependence‡: Tablet: initial, 25 mg once daily; if no withdrawal symptoms occur, increase to 50 mg once daily thereafter Opioid dependence, prevention of relapse following opioid detoxification: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every	Safety and efficacy in children <18 years of age have not been established.	Suspension for injection, extended-release: 380 mg Tablet: 50 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	four weeks by a healthcare provider		
Naloxone	Opioid overdose: Auto-injector: 0.4 via intramuscular or subcutaneous injection into the anterolateral aspect of the thigh once, repeat 0.4 mg after two to three minutes, if necessary Prefilled syringe, vial: 0.4 to 2 mg intravenously or via intramuscular or subcutaneous injection once, may repeat after two to three minutes, if necessary	Opioid overdose: Auto-injector: 0.4 mg via intramuscular or subcutaneous injection once, may repeat after two to three minutes Prefilled syringe, vial: 0.1 mg/kg intravenously (age <5 years) once, 2 mg (age 5 to 18 years) intravenously once, may repeat after two to three minutes	Auto-injector solution (Evzio®): 0.4 mg/0.4 mL Prefilled syringe, solution: 0.4 mg/mL 2 mg/2 mL Vial, solution 0.4 mg/mL
Combination Product			
Buprenorphine/ naloxone	Opioid dependence, treatment induction†: Sublingual film (Suboxone®): 8/2 mg sublingually on day one, followed by 16/4 mg sublingually on day two Opioid dependence, treatment maintenance †: Buccal film (Bunavail®): maintenance (after induction with buprenorphine sublingual tablets), target dose of 8.4/1.4 mg buccally once daily dose adjusted by 2.1/0.3 mg at a time to adequate response, normal range is 2.1/0.3 mg to 12.6/2.1 mg once daily Sublingual film (Suboxone®): maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time to adequate response, normal range is 4/1 mg to 24/6 mg once daily Sublingual tablet: maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time to adequate response, normal range is 4/1 to 24/6 mg once daily Sublingual tablet (Zubsolv®): maintenance (after induction with buprenorphine sublingual tablets), target dose of 11.4/2.9 mg sublingually once daily dose adjusted	Safety and efficacy in children <16 years of age have not been established.	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 2.9/0.71 mg 5.7/1.4 mg 8.6/2.1 mg 11.4/2.9 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	by 1.4/0.36 mg or 2.8/0.72 mg at a time to adequate response, normal range is 2.8/0.72 mg to 17.1/4.2 mg once daily		

† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§ Indication is for ReVia® only.
‖Indiction is for Vivitrol® only.
¶ Indication is for Suboxone® only.

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
United States Substance Abuse and Mental Services Center for Substance Abuse Treatment: **Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (2004)**[13]	· Buprenorphine/naloxone should be used for the induction, stabilization and maintenance phases of treatment for most patients. · Induction doses should be administered as observed treatment; however, subsequent doses may be obtained with a prescription. · In most patients, buprenorphine/naloxone can be used for induction. If buprenorphine monotherapy is used, patients should be transitioned to buprenorphine/naloxone after no more than two days of treatment. If buprenorphine monotherapy is to be used for extended periods, the number of doses to be prescribed should be limited, and the use of the monotherapy formulation should be justified in the medical record. · Buprenorphine/naloxone or buprenorphine should only be used in patients dependent on long-acting opioids who have evidence of sustained medical and psychosocial stability in conjunction with opioid treatment programs. In these patients, buprenorphine monotherapy should be utilized during the induction phase to avoid precipitation of withdrawal. · For patients taking methadone, the methadone dose should be tapered to £30 mg/day for at least one week and patients should have taken their last dose of methadone [3] 24 hours prior to initiating buprenorphine induction. The first dose of buprenorphine should be 2 mg of the monotherapy formulation. If a patient develops signs or symptoms of withdrawal after the first dose, a second dose of 2 mg should be administered and repeated as needed to a maximum of 8 mg of buprenorphine on day one. The decision to transfer a patient, exhibiting withdrawal symptoms, from methadone at doses >30 mg/day to buprenorphine should be based on a physician's judgment as there is insufficient data in this patient population. · Patients who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid were at least 12 to 24 hours prior, should be inducted using buprenorphine/naloxone. Patients should receive a first dose of 4/1 to 8/2 mg of the buprenorphine/naloxone combination. If the initial dose of the combination treatment is 4/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after two hours, a second dose of 4/1 mg may be administered. The total amount of buprenorphine administered in the first day should not exceed 8 mg. · If patients do not exhibit withdrawal symptoms after the first day of induction, the patient's daily dose should be equivalent to the total

Clinical Guideline	Recommendations
	amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be subsequently increased in 2g/0.5 to 4 /1 mg increments daily, if needed for symptomatic relief, with a target dose of 12/3 to 16/4 mg per day within the first week. · Patients experiencing withdrawal symptoms on day two should receive an initial dose of buprenorphine/naloxone equivalent to the total amount of buprenorphine administered on day one plus 4/1 mg (maximum initial dose of 12/3 mg). If withdrawal symptoms are still present two hours after the dose, an additional 4 mg/1 mg dose can be administered. The total dose on day two should not exceed 16/4 mg. Continue dose increases on subsequent days as needed. · The stabilization phase begins when patients are free of withdrawal symptoms and cravings. Most patients will stabilize on daily doses of 16/4 to 24/6 mg; however, doses up to a maximum of 32/8 mg daily may be required in some patients. · During stabilization, patients receiving maintenance treatment should be seen at least weekly. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, less frequent visits (biweekly or monthly) may be an option. Toxicology tests for illicit drugs should be administered at least monthly. · The longest phase of treatment is the maintenance phase which may be indefinite. Decisions to decrease or discontinue buprenorphine should be based on a patient commitment to being medication-free and on physician judgment. · Patients treated for opioid withdrawal should receive psychosocial therapy (e.g., individual or group counseling, self-help programs, and patient monitoring) and have their medical comorbidities managed effectively. · Buprenorphine monotherapy may be used for medically supervised withdrawal. · Detoxification in short-acting opioid addiction can be rapid (three days), moderate (10 to14 days) or long term (indefinite). Buprenorphine long term therapy may be more effective than rapid detoxification from short-acting opioid abuse. · In pregnant women, methadone is currently the standard of care; however, if this option is unavailable or refused by the patient, buprenorphine may be considered as an alternative. Although the Suboxone® and Subutex® product information advises against use in breast-feeding, the effects on the child would be minimal and buprenorphine use in breast-feeding is not contraindicated in this patient population. · In adolescents and young adults, buprenorphine is a useful option; however, the practitioner should be familiar with the state laws regarding parental consent. · In geriatric patients, the literature is lacking; however, due to differences in metabolism and absorption, additional care should be exercised when treating these patients. · In instances of polysubstance abuse, buprenorphine may not have a beneficial effect on the use of other drugs. Extra care should be employed in patients who abuse alcohol or benzodiazepines due to the potentially fatal interactions with buprenorphine. · Patients who need treatment for pain but not for addiction should be treated within the context of a medical or surgical setting and should not

Clinical Guideline	Recommendations
	be transferred to an opioid maintenance program just because they have become physically dependant throughout the course of medical treatment. · Pain, in patients receiving buprenorphine for opioid addiction, should be treated with short-acting opioid pain relievers and buprenorphine should be held. Sufficient time for these medications to be cleared must be allowed before restarting the buprenorphine. Patients with chronic severe pain may not be good candidates for buprenorphine because of the ceiling effect. · In patients recently discharged from controlled environments, intensive monitoring is required, and treating physicians may be called upon to verify and explain treatment regimens, to document patient compliance and to interact with the legal system, employers, and others. These patients may be candidates for buprenorphine treatment even if there is no current opioid abuse. The lowest dose possible of buprenorphine/naloxone should be used (2/0.5 mg). · Opioid addiction in health care professionals requires specialized, extended care since opioid addiction is an occupational hazard.
Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[14]	<u>General considerations</u> · Opioid agonist treatment is the first-line treatment for chronic opioid dependence. · Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. · Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy. · By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. <u>Opioid agonist treatment program and office-based opioid treatment</u> · Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. · Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. · The usual dosage range for optimal effects is 60 to 120 mg/day. · Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. · In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. <u>Methadone therapy</u> · Methadone for the treatment of opioid dependence may only be prescribed out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. · For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg didn't reduce withdrawal · Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of

Clinical Guideline	Recommendations
	exogenously administered opioids. Buprenorphine therapy · Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. · Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. · In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. · The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. · The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.
American Psychiatric Association: **Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)**[15]	Treating dependence and abuse · Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation. · The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. · Maintenance treatment with methadone or buprenorphine is appropriate for patients with ³ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy. · Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence. · Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in: o Decreasing illicit opioid use. o Decreasing psychosocial and medical morbidity. o Improving overall health status. o Decreasing mortality. o Decreasing criminal activity. o Improving social functioning. o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users. · Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients. · Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor. · Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor. · Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form.

Clinical Guideline	Recommendations
	· The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability. · Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression Treating intoxication · Mild to moderate opioid intoxication usually does not require specific therapy. · Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations. Treating withdrawal · Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program. · Effective strategies include: o Substitution of opioid with methadone or buprenorphine. o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms. o Clonidine-naltrexone detoxification.

Conclusions

Buprenorphine, buprenorphine/naloxone and naltrexone are treatment options for opioid dependent patients who are unable or unwilling to receive clinic-based methadone treatment. Naloxone alone is used for the treatment of opioid overdose. Buprenorphine is available as a sublingual tablet, and buprenorphine/naloxone is available as sublingual tablet and film. Naltrexone is available as a tablet or extended-release suspension for injection. Naloxone alone is available as a solution in vials or prefilled syringes and also in an auto-injector device. Buprenorphine and buprenorphine/naloxone sublingual tablets naltrexone tablets, and naloxone vials and syringes are currently available generically.[1-9] Physicians prescribing buprenorphine for opioid dependency in an office-based treatment setting are required to complete a training program as outlined in the Drug Addiction Treatment Act of 2000.[18] Evzio® (naloxone injection) is designed to be administered by laypersons in the presence of a patient with an apparent opioid overdose. Two injections are provided in each package of Evzio® (naloxone injection), should the patient require a second injection before emergency medical services arrive.

Results of clinical trials vary, but generally buprenorphine and buprenorphine/naloxone are considered equally effective and significantly improve outcomes compared to placebo when used for opioid withdrawal.[20-30,341-48] A meta-analysis evaluated naltrexone compared to non-therapy, and found no significant difference in outcomes. However, when considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with RR of 2.93 (95% CI, 1.66 to 5.18).[58] The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group.[59]

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Therapeutic Class Overview
Opioid-Induced Constipation Agents

Therapeutic Class Overview/Summary:
There are currently three agents approved by the Food and Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC). Lubiprostone (Amitiza®), methylnaltrexone bromide (Relistor®), naloxegol oxalate (Movantik®) are indicated for the treatment of OIC in adults with chronic non-cancer pain. Additionally, methylnaltrexone bromide is also FDA-approved for use in adults with OIC who have advanced illness and are receiving palliative care.[1-3] While lubiprostone is also indicated for the treatment of chronic idiopathic constipation, and irritable bowel syndrome with constipation, those indications will not be covered in this review. Opioids are an effective and widely used treatment option to help control many different types of pain. Constipation, which can sometimes be severe, is a common side-effect of opioid use and may limit their acceptability.[4] The cause of constipation associated with opioid use is thought to occur due to multiple etiologies. One factor is the ability of opioids to bind to the μ- and δ-opioid receptors found on smooth muscle within the gastrointestinal tract. This decreases peristalsis in the small intestine and colon by relaxing the intestinal smooth muscles and preventing normal bowel elimination functions. In addition, opioids are thought to interfere with normal fluid and electrolyte levels within the gastrointestinal lumen due to this longer gastrointestinal transit time that causes excessive water and electrolyte reabsorption from feces.[5]

Agents used for the treatment of OIC work via one of two mechanisms. Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating the chloride channel-2 (CIC-2), which is a normal constituent of the apical membrane of the human intestine. By increasing intestinal fluid secretion, lubiprostone increases motility of the intestine, thereby increasing the passage of stool and alleviating symptoms of constipation.[1] Methylnaltrexone bromide and naloxegol oxalate are selective μ-opioid antagonists that prevent the peripheral activation of μ-opioid receptors in certain tissues, such as the gastrointestinal tract, thus reducing the constipation side-effect. At therapeutic doses, neither agent interferes with the analgesic activity of opioids, which is caused by activation of μ-opioid receptors within the central nervous system (CNS).[2-3] Methylnaltrexone bromide is a quaternary amine, which increases its polarity, and helps prevents its penetration into the CNS.[2] Naloxegol oxalate is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). The presence of a polyethylene glycol (PEG) moiety reduces its passive permeability into the CNS while being a substrate for P-gp increases efflux of naloxegol across the blood-brain barrer.[3]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Lubiprostone (Amitiza®)	Chronic Idiopathic constipation; opioid-induced constipation in chronic non-cancer pain, Irritable Bowel Syndrome with Constipation	Capsule: 8 μg 24 μg	-
Methylnaltrexone bromide (Relistor®)	Opioid-induced constipation in chronic non-cancer pain, Opioid-induced constipation in advanced illness	Prefilled Syringe: 8 mg/0.4 mL 12 mg/0.6 mL Vial, single-use: 12 mg/0.6 mL	-
Naloxegol oxalate (Movantik®)	Opioid-induced constipation in advanced illness	Tablet: 12.5 mg 25 mg	-

Evidence-based Medicine

- The efficacy of lubiprostone for the treatment of OIC was in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three 12-week, randomized, double-blinded, placebo-controlled studies. In all three studies, patients had documented opioid-induced constipation at baseline, defined as having less than three spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Use of rescue laxatives was allowed in cases where no bowel movement had occurred in a 3-day period. At baseline, mean oral morphine equivalent daily doses (MEDDs) for the three studies were 99 mg and 130 mg, 237 mg and 265 mg, and 330 mg and 373 mg for placebo-treated and lubiprostone -treated patients, respectively.[1,6,7] Studies one and two have bene published, while study three remains unpublished. The primary endpoint of study one was the "overall responder" rate, defined as ≥1 SBM improvement over baseline frequency were reported for all treatment weeks for which data were available and ≥3 SBMs/week were reported for at least 9 of 12 treatment weeks. There was a statistically significant difference in favor of lubiprostone when compared to placebo for overall responder rate (27.1% compared with 18.9%; treatment difference, 8.2%; P=0.030). The primary endpoint of studies two and three was the mean change from baseline in SBM frequency at week eight. For study two, there was a statistically significant difference in changes from baseline in SBM frequency in favor of lubiprostone when compared to placebo (3.3 compared with 2.4; treatment difference, 0.9; P=0.004). However, in the unpublished study three, there was not a statically significant difference in the mean change from baseline in SBM frequency at week eight between lubiprostone and placebo groups (2.7 compared to 2.5; treatment difference -0.2; P=0.76).[1]
- The efficacy of methylnaltrexone bromide for the treatment of OIC was established in two clinical trials in patients with advanced illness receiving palliative care and one study in patients with chronic non-cancer pain.[2,8,9] All studies were double-blind, placebo-controlled studies that compared methylnaltrexone 0.15 mg/kg and/or 0.3 mg/kg subcutaneously to placebo. The primary endpoint of the first study was the proportion of patients with a rescue-free laxation within four hours after a single dose of study medication or placebo. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within four hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); P<0.0001 for each dose compared with placebo.[2,8] The second study evaluated the same primary end-point and found similar results. In this study the proportion of patients who had rescue-free laxation within four hours after receiving the first dose of the study drug was significantly higher in the methylnaltrexone bromide group than the placebo group (48% compared with 15%, respectively; P<0.001). In addition, the proportion of patients who had rescue-free laxation within four hours after receiving two or more of the first four doses was significantly higher in the methylnaltrexone bromide group compared to placebo (52% compared with 8%, respectively; P<0.001).[2,9] The safety and efficacy of methylnaltrexone bromide for the treatment of OIC in patients with chronic non-cancer pain was evaluated in an unpublished study with results reported only in the FDA-approved package insert. The primary endpoint was the proportion of patients with greater than three spontaneous bowel movements (SBMs) per week during the four-week double-blind period. The results from this study showed that 59% of individuals in methylnaltrexone were found to have at least three SBMs per week compared to 38% in the placebo group (P<0.001).[2]
- The efficacy of naloxegol oxalate for the treatment of OIC in adults receiving opioids for chronic noncancer-related pain was evaluated in two phase III trials. Both studies were identically designed multicenter, randomized, double-blind, placebo-controlled, 12 week trials that evaluated naloxegol 12.5 mg and 25 mg compared to placebo. In both of the trials, the primary efficacy outcome was the rate of response over weeks one through 12 (defined as ≥ SBMs/week and an increase from baseline of ≥ one SBM per week for at least nine of 12 weeks and at least three out of the last four weeks). Results from these two studies revealed that naloxegol 25 mg provided a statistically significant improvement over placebo for the primary outcome (P=0.001 and P=0.02, respectively); however, naloxegol 12.5 mg showed statistical significance only in the first study (P=0.02 and P=0.2, respectively).[3,10]

Key Points within the Medication Class

- There is limited current clinical guidance that address lubiprostone or the μ-opioid antagonists' place in therapy for OIC:[5,11-14]
    - Most, existing guidelines were published prior to approval of these agents or are only briefly mentioned.[12-14]
    - Generally well-established bowel regimens are recommended for an initial case of OIC. This may include a scheduled dose of a stimulant laxative such, as bisacodyl or senna, with or without a stool-softener, such as docusate. Alternatively, daily administration of an osmatic laxative such as lactulose or polyethylene glycol may be used.[5,11,12]
    - All laxatives are potential options and there is no data to suggest that any one approach is superior to any other.
    - The limited guidance that exists regarding the newer agents suggest that they are effective treatment options, but should be reserved for refectory cases of OIC only.[5,11-14]

- Other Key Facts:
    - There are currently no generic products available.
    - Lubiprostone and naloxegol oxalate are available as oral dosage forms.

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Therapeutic Class Review
Opioid-Induced Constipation Agents

Overview/Summary

There are currently three agents approved by the Food and Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC). Lubiprostone (Amitiza®), methylnaltrexone bromide (Relistor®), naloxegol oxalate (Movantik®) are indicated for the treatment of OIC in adults with chronic non-cancer pain. Additionally, methylnaltrexone bromide is also FDA-approved for use in adults with OIC who have advanced illness and are receiving palliative care.[1-3] While lubiprostone is also indicated for the treatment of chronic idiopathic constipation, and irritable bowel syndrome with constipation, those indications will not be covered in this review. Opioids are an effective and widely used treatment option to help control many different types of pain. Constipation, which can sometimes be severe, is a common side-effect of opioid use and may limit their acceptability.[4] The cause of constipation associated with opioid use is thought to occur due to multiple etiologies. One factor is the ability of opioids to bind to the μ- and δ-opioid receptors found on smooth muscle within the gastrointestinal tract. This decreases peristalsis in the small intestine and colon by relaxing the intestinal smooth muscles and preventing normal bowel elimination functions. In addition, opioids are thought to interfere with normal fluid and electrolyte levels within the gastrointestinal lumen due to this longer gastrointestinal transit time that causes excessive water and electrolyte reabsorption from feces.[5]

Agents used for the treatment of OIC work via one of two mechanisms. Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating the chloride channel-2 (CIC-2), which is a normal constituent of the apical membrane of the human intestine. By increasing intestinal fluid secretion, lubiprostone increases motility of the intestine, thereby increasing the passage of stool and alleviating symptoms of constipation.[1] Methylnaltrexone bromide and naloxegol oxalate are selective μ-opioid antagonists that prevent the peripheral activation of μ-opioid receptors in certain tissues, such as the gastrointestinal tract, thus reducing the constipation side-effect. At therapeutic doses, neither agent interferes with the analgesic activity of opioids, which is caused by activation of μ-opioid receptors within the central nervous system (CNS).[2-3] Methylnaltrexone bromide is a quaternary amine, which increases its polarity, and helps prevents its penetration into the CNS.[2] Naloxegol oxalate is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). The presence of a polyethylene glycol (PEG) moiety reduces its passive permeability into the CNS while being a substrate for P-gp increases efflux of naloxegol across the blood-brain barrer.[3]

Methylnaltrexone bromide subcutaneous injection became the first agent FDA-approved for the treatment of OIC in April of 2008, which was later expanded to include patients with OIC and have chronic non-cancer pain. Lubiprostone capsules became the first oral agent for the treatment of opioid-induced constipation in April of 2013. In September 2014, naloxegol oxalate became the most recent agent to be approved by the FDA for OIC and is the first oral peripheral μ-opioid receptor antagonist approved for that indication.[1-3] There is limited current clinical guidance that address lubiprostone or the μ-opioid antagonists' place in therapy for OIC.[5,11-14] Most, existing guidelines were published prior to approval of these agents or are only briefly mentioned.[12-14] Generally well-established bowel regimens are recommended for an initial case of OIC. This may include a scheduled dose of a stimulant laxative such, as bisacodyl or senna, with or without a stool-softener, such as docusate. Alternatively, daily administration of an osmatic laxative such as lactulose or polyethylene glycol may be used.[5,11,12] All laxatives are potential options and there is no data to suggest that any one approach is superior to any other. The limited guidance that exists regarding the newer agents suggest that they are effective treatment options, but should be reserved for refectory cases of OIC only.[5,11-14] There are currently no generic products available.

Medications

Table 1. Medications Included Within Class Review[1-3]

Generic Name (Trade name)	Medication Class	Generic Availability
Lubiprostone (Amitiza®)	Laxative (CIC-2 chloride channel activator)	-
Methylnaltrexone bromide (Relistor®)	Peripheral μ-opioid receptor antagonist	-
Naloxegol oxalate (Movantik®)	Peripheral μ-opioid receptor antagonist	-

CIC-2=chloride channel-2

Indications

Table 2. Food and Drug Administration Approved Indications[1-3]

Indications	Lubiprostone	Methylnaltrexone bromide	Naloxegol oxalate
Chronic idiopathic constipation in adults	a		
Irritable bowel syndrome with constipation (IBS-C) in adult women	a		
Opioid-induced constipation in adults with chronic non-cancer pain	a *	a	a
Opioid-induced constipation in adults with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient		a	

*Efficacy of lubiprostone in the treatment of OIC in patients taking diphenylheptane opioids (e.g. methadone) has not been established

Pharmacokinetics

Table 3. Pharmacokinetics[1-3]

Generic Name	Absorption	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Lubiprostone	Low*	Not Reported	Not reported	Unable to determine
Methylnaltrexone bromide	C_{max}: 0.5 hours; AUC: increased proportionally with dose	53.6	Yes†	8
Naloxegol oxalate	C_{max}: <2 hours‡ AUD: increased proportionally with dose	16	Not evaluated§	6 to 11

C_{max}: Time to maximum concentration
*Following oral administration, concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL)
†Three of five distinct metabolites of methylnaltrexone exhibit μ-opioid receptor antagonist activity (methyl-6α-naltrexol and methyl-6β-naltrexol are active at the μ-opioid receptor; methylnaltrexone sulfate is a weak μ-opioid receptor antagonist)
‡A second peak in concentration was observed at 0.4 to 3 hours after first peak
§The activity of the six metabolites of naloxegol at the μ-opioid receptor has not been determined.

Clinical Trials

The safety and efficacy of agents used for the treatment of opioid-induced constipation have been evaluated in a number of clinical trials.[1-3,6-10] Clinical trials that evaluate these agents for other diagnoses will not be covered in this review.

The efficacy of lubiprostone for the treatment of OIC was in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three 12-week, randomized, double-blinded, placebo-controlled studies. In

all three studies, patients had documented opioid-induced constipation at baseline, defined as having less than three spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Use of rescue laxatives was allowed in cases where no bowel movement had occurred in a 3-day period. At baseline, mean oral morphine equivalent daily doses (MEDDs) for the three studies were 99 mg and 130 mg, 237 mg and 265 mg, and 330 mg and 373 mg for placebo-treated and lubiprostone -treated patients, respectively.[1,6,7] Studies one and two have bene published, while study three remains unpublished. The primary endpoint of study one was the "overall responder" rate, defined as ≥1 SBM improvement over baseline frequency were reported for all treatment weeks for which data were available and ≥3 SBMs/week were reported for at least 9 of 12 treatment weeks. There was a statistically significant difference in favor of lubiprostone when compared to placebo for overall responder rate (27.1% compared with 18.9%; treatment difference, 8.2%; P=0.030). The primary endpoint of studies two and three was the mean change from baseline in SBM frequency at week eight. For study two, there was a statistically significant difference in changes from baseline in SBM frequency in favor of lubiprostone when compared to placebo (3.3 compared with 2.4; treatment difference, 0.9; P=0.004). However, in the unpublished study three, there was not a statically significant difference in the mean change from baseline in SBM frequency at week eight between lubiprostone and placebo groups (2.7 compared to 2.5; treatment difference -0.2; P=0.76).[1]

The efficacy of methylnaltrexone bromide for the treatment of OIC was established in two clinical trials in patients with advanced illness receiving palliative care and one study in patients with chronic non-cancer pain.[2,8,9] All studies were double-blind, placebo-controlled studies that compared methylnaltrexone 0.15 mg/kg and/or 0.3 mg/kg subcutaneously to placebo. The primary endpoint of the first study was the proportion of patients with a rescue-free laxation within four hours after a single dose of study medication or placebo. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within four hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); P<0.0001 for each dose compared with placebo.[2,8] The second study evaluated the same primary end-point and found similar results. In this study the proportion of patients who had rescue-free laxation within four hours after receiving the first dose of the study drug was significantly higher in the methylnaltrexone bromide group than the placebo group (48% compared with 15%, respectively; P<0.001). In addition, the proportion of patients who had rescue-free laxation within four hours after receiving two or more of the first four doses was significantly higher in the methylnaltrexone bromide group compared to placebo (52% compared with 8%, respectively; P<0.001).[2,9] The safety and efficacy of methylnaltrexone bromide for the treatment of OIC in patients with chronic non-cancer pain was evaluated in an unpublished study with results reported only in the FDA-approved package insert. The primary endpoint was the proportion of patients with greater than three spontaneous bowel movements (SBMs) per week during the four-week double-blind period. The results from this study showed that 59% of individuals in methylnaltrexone were found to have at least three SBMs per week compared to 38% in the placebo group (P<0.001).[2]

The efficacy of naloxegol oxalate for the treatment of OIC in adults receiving opioids for chronic noncancer-related pain was evaluated in two phase III trials. Both studies were identically designed multicenter, randomized, double-blind, placebo-controlled, 12 week trials that evaluated naloxegol 12.5 mg and 25 mg compared to placebo. In both of the trials, the primary efficacy outcome was the rate of response over weeks one through 12 (defined as ≥ SBMs/week and an increase from baseline of ≥ one SBM per week for at least nine of 12 weeks and at least three out of the last four weeks). Results from these two studies revealed that naloxegol 25 mg provided a statistically significant improvement over placebo for the primary outcome (P=0.001 and P=0.02, respectively); however, naloxegol 12.5 mg showed statistical significance only in the first study (P=0.02 and P=0.2, respectively).[3,10]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jamal et al[6] Lubiprostone 24 µg BID vs placebo BID A one-time dose reduction to lubiprostone 24 µg QD was allowed due to adverse events. Rescue medication could be used if there was no SBM in a three day period.	DB, MC, PC, PG, RCT Male and non-pregnant females ≥18 years of age, stable opioid dose for ≥30 days, diagnosis of OIC as well as one or more of the following characteristics during each screening week: hard or very hard stools, sensation of incomplete evacuation, or moderate to very severe straining	N=431 12 weeks	Primary: Overall SBM response rate Secondary: Change from baseline in SBM frequency at weeks 8, 12, and overall; weekly responder rates; percentage of patients with a first SBM within 24 and 48 hours postdose; and HRQOL (PAC-QOL and EQ-5D scores), mean change from baseline for straining associated with SBMs, stool consistency, constipation severity, abdominal bloating, and abdominal discomfort	Primary: Overall responders were defined as reporting at least moderate response (≥1 SBM improvement over baseline frequency) for all treatment weeks for which observed data were available, as well as a full response (additional ≥3 SBMs per week) for at least 9 of the 12 treatment weeks. Significantly more patients were overall SBM responders throughout the 12-week treatment period in the lubiprostone group than in the placebo group (27.1% [58/214] vs 18.9% [41/217], respectively; P=0.030). Secondary: The percentage of weekly SBM responders was significantly greater in the lubiprostone group compared with the placebo group at weeks one and four (P<0.05) and was numerically greater, but not statistically significant at all other weeks. Mean changes from baseline in SBM frequencies were significantly greater with lubiprostone compared with placebo overall (P=0.001) and at 9 of the 12 treatment weeks (P≤0.040). Patients treated with lubiprostone had significantly more SBMs within 24 (P=0.008) and 48 (P=0.007) hours after the first dose relative to placebo. Median time to first SBM was significantly shorter with lubiprostone vs placebo (23.5 vs 37.7 hours, respectively; P=0.004), with a significantly higher proportion of patients treated with lubiprostone reporting their first SBM within 4, 8, 12, 24, and 48 hours of the first dose (P≤0.009). Baseline PAC-QOL and EQ-5D scores were comparable for the placebo and lubiprostone treatment groups. There were no significant differences observed over the 12-week treatment period in PAC-QOL and EQ-5D measures between the placebo and lubiprostone treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Statistically significant improvements, were observed in patients treated with lubiprostone vs placebo in straining, stool consistency, and constipation severity (P=0.004, P<0.001, and P=0.010, respectively). Numerical differences favoring lubiprostone were observed between the treatment groups for abdominal bloating and abdominal discomfort; however, the differences did not reach statistical significance.
Cryer et al[7] Lubiprostone 24 µg BID vs placebo BID A one-time dose reduction to lubiprostone 24 µg QD was allowed due to adverse events. Rescue medication could be used if there was no SBM in a three day period.	DB, MC, PC, PG, RCT Male and non-pregnant females ≥18 years of age, stable opioid dose for ≥30 days, diagnosis of OIC as well as one or more of the following characteristics during each screening week: hard or very hard stools, sensation of incomplete evacuation, or moderate to very severe straining	N=418 12 weeks	Primary: Change from baseline in the frequency of SBMs at week eight Secondary: Changes from baseline in the frequency of SBMs at week 12 and overall, percentage of patients with the first postdose SBM within 24 and 48 hours of administering study drug, and overall responder rates, patient-assessed overall treatment effectiveness and overall mean change from baseline in constipation-	Primary: The change from baseline in SBM frequency was significantly greater with lubiprostone compared with placebo at week eight for patients in the ITT population who did not have a dose reduction by week eight (mean, 3.3 vs 2.4 SBMs/week, P=0.005). Secondary: The overall change from baseline in SBM frequency was also significantly greater with lubiprostone compared with placebo (mean, 2.2 vs 1.6 SBMs/week, P=0.004); however, at week 12, the difference numerically favored lubiprostone, but did not reach statistical significance. A significantly greater percentage of patients treated with lubiprostone compared with placebo achieved their first SBM within 24 (P=0.018) and 48 (P=0.050) hours after administration of the first dose of study medication. Although the median time to first SBM in patients treated with lubiprostone was reduced by almost half compared with that of placebo (28.5 vs 46.0 hours, respectively), the difference between treatment groups did not reach statistical significance (P=0.053). Based on patient self-assessments recorded in diary entries, pairwise comparisons showed improvements that significantly favored lubiprostone over placebo for abdominal discomfort (P=0.024), straining (P<0.001), constipation severity (P=0.007), and stool consistency (P<0.001). Patients reported, on average, a change in stool consistency from hard at baseline to approximately normal after lubiprostone treatment. Abdominal bloating and bowel habit regularity were not significantly improved with lubiprostone compared with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			associated symptoms, bowel habits, and stool consistency	placebo; however, there was a slightly larger improvement from baseline in the bowel habit regularity score with lubiprostone (−0.6) compared with placebo (−0.5). Patient ratings of overall treatment effectiveness were significantly better for lubiprostone compared with placebo at all postbaseline time points (P<0.001 to P=0.024) except week three.
Slatkin et al[8] (abstract) Methylnaltrexone 0.15 mg/kg SC x1 dose vs methylnaltrexone 0.3 mg/kg SC x1 dose vs placebo	DB, MC, PC, RCT Patients receiving palliative opioid therapy and had opioid induced constipation	N=154 Single dose	Primary: The proportion of patients with a rescue-free laxation within four hours of the double-blind dose of study medication Secondary: Not reported	Primary: Methylnaltrexone-treated patients had a significantly higher rate of laxation within four hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); P<0.0001 for each dose compared with placebo. Secondary: Not reported
Thomas et al[9] Methylnaltrexone 0.15 mg/kg to 0.30 mg/kg SC QOD vs placebo Other laxatives were allowed as needed, though not within four hours before or after receiving a	DB, MC, PC, RCT Patients ≥ 18 years of age with a terminal disease (life expectancy of one month or more) with a diagnosis of OIC, received opioids for two weeks or more	N=133 2 weeks	Primary: Proportion of patients with rescue-free laxation within four hours after the first study dose of the study drug and the proportion of patients with rescue-free laxation within four hours after	Primary: The proportion of patients who had rescue-free laxation within four hours after receiving the first dose of the study drug was significantly higher in the methylnaltrexone group than the placebo group (48% compared with 15%, respectively; P<0.001). The proportion of patients who had rescue-free laxation within four hours after receiving two or more of the first four doses was significantly higher in the methylnaltrexone group compared to (52% compared with 8%, respectively; P<0.001). Secondary: In the methylnaltrexone group, 24 patients (39%) had rescue-free laxation within four hours after four or more of seven doses during a 13-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
study dose.	and a stable regimen of opioids and laxatives for three or more days before study entry, either fewer than three laxations during the preceding week and no clinically meaningful laxation within 24 hours before the first study dose or no clinically meaningful laxation within 48 hours before the first study dose		two or more of the first four doses Secondary: Proportion of patients with rescue-free laxation within four hours after four or more of seven doses, the proportion of patients with rescue-free laxation within four or 24 hours after each dose, the proportion of patients with three or more laxations per week, the time to laxation, overall pain scores, and symptoms of opioid withdrawal	day period, as compared with four patients in the placebo group (6%) (P<0.001). After each study dose (dose two through seven), there was a significant difference in the proportion of patients that had rescue-free laxation within four hours which favored the methylnaltrexone group compared to placebo (P<0.005 for each dose). During the double-blind study, 79% of the methylnaltrexone group and 46% of the placebo group had a laxation response within four hours after one or more doses (no P value reported). Rescue-free laxation within 24 hours after each of the seven doses occurred in 55 to 66% of the methylnaltrexone group and in 29 to 39% of the placebo group. There was a significant difference between treatment groups for doses one through four (P<0.05); however, there was no statistically significant difference for doses five through seven (no P value reported). The proportion of patients with three or more rescue-free laxations per week was significantly higher in the methylnaltrexone group than in the placebo group (68% compared with 45%, respectively; P=0.009). The time to laxation after the first dose for patients in the methylnaltrexone group was four hours or less, with half responding within 30 minutes. Among all patients, the median time to laxation after the first dose was 6.3 hours in the methylnaltrexone group and more than 48 hours in the placebo group (P<0.001). The shorter time to laxation in the methylnaltrexone group persisted for each of the seven doses (P<0.002 for all comparisons). Patients in the two study groups had similar mean pain scores at baseline and at each evaluation, with minimal changes over time (no P values reported). Scores on the Modified Himmelsbach Withdrawal Scale remained stable throughout the study for both treatment groups (no P value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chey et al[10] Naloxegol 12.5 mg QD vs naloxegol 25 mg QD vs placebo QD Bisacodyl then enema were allowed as rescue medication.	DB, MC, PC, PG, RCT Patients 18 to 85 years of age receiving 30 to 1,000 mg per day of oral morphine equivalents for ≥ four weeks before enrollment for noncancer-related pain	N=652 12 weeks	Primary: 12-week response rate (≥ 3 SBMs per week and an increase from baseline of ≥ 1 SBMs per week for ≥ 9 of 12 weeks and for ≥ 3 of the final 4 weeks) Secondary: Response rate in the sub-population of patients with an inadequate response to laxatives before enrollment, time to first postdose SBM and change from baseline for mean number of days per week with at least one SBM but no more than three SBMs	Primary: There was a statistically significant difference in response rates for the naloxegol 25 mg group as compared to placebo (44.4% and 29.4% respectively; P=0.001).There was also a statistically significant difference in response rates for the naloxegol 12.5 mg group as compared to placebo (40.8% and 29.4% respectively; P=0.02). Secondary: A total of 55% of patients from the sample group were predefined as the laxative inadequate response (LIR) subgroup. The use of daily laxatives was reported by 42% of this subgroup while 31% of this subgroup reported the use of two laxative classes anytime during the 14 days prior to enrollment. A higher percentage of patients in this LIR subgroup responded with naloxegol 12.5 mg compared to placebo (43% vs 29%; P=0.03) and with naloxegol 25 mg compared to placebo (49% vs 29%; P=0.002). There was a shorter time to the first postdose SBM and a higher mean number of days per week with ≥ 1 SBM observed with the naloxegol 25 mg group compared to the placebo group (P<0.001). In addition, there was a shorter time to the first postdose SBM and a higher mean number of days per week with ≥ 1 SBM observed with the naloxegol 12.5 mg group compared to the placebo group (P<0.001). The median times to first postdose SBM were 6, 20, and 36 hours with naloxegol 25 mg, naloxegol 12.5 mg and placebo, respectively. There was a significant difference in number of days per week with one to three SBMs per day on average over 12 weeks between naloxegol 25 mg and placebo (P<0.001), but not with the naloxegol 12.5 mg group.
Chey et al[10] Naloxegol 12.5 mg QD	DB, MC, PC, PG, RCT	N=700 12 weeks	Primary: 12-week response rate (≥	Primary: There was a significantly higher response rate with the naloxegol 25 mg group compared with placebo (39.7% and 29.3% respectively;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs naloxegol 25 mg QD vs placebo QD Bisacodyl then enema were allowed as rescue medication.	Patients 18 to 85 years of age receiving 30 to 1,000 mg per day of oral morphine equivalents for ≥ four weeks before enrollment for noncancer-related pain		3 SBMs per week and an increase from baseline of ≥ 1 SBM per week for ≥ 9 of 12 weeks and for ≥ 3 of the final four weeks) Secondary: Response rate in the sub-population of patients with an inadequate response to laxatives before enrollment, time to first postdose SBM and change from baseline for mean number of days per week with at least 1 SBM but no more than 3 SBMs	P=0.02). There was not found to be a significant difference in the response rate for the naloxegol 12.5 mg group compared with placebo (34.9% and 29.3% respectively; P=0.20). Secondary: A total of 53% of patients from the sample group were predefined as the laxative inadequate response (LIR) subgroup. The use of daily laxatives was reported by 50% of the subgroup whereas 27% reported the use of two laxative classes anytime during the 14 days prior to enrollment. A higher percentage of patients in this LIR subgroup responded with naloxegol 25 mg compared to placebo (47% vs 31%; P=0.01). This secondary endpoint was not tested for naloxegol 12.5 mg versus placebo since the primary endpoint was not statistically significant. There was a shorter time to the first postdose SBM and a higher mean number of days per week with ≥ 1 SBM observed with the naloxegol 25 mg group compared to the placebo group (P<0.001) but not with the naloxegol 12.5 mg group. The median times to first postdose SBM were 12 and 37 hours with naloxegol 25 mg and placebo, respectively. There was a significant difference in number of days per week with one to three SBMs per day on average over 12 weeks between naloxegol 25 mg and placebo (P<0.001) and the naloxegol 12.5 mg group and placebo (P<0.01).

Drug regimen abbreviations: BID=twice daily, QD=once daily, QOD=every other day, SC=subcutaneous
Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: BM=bowel movement, EQ-5D=EuroQoL-5 dimension, HRQOL=health related quality of life, ITT=intention-to-treat, LIR=laxative inadequate response, OIC=opioid-induced constipation, PAC-QOL=Patient Assessment of Constipation-Quality of Life, SBM=spontaneous bowel movement

Special Populations

Table 5. Special Populations[1-3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Lubiprostone	Clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether elderly patients respond differently from younger patients. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment is required in patients with renal impairment	Starting dose should be reduced in patients with moderate or severe dysfunction (Child-Pugh class B or C). No dose adjustment require for mild hepatic dysfunction (Child-Pugh class A).	C	Unknown; use with caution
Methylnaltrexone bromide	No overall differences in safety or effectiveness were observed between elderly patients and younger patients. Safety and effectiveness in pediatric patients have not been established.	Reduce dose by one half in patients with severe renal dysfunction (CrCl <30 mL/min). No dosage adjustment required for mild or moderate renal dysfunction (CrCl ≥30 mL/min).	No dose adjustment require for mild or moderate hepatic dysfunction. No dosing guidelines for patients with severe hepatic dysfunction.	C	Unknown; use with caution
Naloxegol oxalate	No overall differences in safety or effectiveness were observed between elderly patients and younger patients. Safety and effectiveness in pediatric patients have not been established.	Reduce dose to 12.5 mg once daily if the patient has a CrCl <60 mL/min. No dose adjustment required for CrCl ≥60.	No dose adjustment require for mild or moderate hepatic dysfunction. Not evaluated in severe hepatic dysfunction.	C	Unknown; use with caution

Adverse Drug Events

Table 6. Adverse Drug Events[1-3]

Adverse Event (%)	Lubiprostone	Methylnaltrexone bromide	Naloxegol oxalate
Abdominal distension	3	-	-
Abdominal pain	4	21 to 29	12 to 21
Chills	-	1	-
Diarrhea	8	6	6 to 9
Dizziness	-	7	-
Flatulence	4	13	3 to 6
Headache	2	-	4
Hot Flashes	-	3	-
Hyperhidrosis	-	6	<1 to 3
Nausea	11	9 to 12	7 to 8
Vomiting	3	-	3 to 5

-Adverse event not reported or ≤1%

Contraindications

Table 7. Contraindications[1-3]

Contraindications	Lubiprostone	Methylnaltrexone bromide	Naloxegol oxalate
Concomitant use of strong CYP3A4 inhibitors			a
Gastrointestinal obstruction, known or suspected, and patients at an increased risk of recurrent obstruction; gastrointestinal perforation may occur		a	a
Hypersensitivity to the active drug or any excipient			a
Mechanical gastrointestinal obstruction, known or suspected	a		

CYP=cytochrome P450

Warnings/Precautions

Table 8. Warnings and Precautions[1-3]

Warnings/Precautions	Lubiprostone	Methylnaltrexone bromide	Naloxegol oxalate
Cases of gastrointestinal perforation have been reported in adult patients; monitor for development of severe, persistent, or worsening abdominal pain		a	a
Confirm the absence of an obstruction prior to initiating therapy	a		
Diarrhea has been reported; do not prescribe to patients that have severe diarrhea; use is not recommended in patients that experience severe diarrhea	a	a	
Dyspnea has been reported; use with caution	a		
Nausea has been reported; take with food to reduce symptoms	a		
Symptoms of opioid withdrawal have been reported; monitor for appropriate analgesia and withdrawal symptoms		a	a

Drug Interactions

No *in vivo* drug interactions have been reported with lubiprostone.[1]

Table 7. Drug Interactions[1-3]

Generic Name	Interacting Medication or Disease	Potential Result
Methylnaltrexone bromide, naloxegol oxylate	Other opioid antagonist	Potential additive effect and increased risk for opioid withdrawal.
Naloxegol oxylate	Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)	Increased plasma concentration of naloxegol; increased risk of adverse events. Concurrent use is contraindicated.
Naloxegol oxylate	Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil)	Increased plasma concentration of naloxegol; increased risk of adverse events. Avoid use of moderate CYP3A4 inhibitors if possible. If unavoidable, reduce naloxegol oxylate dose to 12.5 mg once daily and monitor for adverse reactions.
Naloxegol oxylate	Grapefruit or grapefruit juice	Can increase plasma concentration of naloxegol; avoid consumption of grapefruit or grapefruit juice during treatment with naloxegol oxylate.
Naloxegol oxylate	Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort)	Significantly decreases plasma concentration of naloxegol and may decrease efficacy; use with strong CYP3A4 inducers is not recommended

CYP=cytochrome P450

Dosage and Administration

Table 8. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Lubiprostone	Chronic Idiopathic constipation; opioid-induced constipation in chronic non-cancer pain: Capsule: 24 µg BID with food and water* Irritable Bowel Syndrome with Constipation: Capsule: Initial: 8 µg BID with food and water*	Safety and effectiveness in pediatric patients have not been established.	Capsule: 8 µg 24 µg
Methylnaltrexone bromide	Opioid-induced constipation in chronic non-cancer pain: Injection: 12 mg SC QD Opioid-induced constipation in advanced illness: Injection: 8 mg SC QOD PRN (38 kg to <62 kg), 12 mg SC QOD PRN (62 kg to 114 kg), 0.15 mg/kg SC QOD PRN (<38 kg or >114 kg)	Safety and effectiveness in pediatric patients have not been established.	Prefilled Syringe: 8 mg/0.4 mL 12 mg/0.6 mL Vial, single-use: 12 mg/0.6 mL
Naloxegol oxylate	Opioid-induced constipation in advanced illness: Tablet: Initial, 25 mg QD in the morning; may decrease to 12.5 mg if unable to tolerate 25 mg dose	Safety and effectiveness in pediatric patients have not been established.	Tablet: 12.5 mg 25 mg

Drug regimen abbreviations: BID=twice daily, QD=once daily, QOD=every other day, PRN=as needed
*Initial dose may be reduced in patients with impaired hepatic function.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network (NCCN): **NCCN clinical practice guidelines in oncology: palliative care (2013)**[12]	Constipation · If constipation is present: o Assess for cause and severity of constipation o rule out impaction, especially if diarrhea accompanies constipation (overflow around impaction) o Rule out obstruction (physical exam, abdominal x-ray, consider GI consult) o Treat other causes (e.g., hypercalcemia, hypokalemia, hypothyroidism, diabetes mellitus, medications o Add and titrate bisacodyl 10 to 15 mg daily to three times a day with a goal of one non-forced bowel movement every one to two days o If impacted § Administer glycerine suppository ± mineral oil retention enema § perform manual disimpaction following pre-medication with analgesic ± anxiolytic · If constipation persists: o Reassess for cause and severity of constipation o recheck for impaction or obstruction o consider adding other laxatives, such as bisacodyl (one suppository rectally daily or twice daily), polyethylene glycol (1 capful/8 oz water twice daily); lactulose (30 to 60 mL twice to four times a day), sorbitol, magnesium hydroxide, magnesium citrate o consider methylnaltrexone for opioid-induced constipation (0.15 mg/kg subcutaneously every other day, no more than once daily) o Tap water enema until clear o Consider use of a prokinetic agent (e.g., metoclopramide 10 to 20 mg four times a day)
American Gastroenterological Association (AGA): **Medical Position Statement on Constipation (2013)**[13]	· After discontinuing medications, when appropriate, that can cause constipation and performing blood and other tests as guided by clinical features, a therapeutic trial (i.e., fiber supplementation and/or osmotic or stimulant laxatives) is recommended. · If inadequate response, an anorectal manometry balloon expulsion test can be done. If normal but colonic transit is slow or normal consider laxatives (i.e., PEG, milk of magnesia (MOM), bisacodyl). · A newer agent, such as lubiprostone or linaclotide, should be considered when symptoms do not respond to laxatives. · Pelvic floor retraining by biofeedback therapy rather than laxatives is recommended for defecatory disorders (improves symptoms in more than 70% of patients). · Anorectal tests and colonic transit should be reevaluated when symptoms persist despite an adequate trial of biofeedback therapy. · Suppositories or enemas rather than oral laxatives alone should be considered in patients with refractory floor dysfunction (weak recommendation).
World Gastroenterology Organization	General approach and step-therapy · First-line recommendation: o Changes in lifestyle and diet are recommended.

Clinical Guideline	Recommendations
(WGO): **Constipation: a Global Perspective (2010)**[14]	o If appropriate, stop or reduce constipation-inducing medications. o Addition of fiber supplementation or bulking agents (except in patients with chronic dilation) is recommended. o Gradual increase in fiber and fluid intake is recommended. · Second-line recommendation: o Use of osmotic laxatives (with the best evidence for use of PEG, but there is also good evidence for lactulose). o Lubiprostone and linaclotide act by stimulating ileal secretion and thus increasing fecal water. · Third-line recommendation: o Use of stimulant laxatives (such as bisacodyl, sodium picosulfate or senna for occasional use), enemas, or prokinetic agents (can be used daily).

Conclusions

There are currently three agents approved by the FDA for the treatment OIC, lubiprostone (Amitiza®), methylnaltrexone bromide (Relistor®), and naloxegol oxalate (Movantik®). Each has been approved for the treatment of OIC in adults with chronic non-cancer pain. Additionally, methylnaltrexone bromide is also FDA-approved for use in adults with OIC who have advanced illness and are receiving palliative care.[1-3] Lubiprostone is also indicated for the treatment of chronic idiopathic constipation, and irritable bowel syndrome with constipation. Agents used for the treatment of OIC work via one of two mechanisms. Lubiprostone is a locally acting chloride channel activator that increases intestinal fluid secretion, which increases motility of the intestine, thereby increasing the passage of stool and alleviating symptoms of constipation.[1] Methylnaltrexone bromide and naloxegol oxalate are selective μ-opioid antagonists that prevent the peripheral activation of μ-opioid receptors in certain tissues, such as the gastrointestinal tract, thus reducing the constipation side-effect. At therapeutic doses, neither agent interferes with the analgesic activity of opioids, which is caused by activation of μ-opioid receptors within the central nervous system (CNS).[2-3] Methylnaltrexone bromide is a quaternary amine, which increases its polarity, and helps prevents its penetration into the CNS.[2] Naloxegol oxalate is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). The presence of a polyethylene glycol (PEG) moiety reduces its passive permeability into the CNS while being a substrate for P-gp increases efflux of naloxegol across the blood-brain barrer.[3]

Lubiprostone capsules and naloxegol oxylate tablets are oral agents taken every day scheduled. Lubiprostone is administered twice daily; while naloxegol is administered once daily. Methylnaltrexone bromide is a subcutaneous injection administered every other day as needed. The safety and efficacy of agents used to treat OIC have been established in a number of clinical trials.[1-3,6-10] There is limited current clinical guidance that address lubiprostone or the μ-opioid antagonists' place in therapy for OIC.[5,11-14] Most, existing guidelines were published prior to approval of these agents or are only briefly mentioned.[12-14] Generally well-established bowel regimens are recommended for an initial case of OIC. All laxatives are potential options and there is no data to suggest that any one approach is superior to any other. The limited guidance that exists regarding the newer agents suggest that they are effective treatment options, but should be reserved for refectory cases of OIC only.[5,11-14] Naloxegol oxylate is associated with several severe drug-interactions, which may limit its use.[3] There are currently no generic products approved for the treatment of OIC.

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Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

On March 11, 2014, the FDA approved a new combination product Xartemis XR® (oxycodone/acetaminophen), which contains oxycodone and acetaminophen. It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[24]

Hysingla ER® (hydrocodone ER) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some extended-release properties after tampering. Attempts to

dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[1] In addition, the tablets appear to be associated with less "drug liking" based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of non-dependent recreational opioid users.[25] The abuse deterrent properties of Hysingla ER® (hydrocodone extended-release) is a potential strength of the formulation, as well as once daily dosing and demonstrated efficacy in the treatment of chronic pain. Potential weaknesses of Hysingla ER® (hydrocodone extended-release) include the high cost relative to generic long-acting opioid formulations, the high degree of subjects' willingness to take milled Hysingla ER® (hydrocodone extended-release) tablets again via oral ingestion in a clinical abuse potential study and the drug interaction that exists between Hysingla ER® (hydrocodone extended-release) and "strong laxatives" which many patients on chronic opioid treatment require.

The current formulation of OxyContin® (oxycodone ER) utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[26-28] When subjected to small volumes of an aqueous environment, oxycodone ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.[26] In addition, a crushed formulation of oxycodone ER was rated lower than the crushed formulation of the original OxyContin® (oxycodone ER) and oxycodone powder when administered intranasally. There were also more reports of intranasal irritation with the reformulated oxycodone ER.[27,28]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[29] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third extended-release opioid analgesic to obtain this designation and the first among the morphine extended-release products.[30] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[3] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[30]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	a
Hydrocodone	The management of pain severe enough to	Capsule, extended	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Hysingla ER®, Zohydro ER®)	require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	release (Zohydro ER®): 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡	
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡	a
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg Tablet for oral suspension: 40 mg	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		release: 10 mg 20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¶	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	a #
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	a
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		100 mg/4 mg‡	
Oxycodone/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, extended release: 7.5 mg/325 mg	-

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone ER 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[4,31]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[32-34]
- A trial comparing hydrocodone ER capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone ER had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (P<0.0001).[35]
- In one trial, hydromorphone ER demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[36] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[37]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[38,39]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[39] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[41]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[29]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[42]

- Oxycodone ER has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[43-45] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[46]
- Oxymorphone ER has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain.[47,48] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER from morphine sulfate or oxycodone ER. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[47] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[49]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol ER compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[50] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol ER and oxycodone ER relative to placebo (P<0.001).[51] Schwartz et al evaluated tapentadol ER among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[52]
- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (*P*<0.0001).[53]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole.
  - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine.[55,56]
  - Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[56]

- Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock ER or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain.[55]
- Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.[55,56]
- In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[55]
- Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.[55]
- Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.[55]
- In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.[55,56]

· Other Key Facts:
- There are currently four abuse deterrent formulations of extended-release, long acting opioids approved by the FDA. These include oxycodone ER (OxyContin®), morphine sulfate/naltrexone (Embeda) and two hydrocodone ER products (Zohydro ER® and Hysingla ER®).
- All long-acting opioids are pregnancy category C, with the exception of oxycodone.
- Only fentanyl transdermal system is approved in children (age 2 to 17 years).
- Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
- Only oxymorphone is contraindicated in severe hepatic disease.
- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) and Hysingla ER (hydrocodone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]
- Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven. Fentanyl may be applied to the chest, back, flank or upper arm while buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1,2]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16

French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER® (hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,14-16]

- Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

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Therapeutic Class Review
Long-acting Opioids

Overview/Summary

As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms. Several agents are currently available as a generic product.

Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

On March 11, 2014, the FDA approved a new combination product oxycodone/acetaminophen (Xartemis XR®). It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[24]

Hysingla ER® (hydrocodone ER) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some extended-release properties after tampering. Attempts to dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[1] In addition, the tablets appear to be associated with less “drug liking” based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of

non-dependent recreational opioid users.[25] The abuse deterrent properties of Hysingla ER® (hydrocodone extended-release) is a potential strength of the formulation, as well as once daily dosing and demonstrated efficacy in the treatment of chronic pain. Potential weaknesses of Hysingla ER® (hydrocodone extended-release) include the high cost relative to generic long-acting opioid formulations, the high degree of subjects' willingness to take milled Hysingla ER® (hydrocodone extended-release) tablets again via oral ingestion in a clinical abuse potential study and the drug interaction that exists between Hysingla ER® (hydrocodone extended-release) and "strong laxatives" which many patients on chronic opioid treatment require.

The current formulation of OxyContin® (oxycodone ER) utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[26-28] When subjected to small volumes of an aqueous environment, oxycodone ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.[26] In addition, a crushed formulation of oxycodone ER was rated lower than the crushed formulation of the original OxyContin® (oxycodone ER) and oxycodone powder when administered intranasally. There were also more reports of intranasal irritation with the reformulated oxycodone ER.[27,28]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[29] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third extended-release opioid analgesic to obtain this designation and the first among the morphine extended-release products.[30] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[3] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[30]

Medications

Table 1. Medications Included Within Class Review[1-18]

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine (Butrans®)	Opiate partial agonist	-
Fentanyl (Duragesic®*)	Opioid agonist	a
Hydrocodone (Hysingla ER®, Zohydro ER®)	Opioid agonist	-
Hydromorphone (Exalgo®*)	Opioid agonist	a
Methadone (Dolophine®*, Methadose®*, Methadone Intensol®*)	Opioid agonist	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	Opioid agonist	a
Oxycodone (OxyContin®*)	Opioid agonist	a †
Oxymorphone (Opana® ER*)	Opioid agonist	a
Tapentadol (Nucynta ER®)	Opioid agonist	-
Combination Products		
Morphine sulfate/naltrexone (Embeda®)	Opioid agonist/opioid antagonist	-
Oxycodone/acetaminophen (Xartemis XR®)	Opioid agonist/analgesic, antipyretic	-

*Generic is available in at least one dosage form or strength.
†Generic availability is sporadic and does not include all strengths.

Indications

Table 2. Food and Drug Administration Approved Indications[1-18]

Generic Name	Indications
Single Entity Agents	
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.§
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Combination Products	
Morphine sulfate/ naltrexone	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡
Oxycodone/ acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†Avinza® 90 mg and 120 mg capsules and Kadian® /MS Contin 100 mg and 200 mg capsules/tablets are only for use in patients who are tolerant to opioids.
§OxyContin® 60 mg and 80 mg tablets or a single dose >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.
‡Embeda® 100 mg/4 mg capsules are only for use in patients who are tolerant to opioids.

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental

Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). Regulatory exceptions to the general requirement for certification to provide opioid agonist treatment include the following the situations: during inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07[c], to facilitate the treatment of the primary admitting diagnosis), and during an emergency period of no longer than three days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07[b]).[6-10]

Pharmacokinetics

Table 3. Pharmacokinetics[1-18,31,32]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Buprenorphine	15	27	Norbuprenorphine	26
Fentanyl	92	75 as metabolites; <7 to 10 as unchanged	None reported	20 to 27
Hydrocodone	Not specified†	6.5%*	Norhydrocodone, hydromorphone	7 to 9
Hydromorphone	24	75; 7 as unchanged	Unknown	11
Methadone	36 to 100	Not specified	None reported	7 to 59
Morphine sulfate	<40	90; 2 to 12 unchanged	Morphine-6-glucuronide	1.5 to 15.0
Oxycodone	60 to 87	19 unchanged; 50 conjugated oxycodone; 14 or less conjugated oxymorphone	Noroxycodone, oxymorphone	4.5 to 8.0
Oxymorphone	10	<1 unchanged; approximately 39 major metabolites	None reported	7.25 to 9.43
Tapentadol	32	99; 70 conjugated; 3 unchanged drug	None reported	4 to 5
Combination Products				
Morphine sulfate/ naltrexone	<40 (morphine sulfate); highly variable (naltrexone)	90; 2 to 12 unchanged (morphine sulfate and metabolites); not reported (naltrexone)	Morphine-6-glucuronide (morphine sulfate)/ 6-β-naltrexol (naltrexone)	29
Oxycodone/ acetaminophen	60 to 87/APAP not reported	19 unchanged; 50 conjugated/<9	Noroxycodone, oxymorphone/none	4.5 ± 0.6/ 5.8 ± 2.1

APAP=acetaminophen
*Data for Hysingla ER®: 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively. Data for Zohydro ER® not specified.
†In a single-center, randomized, cross over study in 24 healthy subjects, the bioavailability was similar to an equivalent daily hydrocodone dose as the listed drug, Vicoprofen® (hydrocodone bitartrate/ibuprofen) over a 24-hour period

Clinical Trials

As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of noncancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain is available. Clinical trials demonstrating the effectiveness and safety of the long-acting opioids are outlined in Table 4. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in adverse event profiles and associated improvements in quality of life or sleep domains.[33-78]

Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Five hundred eighty-eight patients who were not responsive to their prior analgesic therapy were randomized into the study after up to 45 days of an open-label conversion and dose-titration period. Patients received either hydrocodone ER tablets or matching placebo in a 1:1 ratio. Those patients randomized to placebo were given a blinded taper of hydrocodone ER tablets according to a prespecified tapering schedule, three days on each step-down dose (reduced by 25 to 50% from the previous dose). Patients were allowed to use rescue medication (immediate-release oxycodone 5 mg) up to six doses (six tablets) per day depending on their randomized hydrocodone ER dose. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178, P=0.0016). Treatment with hydrocodone ER tablets resulted in a higher proportion of responders which was defined as patients with at least a 30% and 50% improvement (P=0.0033 and P=0.0225 for 30% and 50% respectively). Additionally, there was significant improvements in Patient's Global Impression of Change (PGIC) scores as compared with placebo (P=0.0036). There was, however, no significant improvement in Medical Outcome Study Sleep Scale – Revised (MOS Sleep-R).[4,33] A second study (open-label and extension) confirmed the safety and effectiveness of hydrocodone ER tablets found with the previous clinical trial over a long-term therapy (at least one year).[34]

FDA approval of buprenorphine transdermal system was based on four unpublished, 12-week double-blind clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. The description of these trials has been obtained from the prescribing information and the manufacturer product dossier. Two of these four trials demonstrated efficacy in patients with chronic low back pain. In one trial (N=1,160), treatment with buprenorphine transdermal system resulted in significant treatment differences in the average pain score over the last 24 hours at week 12 in favor of transdermal buprenorphine 20 µg/hr and oxycodone immediate-release compared to buprenorphine 5 µg/hr (P<0.001 for both). In the second trial (N=1,024), treatment with either 10 or 20 µg/hr of buprenorphine transdermal system resulted in a treatment difference in favor of buprenorphine (95% confidence interval [CI], -1.02 to -0.14; P=0.01) compared to placebo. Two other trials failed to show efficacy for buprenorphine transdermal system in patients with low back pain and osteoarthritis, respectively. In the first trial (N=134), treatment with either buprenorphine 5, 10, or 20 µg/hr or a combination of oxycodone and acetaminophen was compared to placebo in patients with low back pain. Differences in the mean change from baseline for "pain on average" and "pain right now", the two primary endpoints, between the buprenorphine transdermal system and the placebo groups were significant for the maintenance period (P=0.04 and P=0.045, respectively). However, differences between placebo and oxycodone and acetaminophen combination, the active control, were not significant (P value not reported). When the trial was evaluated using pain scores at week 12 (an analysis preferred by the FDA), the buprenorphine transdermal system treatment group did not yield a significant difference from placebo (P value not reported). In another trial (N=418), treatment with either buprenorphine transdermal system 20 µg/hr or oxycodone immediate-release was compared to buprenorphine transdermal system 5 µg/hr in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours scores from baseline, the primary endpoint, was greater in the buprenorphine transdermal system 20 µg/hr and oxycodone immediate-release treatment groups as compared to the buprenorphine transdermal system 5 µg/hr group, but did not achieve significance (P values not reported). Furthermore, none of the results of the sensitivity analyses were significant, supporting the conclusion that this trial lacked assay sensitivity and is a failed trial.[1,79]

Two smaller, double-blind, crossover trials compared buprenorphine transdermal system to placebo in patients with chronic low back pain. In both trials, patients were randomized to receive buprenorphine transdermal system or placebo for four weeks and crossed over to alternate treatments at the end of week 4 for a total of eight weeks. In the first trial (N=79), the treatment difference between buprenorphine 5 to 20 µg/hour and placebo in the average pain score over the last week at the end of each treatment phase, the primary endpoint, was small but statistically significant when reported using a five-point ordinal scale (P=0.0226). When the same endpoint was reported using a visual analogue scale, there was no

statistically significant difference between the two treatment groups (P=0.0919).[35] In the second trial (N=78), the difference in average pain score over the last 24 hours for buprenorphine 10 to 40 µg/hour was significantly lower compared to placebo when reported using both the visual analogue scale and the five-point ordinal scale (P=0.005 and P=0.016, respectively).[36]

In total, 18 clinical pharmacology trials and 15 chronic pain trials have been completed with buprenorphine transdermal system. Overall, there is a consistent pattern of pain reduction or continuing stable pain control in chronic, non-cancer, non-neuropathic pain models, supporting the analgesic efficacy of buprenorphine transdermal system.[79]

Fentanyl transdermal systems have demonstrated efficacy in the treatment of neuropathic pain, moderate to severe chronic pain due to nonmalignant and malignant disease, and moderate to severe osteoarthritis pain in both open-label and placebo-controlled trials.[37-39] The effectiveness of fentanyl in relieving pain also appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[44-46]

Hydrocodone ER has demonstrated safety and efficacy in a phase III placebo controlled trial. The trial evaluated the safety and efficacy of hydrocodone ER in opioid-experienced adults with moderate to severe chronic low back pain in a 12 week double-blind, multicenter, randomized, placebo-controlled trial. 302 subjects were randomized in a 1:1 fashion to receive either hydrocodone ER or placebo after a conversion/titration phase of up to six weeks in length to establish each subject's appropriate dose of hydrocodone ER. The primary endpoint evaluated was the change in mean pain intensity score from baseline to end of treatment, which was based on the 11-point numerical rating scale that was recorded daily in an electronic diary. The numerical rating scale scores ranged from zero to ten, with zero equal to "no pain" and ten equal to the "worst pain imaginable." The secondary endpoints measured were "treatment responders," defined by the percentage of subjects with at least a 30% average improvement in pain intensity scores from baseline to end of treatment and subject satisfaction with their pain medication, measured by the mean increase in Subject Global Assessment of Medication scores from baseline to end of treatment. The Subject Global Assessment of Medication is conducted by asking subjects, "How satisfied are you with your pain medicine?" The answers accepted are "not at all," "a little bit," "moderately," "very much" and "completely". The answers are given a score of 1 to 5, respectively, and a higher Subject Global Assessment of Medication indicated greater satisfaction with subjects' treatments. Mean change from baseline to end of treatment in pain intensity score ± SD was significantly lower for hydrocodone ER vs placebo (0.48 ± 1.56 vs to 0.96 ± 1.55, respectively; P=0.008). There was a significantly higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (68% vs 31%, respectively; P<0.001) at the end of treatment, and Subject Global Assessment of Medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (0.8 ± 1.3 vs 0.0 ± 1.4, respectively; P<0.0001).[47]

The available published clinical trial information demonstrating the efficacy and safety of hydromorphone ER is currently limited. In a placebo-controlled trial, the medication demonstrated superior efficacy in the treatment of lower back pain with regards to reducing pain intensity (P<0.001) and pain scores (P<0.01). In addition, treatment was well tolerated.[50] In a 2007 noninferiority analysis of a hydromorphone ER formulation available only in Europe compared to oxycodone ER, it was demonstrated that the two agents provided similar pain relief in the management of osteoarthritic pain.[49]

Methadone has demonstrated "superior" efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[53,54]

A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). In addition, both treatments reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each of the treatments statistically improved certain sleep parameters compared to placebo, and when

compared head-to-head; Avinza®, administered in the morning, significantly improved overall quality of sleep compared to MS Contin® (P value not reported).[49] In another cross-over trial, morphine sulfate (MS Contin®) was compared to treatment with fentanyl transdermal systems. In this trial, more patients preferred treatment with fentanyl (P<0.001), and reported on average, lower pain intensity scores than during the morphine sulfate phase (P<0.001).[57]

Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[29] Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[60]

Oxycodone ER has demonstrated "superior" efficacy over placebo for the treatment of neuropathic pain and chronic refractory neck pain.[61-63] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[64]

Oxymorphone ER has established safety and efficacy in the management of cancer pain.[66,67] Specifically, the agent produced comparable mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain. Patients were initially stabilized on morphine sulfate or oxycodone ER and then switched to treatment with oxymorphone ER. The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER. No significant changes were observed in mean visual analog pain scores, quality of life domains, or quality of sleep for any of the treatment groups.[67] In another placebo-controlled trial, oxymorphone ER demonstrated "superior" efficacy for the treatment of osteoarthritis pain.[68]

The efficacy and safety of tapentadol ER was evaluated in three placebo-controlled and active controlled comparator trials along with one 52-week long-term safety trial. Afilalo et al conducted a 12-week randomized, double-blind, multicenter, active- and placebo-controlled trial among adults (N=1,030) with osteoarthritis of the knee who were assigned to receive tapentadol ER or oxycodone ER (titrated to response) or placebo. Significant pain relief was achieved with tapentadol ER vs placebo, with a least squares mean (LSM) difference of - 0.7 (95% confidence interval [CI], -1.04 to -0.33) at week 12 of the maintenance period compared to placebo. Comparatively, the average pain intensity rating at endpoint compared to baseline with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (LSM difference vs placebo: -0.3), but was not significantly lower at week 12 of the maintenance period (LSM of -0.3; P values not reported). The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week 12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone ER compared to placebo (24.9 vs 35.9%; P=0.002). Tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period vs placebo (32.0 vs 24.3%; P=0.027) compared to treatment with oxycodone ER which resulted in a reduction vs placebo of 17.3 vs 24.3% (P=0.023).[70] Buynak et al evaluated the efficacy of tapentadol ER compared to placebo in a prospective, double-blind, placebo controlled, active comparator trial with oxycodone ER in adults (N=981) with moderate to severe lower back pain. Throughout the 12 week maintenance period, average pain intensity scores (primary endpoint) improved in both the tapentadol ER and oxycodone ER groups relative to placebo. The mean change in pain intensity from baseline to week 12 was -2.9 for tapentadol ER and -2.1 for placebo, resulting in a LSM difference vs placebo of -0.8 (P<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for the tapentadol ER group and -2.1 for the placebo group, corresponding to a LSM difference vs placebo of -0.7 (P< 0.001).[71] Schwartz et al evaluated the efficacy of tapentadol ER in a 12 week, randomized, double-blind, placebo-controlled, maintenance trial among adults (N=395) with at least a six month history of painful diabetic peripheral neuropathy. The LSM change in average pain intensity from the start of double-blind treatment to week 12 (primary endpoint) was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, corresponding to a LSM difference of -1.3 (95% CI, -1.70 to -0.92; P<0.001). The mean changes in average pain intensity scores from baseline to

week 12 among those receiving tapentadol ER were similar regardless of gender, age (<65 years or >65 years), and history of previous opioid use. At least a 30% improvement in pain intensity was observed in 53.6% of tapentadol ER -treated patients and 42.2% of placebo-treated patients (P=0.017) at week 12; and ≥50% improvement in pain intensity was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients.[68] Wild et al evaluated the long-term safety of tapentadol ER in a randomized, active-controlled, open-label, trial compared to oxycodone ER among adults with chronic knee or hip osteoarthritis or low back pain. The proportion of patients who completed treatment in the tapentadol ER and oxycodone ER groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1 vs 36.8%). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone ER group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), vomiting (7.0 vs 13.5%), and pruritis (5.4 vs 10.3%) were lower in the tapentadol ER group than in the oxycodone ER group, respectively. There were no clinically-relevant, treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone ER group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone ER group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone ER groups (5.5 vs 4.0%, respectively).[73]

The efficacy of the combination product oxycodone/acetaminophen efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/acetaminophen and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/acetaminophen was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in pain intensity after two hours was 63.1% for oxycodone/acetaminophen compared to 27.2% for placebo (*P*<0.0001).[77]

Methadone is the only long-acting narcotic that is FDA-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[78]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moderate to Severe Pain				
Study HYD3002[33] (abstract) Hydrocodone ER tablets 20 to 120 mg QD vs placebo Opioid-naïve patients started at 20 mg QD while opioid-experienced patients received 25% to 50% of their incoming opioid total daily dose. Doses were up-titrated every three to five days until stable or at the maximum 120 mg QD. Oxycodone IR 5 to 10 mg every four to six hours was allowed. A pre-randomization phase consisted of	DB, MC, PC, RCT Patients ≥18 years of age with non-malignant, non-neuropathic moderate to severe low back pain for at least three months not adequately controlled by their stable incoming analgesic non-opioid or opioid (≤100 mg oxycodone equivalent) regimen and to have demonstrated adequate analgesia and acceptable tolerability with hydrocodone ER treatment during the run-in period	N=588 12 weeks	Primary: Weekly mean pain intensity score calculated using the daily "average pain over the last 24 hours" scores for chronic low back pain at week 12 Secondary: Response to treatment, sleep disturbance MOS Sleep-R) at weeks 4, 8, and 12, and PGIC at end of study, safety	Primary: Mean (SD) "average pain over the last 24 hours" score at baseline in the placebo group was 7.4 (1.19) and 7.4 (1.13) in the hydrocodone ER group. Pre-randomization mean scores for the placebo and hydrocodone ER groups were 2.8 (1.15) and 2.8 (1.16), respectively. At the end of the 12-week study period, LS mean scores increased to 4.23 (0.126) and 3.70 (0.128) for the placebo and hydrocodone ER groups respectively. LS mean (SD) difference was -0.53 (0.180) (95% CI, -0.882 to -0.178; P=0.0016). Secondary: A statistically significant difference in favor of hydrocodone ER compared to placebo was seen between treatment groups for the proportion of patients with a ≥30% reduction in pain (P=0.0033) and a ≥50% reduction in pain (P=0.0225). Improvements in pain ≥30% and ≥50% were seen in 65% and 48% of the hydrocodone ER patients and 53% and 39% of the placebo patients, respectively. MOS Sleep-R sleep disturbance subscale analysis showed that, by the end of the run-in period, the sleep disturbance subscale showed improvements in both treatment groups (from 44.72 at baseline to 51.48 at end of run in for placebo and 44.38 at baseline to 50.33 at end of run-in for hydrocodone ER); however, there was no significant difference between the two groups during the double-blind period. The proportion of patients reporting "very much improved" or "much improved" on the PGIC rating scale was significantly higher (61%) in the hydrocodone ER treatment group compared with the placebo group (49%) (P=0.0036). Treatment emergent adverse events that occurred at an incidence of ≥5% during the run-in period included: gastrointestinal disorders (nausea, vomiting, and constipation) and nervous system disorders (dizziness, headache, and somnolence). Treatment emergent adverse events that occurred at an incidence of ≥5% during the double-blind period included only gastrointestinal disorders (nausea and vomiting). The Treatment emergent adverse events that occurred more frequently in patients receiving hydrocodone ER than in patients receiving placebo and those with a difference of ≥2% included nausea, vomiting, and influenza.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
a baseline period (up to 14 days) and a dose titration open-label (run-in) period (45 days) in which all patients received hydrocodone ER. At randomization patients continued hydrocodone ER or received placebo (double-blind period).				Confirmed diversion or suspected diversion by patients in either the run-in period or double-blind period was reported for 39 patients (4.3%). Few patients (≤1%) experienced adverse events associated with opioid withdrawal during opioid conversion or during cessation of hydrocodone ER treatment.
Gordon et al[35] Buprenorphine transdermal system 5, 10 or 20 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	N=79 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last week on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 mm (no pain) to 100 mm (excruciating pain) Secondary: PDI, Pain and Sleep Questionnaire, level of activity, SF-36, treatment effectiveness on a	Primary: In the ITT analysis, the average pain score reported by patients using the five-point scale at the last week of each treatment phase was 1.8±0.6 for buprenorphine and 2.0±0.7 for placebo (P=0.0226). When the pain score was reported using the VAS, the score was 40.2±20.2 for buprenorphine and 44.4±20.2 for placebo (P=0.0919). Secondary: In the per-protocol analysis, when buprenorphine was compared to placebo at the last week of each treatment phase, there were no treatment differences with regard to improvement in any of the subscales or the total score of the PDI (results not reported; P=0.4860), the Pain and Sleep Questionnaire (172.4±122.8 vs 178.2±112.6; P value not reported), the level of activity (43.8±23.0 vs 43.9±23.7; P=0.9355) or the SF-36 (results not reported; P value not reported). There was no difference between the two treatment groups in patient- and investigator-rated treatment effectiveness at the end of each treatment phase. The patient-rated scores were 1.3±1.1 and 0.9±1.0 for buprenorphine and placebo, respectively (P=0.1782), while the investigator-rated scores were 1.2±1.0 and 0.9±1.0, respectively (P=0.1221). Forty-three percent of patients preferred the buprenorphine treatment phase, 38% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Codeine/ acetaminophen 30/300 mg one or two tablets every 4 to 6 hours as needed was allowed.			four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	patients preferred the placebo phase and 19% of patients had no preference (P=0.6473). Similarly, 43% of investigators preferred buprenorphine for their patients, 36% of investigators preferred placebo and 21% of investigators had no preference (P=0.5371). More patients reported drowsiness with buprenorphine compared to placebo (P=0.0066). More patients reported at least one adverse event during treatment with buprenorphine compared to placebo (P=0.0143). The most commonly reported adverse events include nausea, somnolence and application site reactions. ES Phase: Forty-two of 51 patients (82%) who completed the DB phase continued to receive OL buprenorphine treatment. The average PI score over the past 24 hours measured by VAS were significantly lower at the end of the ES phase compared to the DB phase (13.2±20.2 vs 39.5±19.1; P=0.0001). There were no differences between the ES and DB phases in the average pain score over the last week and all other study endpoints, with the exception of the standardized physical component of the SF-36, which was significantly lower in the ES phase compared to the DB phase (P=0.0226).
Gordon et al[36] Buprenorphine transdermal system 10 to 40 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with moderate to severe chronic low back pain for >3 months, requiring one or more tablet of opioid analgesics daily	N=78 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last 24 hours on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 (no pain) to 100 mm (excruciating pain) Secondary: Pain and Sleep Questionnaire, PDI, SF-36, treatment effectiveness on a	Primary: In the ITT analysis, buprenorphine was associated with a lower average pain score over the last 24 hours compared to placebo. When reported using VAS, the pain score was 44.6±21.4 for buprenorphine and 52.4±24.0 for placebo (P=0.005). The score reported using the five-point scale was 2.0±0.7 and 2.2±0.8 for buprenorphine and placebo, respectively (P=0.016). Secondary: The overall score of the Pain and Sleep Questionnaire was significantly lower for buprenorphine compared to placebo (117.6±125.5 vs 232.9±131.9; P=0.027). No significant differences were noted between the two treatment groups with regard to the PDI and SF-36 (P value not reported for all endpoints). The treatment effectiveness of buprenorphine was rated significantly higher than placebo by patients (1.8±1.1 vs 1.0±1.1; P=0.016) and investigators (1.8±1.1 vs 1.0±1.1; P=0.013). Sixty-six percent of patients preferred the buprenorphine treatment phase, 24% of

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at a stable dose for 2 weeks before randomization and antidepressants or anticonvulsants at a stable dose for 8 weeks before randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Acetaminophen 325 mg one or two tablets every 4 to 6 hours as needed was allowed.			four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	patients preferred the placebo phase and 10% of patients had no preference (P=0.001). Similarly, 60% of investigators preferred the buprenorphine treatment phase for their patients, 28% of investigators preferred the placebo phase and 12% of investigators had no preference (P=0.008). Significantly more patients in the buprenorphine group reported adverse events compared to patients in the placebo group (65.0 vs 64.7%; P=0.003). The most commonly reported adverse events with buprenorphine were nausea, dizziness, pruritus, vomiting and somnolence. ES Phase: Forty of 49 patients (81.6%) who completed the ES phase continued to receive OL buprenorphine treatment. The improvements in daily PI, PDI and SF-36 were maintained throughout the ES phase.
Karlsson et al[37] Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of

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doses Supplemental analgesic medication was permitted throughout the study. Paracetamol* up to 2,000 mg/day was allowed.	before visit 1		disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Conaghan et al[38] Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol* 1,000 mg orally four times daily vs codeine/ paracetamol* 8/500 mg or 30/500 mg orally one or two tablets four times daily Supplemental analgesic medication was	AC, MC, OL, PG, RCT Patients ≥60 years of age with a clinical diagnosis of OA of the hip and/or knee with severe pain and taking the maximum tolerated dose of paracetamol (four or more 500 mg tablets each day)	N=220 10 weeks of titration period followed by 12 weeks of assessment period	Primary: Average pain score over the last 24 hours on Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, laxative use, sleep parameters on the Medical Outcome Study-Sleep Scale, time to achieve stable	Primary: In the ITT analysis, the treatment difference between buprenorphine plus paracetamol and codeine/paracetamol with regard to the average daily pain score was -0.07 (95% CI, -0.67 to 0.54; P value not reported), demonstrating that buprenorphine plus paracetamol was non-inferior to codeine/paracetamol. Secondary: In the per-protocol analysis, patients receiving buprenorphine plus paracetamol required 33% fewer supplemental analgesic medications compared to those receiving codeine/paracetamol. The treatment difference was -0.98 (95% CI, -1.55 to -0.40; P=0.002). Fifty percent of patients in each treatment group required laxatives during the study (P value not reported). In the per-protocol analysis, the mean sleep disturbance score on the Medical Outcome Study-Sleep Scale decreased from 33.90±22.09 at baseline to 24.30±25.32 at the end of the study in the buprenorphine plus paracetamol group, while the score decreased from 41.8±28.6 to 32.9±26.1 in the codeine/paracetamol group (P value not reported). Patients receiving buprenorphine plus paracetamol reported improvement in sleep adequacy, with an increase in score from 50.80±25.35 at baseline to 62.50±28.26 at the

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permitted throughout the study. Ibuprofen up to 1,200 mg/day was allowed.			pain control, length of time on anti-emetics, discontinuation rate during the titration period and safety	end of the study, whereas the score increased from 56.10±25.84 to 59.10±26.41 in patients receiving codeine/paracetamol (P value not reported). There was no difference in the number of hours slept between the two groups. The number of patients with optimal sleep slightly increased in the buprenorphine plus paracetamol group and slightly decreased in the codeine/paracetamol group. The snoring score did not change with buprenorphine plus paracetamol and slightly improved with codeine/paracetamol. Neither treatment had any effect on shortness of breath, headache or somnolence (P values not reported for all parameters). The mean time to achieve stable pain control during the titration period was 19.5±11.5 days for buprenorphine plus paracetamol and 21.80±13.76 days for codeine/paracetamol (P value not reported). The median percentage of days on which anti-emetics were used during the titration period was 18.5% (interquartile range, 0 to 70.6) for buprenorphine plus paracetamol and 0% (interquartile range, 0 to 26.8) for codeine/paracetamol (P value not reported). Forty-three of 110 patients in the buprenorphine plus paracetamol group withdrew from the study during the titration period; 34 patients withdrew due to adverse events and five patients withdrew due to lack of therapeutic effect. In the codeine/paracetamol group, 63 of 110 patients withdrew during the titration period; 23 patients withdrew were due to adverse events and 12 patients withdrew due to lack of therapeutic effect. Eighty-six percent and 82% of patients in the buprenorphine plus paracetamol and codeine/paracetamol groups, respectively, reported treatment emergent adverse events. The most commonly reported adverse events in the buprenorphine plus paracetamol group were nausea, application site reaction and constipation.
Agarwal et al[39] Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	OL, PRO Patients >18 years of age with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in PI and daily activity Secondary: Pain relief, cognition, physical function and mood	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in PI. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in PI in the peripheral neuropathy group compared to the CRPS-1 (P=0.06) and postamputation (P=0.07) groups among the ITT population. Among completers, fentanyl was more effective in

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				reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (P<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (P<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in PI and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6%, 37.5% and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain. Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (P value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (P value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (P value not significant).
Finkel et al[40] Fentanyl transdermal system 12.5 to 100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment; changes in pain level, PPS, and CHQ and safety Secondary: Not reported	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily PI levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of

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				11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66 patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Mercadante et al[41] Fentanyl transdermal patch 12 µg/hour, doses were titrated according to the clinical response Morphine (5 mg) was allowed for breakthrough pain.	OL, OS Opioid-naïve patient with advanced cancer and moderate pain	N=50 4 weeks	Primary: PI, opioid-related adverse events, doses, quality of life Secondary: Not reported	Primary: Thirty-one patients completed all four weeks of the trial. Pain control was achieved within 1.7 days after the start of therapy. PI significantly decreased from baseline through the remaining weekly evaluations (P<0.001). Significant differences in doses were observed after two weeks and were almost doubled at four weeks. The mean fentanyl escalation index was 4.04% and 0.012 mg, respectively. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. The pain mechanism did not significantly affect the changes in PI and doses of fentanyl. The mean fentanyl escalation index was similar in patients presenting difference pain mechanisms. There were significant changes in opioid-related symptoms and quality of life between weekly evaluations. Secondary:

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				Not reported
Park et al[42] Fentanyl transdermal patch 12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	OL, PRO Patients ≥19 years of age, with overall good health, and complaining of chronic pain of the spine and limbs that scored >4 points on a numerical rating scale 72 hours prior to baseline data	N=65 12 weeks	Primary: Percentage of change in PI from before the administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's function/sleep interference, dose, safety	Primary: Changes in average PI, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual PI, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; P<0.001). The pain intensities evaluated by the patients, at rest and when moving, were decreased from 5.40 to 1.95 (63.9%; P<0.0001). Secondary: Within three visits, the sum of patients who answered "very satisfied" or "satisfied" was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of 'very satisfied' and "satisfied" measured in week four and the rates on the last visit constituted a significant increase (P<0.05). The determinants of the patient's satisfaction with pain treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (P<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (P<0.0001). The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (P<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al[43] Fentanyl transdermal system 25 to 100 µg/hour every 72 hours	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; P=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from

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vs placebo	criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids		of pain relief affecting mobility and quality of life	baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (P=0.009 and P=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (P=0.051 and P=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; P=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; P<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all P<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (P=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; P=0.041).
Ahmedzai et al[44] Fentanyl transdermal system replaced every 72 hours for 15 days vs morphine SR (MST-Continus™) every 12 hours for 15 days	MC, OL, RCT, XO Patients 18 to 89 years of age with cancer who required strong opioid analgesia and were receiving a stable dose of morphine for ≥48 hours	N=202 30 days	Primary: Pain control, effect on sedation and sleep, bowel function, treatment preference and adverse events Secondary: Not reported	Primary: No significant differences on any of the pain scales were detected between the fentanyl and morphine phases. During the fentanyl phase, patients used more rescue medications than during the morphine phase. Rescue medication was used for 53.9% of days during treatment with fentanyl, compared to 41.5% of days for morphine (P=0.0005) throughout the whole of the phases. A sizeable proportion of patients required upward titration of study medication (47.1% required ≥1 fentanyl dose change and 27.4% required ≥1 morphine dose change). One patient required a downward titration in fentanyl dose. Fentanyl was associated with significantly less daytime drowsiness than morphine (mean percent area under the curve, 34.0; 95% CI, 29.1 to 38.9; vs 43.5; 95% CI, 38.5 to 48.5; respectively, as assessed by VAS in the patient diaries). Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine (mean scores, 32.4; 95% CI, 26.9 to 37.9; vs 22.4; 95% CI, 17.8 to 27.1; for fentanyl and morphine, respectively). The only difference in diary data was that patients reported shorter sleep duration when on fentanyl compared to when on morphine over the whole 15-day treatment period (mean, 8.1; 95% CI, 7.9 to 8.3 hours; vs 8.3; 95% CI, 8.0 to 8.5 for

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				morphine). Fentanyl treatment was associated with significantly less constipation than morphine (P<0.001). At the end of the trial, significantly more patients indicated that fentanyl had caused less interruption to their daily activities, and the activities of family and care takers, and had been more convenient to take than the morphine tablets. The percentages expressing preference were as follows: less interruption of daily activities, 55.2% fentanyl; 20.4% morphine; less interruption to care givers, 49.0% fentanyl; 22.3% morphine; and more convenient medication, 58.3% fentanyl; 22.3% morphine. Of the 202 patients who entered the study, 136 felt able to express an opinion about the two treatments. Of these, 14 (10%) had no preference, 73 (54%) preferred fentanyl, and 49 (36%) preferred the morphine tablets (P=0.037). The EORTC quality of life questionnaire revealed no other significant differences between the two treatments. When scores for nausea and vomiting were separated, the mean score for nausea was significantly lower in the fentanyl group (1.7; 95% CI, 1.5 to 1.8; vs 1.8; 95% CI, 1.7 to 2.0; P=0.04). Although more adverse events were reported during fentanyl treatment, the end of treatment questionnaire indicated that significantly fewer patients considered that fentanyl caused adverse events compared to morphine (40.4 vs 82.5%; P<0.001). Secondary: Not reported
Allan et al[45] Fentanyl transdermal system 25 µg/hour replaced every 72 hours; dosage was titrated based on pain levels vs	MC, OL, PG, RCT Adults patients with chronic lower back pain requiring regular strong opioid treatment	N=673 13 months	Primary: Comparison of pain relief achieved with each treatment and incidence of constipation Secondary: SF-36 quality of life, treatment	Primary: Pain relief achieved with both treatments was similar. Mean VAS scores at study endpoint was 56.0±1.5 and 55.8±1.5 for fentanyl and morphine. Based on the 95% CI, the difference between groups established noninferiority (-3.9 to 4.2). After one week of treatment, pain relief was evident with VAS scores being 58.5±1.3 and 59.9±1.4 for fentanyl and morphine. Fentanyl was associated with significantly less constipation than morphine. Baseline levels of constipation were similar, but at endpoint 31% of fentanyl patients (93/299) and 48% of morphine patients (145/298) were constipated (P<0.001).

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morphine SR 30 mg every 12 hours; dosage was titrated based on pain levels			assessment, investigator's overall assessment of disease progression, number of working days lost and adverse events	Secondary: Mean SF-36 quality of life scores improved to a similar extent in both treatment groups between baseline and endpoint for all domains of overall physical health (P<0.001), physical functioning, role-physical, bodily pain, vitality, social functioning and role-emotional. However, the scores for overall mental health did not change significantly from baseline to endpoint in either group (P=0.937 for fentanyl and P=0.061 for morphine). The mean dose of fentanyl on day one was 25 µg/hour (range 25 to 50 µg/hour) and the mean dose at study end was 57 µg/hour (range 12.5 to 250 µg/hour). The mean dose of morphine on day one was 58 mg (range 6 to 130 mg) and the mean dose at study end was 140 mg (range 6 to 780 mg). The proportion of patients who improved by at least one pain category (e.g., from severe to moderate) during the course of the trial was 50 to 70% in both treatment groups. While patients in the fentanyl group improved more than the patients in the morphine group for pain during the day and pain at rest, the groups improved to a similar degree for pain on movement and pain at night. The dose of supplemental medication for breakthrough pain did not differ significantly between the treatment groups. Investigator ratings of disease progression were similar across treatment groups. At endpoint, investigators considered that 49% of fentanyl and 45% of morphine patients had stable disease; 10 and 8%, respectively, had deteriorated and 21 and 23%, respectively, had improved. Based on the number of patients with jobs, loss of working days was applicable to a small population of patients. The proportion of patients reporting >3 weeks off at baseline decreased from 34 and 25% of fentanyl and morphine to 16% for both groups. No differences between treatment groups in patients with lower back pain were observed. Most participants (95%) reported at least one adverse event during the study. The proportion of patients receiving fentanyl and morphine who reported adverse events that were considered to be at least possibly related to the trial medication were 87 and 91%. Adverse events led to discontinuation of trial medication in 37% of the fentanyl group and 31% of the morphine group (P=0.098). The most common adverse events leading to discontinuation were nausea (37% of discontinuations in each group), vomiting (24% fentanyl and 20% morphine) and constipation (11% fentanyl and 23% morphine).

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Clark et al[46] Fentanyl transdermal system, initially 25 µg/hour every 72 hours, with dosage adjustments to achieve adequate pain control vs morphine SR, initially 15 to 30 mg every 12 hours, with dosage adjustments to achieve adequate pain control	Systematic review (8 trials) Patients ≥18 years of age with defined and documented chronic non-cancer pain (including lower back pain, pain due to rheumatoid arthritis, or OA of the knee or hip) or cancer pain, that had reached a stage requiring treatment with a strong opioid	N=2,525 28 days to 13 months	Primary: Pain results and adverse events Secondary: Not reported	Primary: Treatment with fentanyl and morphine was equally effective in improving average pain from baseline to Day 28 (mean changes in scores were -21.8 and -20.6, respectively). In the subgroup analysis, both treatments were similarly effective in improving the average pain scores (-24.5 vs -25.9, respectively in the cancer pain subgroup and -21.0 and -17.7, respectively in the non-cancer pain subgroup). Improvements in pain "right now" scores between baseline and day 28 were significant for both treatment groups, and for both cancer pain patients and non-cancer pain patients (all measures P<0.001). The changes in pain "right now" from baseline to day 28 were significantly greater in the fentanyl treatment group compared to the morphine treatment group in the total patient sample (P=0.017). The cancer pain subgroup showed a similar trend towards better pain relief from baseline to day 28 with fentanyl treatment but this was not statistically significant (P=0.171). Overall the type of pain did not influence the incidences of adverse events. However, in the total patient sample, as well as in both pain type subgroups, significantly fewer adverse events occurred in the fentanyl treatment group compared to the morphine treatment group (all measures P<0.001). Additionally, serious adverse events were also reported significantly less frequently in the fentanyl treatment group (P=0.006). The highest rate of serious adverse events was reported in patients with cancer pain and included 61 deaths. Constipation was the most commonly reported adverse event in the morphine treatment group, and significantly fewer patients reported nausea during the first 28 days of treatment with fentanyl compared to morphine (P<0.001). Patients treated with fentanyl also reported less somnolence compared to morphine-treated patients (P<0.001). Secondary: Not reported
Rauck, et al[47] Hydrocodone ER 20 to 100 mg every 12 hours vs	DB, MC, PC, RCT Diagnosis of moderate to severe chronic low back pain,	N=302 12 weeks	Primary: Change in mean daily PI score from baseline ± SD Secondary: Percentage of	Primary: The mean change from baseline in daily PI scores ± SD was significantly lower for hydrocodone ER vs placebo (0.48 ± 1.56 vs 0.96 ± 1.55; P=0.008, respectively). Secondary: There was a significantly higher percentage of treatment responders in the hydrocodone ER group vs placebo (68% vs 31%; P<0.001, respectively) at the end of treatment. In

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placebo	18 to 75 years of age, average pain score of at least 4 on the NRS for 24 hour period prior to screening		treatment responders, mean increase in SGAM scores ± SD from baseline to end of treatment	addition, mean SGAM scores ± SD increased from baseline to end of treatment in the hydrocodone ER group vs placebo (0.8 ± 1.3 vs 0.0 ± 1.4; P<0.0001, respectively).
Hale et al[48] Hydromorphone ER 12 to 64 mg QD vs placebo Patients were enrolled in a 2 to 4 week OL enrichment phase (conversion and titration), followed by a randomized withdrawal phase for opioid-tolerant patients. Hydromorphone IR was allowed as rescue medication during all phases of the study.	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a documented diagnosis of moderate-to-severe chronic lower back pain for ≥3 hours/day and ≥20 days/month for six months and had their pain classified as non-neuropathic or neuropathic	N=268 12 weeks (DB phase only)	Primary: Mean change from baseline to week 12 or final visit in weekly PI based on patient diary numeric rating scale scores Secondary: Mean change from baseline to week 12 in weighted mean PI number rating scale score, mean change from baseline to each visit in PI during the 12 weeks of treatment recorded in the office, time to treatment failure, mean change from baseline in patient global assessment,	Primary: Hydromorphone significantly reduced PI compared to placebo (P<0.001). Secondary: The change from baseline in PI over the entire 12 weeks was statistically significant for hydromorphone compared to placebo (P<0.001). A significantly larger increase in mean PI numeric rating scale scores was seen in the placebo group compared to hydromorphone (1.2 vs 0.4; P<0.001). Weekly office visit number rating scale scores showed greater improvement following treatment with hydromorphone compared to placebo beginning at visit one and continued throughout the 12 weeks of treatment. The difference between the groups was significant (P<0.05) at every office visit except week three. Discontinuations due to treatment failure occurred sooner (P<0.001) and more frequently among patients in the placebo group. The difference was apparent by two weeks and the difference in discontinuation rates increased over the entire 12 weeks of treatment. Treatment with hydromorphone significantly improved patient global assessment scores at week 12 or at the final visit (P<0.001). A higher proportion of patients rated their treatment as good, very good or excellent compared to placebo at week 12 or final visit (80.5 vs 62.4%). The overall percentage of patients requiring rescue medication at least once over the 12 week course was similar between hydromorphone and placebo groups (96.2 vs 97.0%). The mean number of rescue medication tablets used per day at the week 12 visit also was similar between the groups (P=0.49). Weekly RMDQ scores were “superior” in patients treated with hydromorphone compared

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			rescue medication use, mean changes from baseline in RMDQ total scores and the proportion of total study dropouts in each treatment group	to placebo. Hydromorphone-treated patients showed a median change from baseline to week 12 or final visit of 0 on this measure; placebo-treated patients showed a median change of 1, indicating that placebo patients' self-reported functional status was significantly worse compared to hydromorphone (P<0.005). Significant differences were seen at weeks one, two, three, eight and 12 (or final visit). The difference between treatment groups was not statistically significant at weeks four, six or ten. A significantly higher proportion of patients in the placebo group discontinued the study compared to patients in the hydromorphone group (67.2% [90/134] vs 50.7% [68/134]; P<0.01).
Hale et al[49] Hydromorphone ER 8 to 64 mg QD vs oxycodone ER 10 to 80 mg BID	MC, OL, PG Patients ≥18 years of age who met ACR clinical criteria for OA of the knee or hip for ≥3 months before enrollment, with a mean daily pain rating at the affected joint of moderate to severe, despite chronic use of stable doses (≥30 days with no regimen change) of NSAIDs or other nonsteroidal, nonopioid therapies (with or without as-	N=147 6 weeks	Primary: Mean pain relief score at end point Secondary: Change from baseline to end point in the mean pain relief score; mean PI score at end point; change from baseline to end point in mean PI score; change from baseline to end point in mean total daily dose of study medication; change from baseline to end point in mean daily number of tablets of study medication; and changes from visit one to subsequent	Primary: The mean (SD) pain relief score was 2.30 (0.95) in the hydromorphone group and 2.30 (1.00) in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.30 to infinity. Secondary: The mean changes in pain relief from baseline to end point are reported in graphic form; as such the results could not be accurately interpreted. The mean time to the third day of moderate to complete pain relief was 6.20 (4.00) days in the hydromorphone group and 5.50 (2.57) days in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.31 to infinity. The mean (SD) changes in PI from baseline to end point were -0.6 (0.80) points in the hydromorphone ER group and -0.4 (1.15) in the oxycodone ER group; the 1-sided 95% CI for the difference of means was -0.53 to infinity. The results of the patient and investigator global evaluations indicated that both treatments were considered clinically effective. Patient global evaluations improved from baseline by a mean (SD) of 1.20 (1.01) points in the hydromorphone group and by 1.00 (1.33) points in the oxycodone group. The magnitude of change was not significantly different between groups. The overall effectiveness of treatment was rated as good, very good or excellent by 67.2% of patients in the hydromorphone group and 66.7% of patients in the oxycodone group. The mean patient global evaluation scores at end point were similar in the two groups (2.90 [1.06] and 2.90 [1.11], respectively). Similarly, investigator global evaluations improved by 1.20 (1.01) and 1.10 (1.16) points, with a

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	needed opioids)		visits in the MOS sleep scale, investigator and patient global evaluations and WOMAC	median of one point in each group. The effectiveness of treatment was rated as good, very good or excellent by 71.9% of investigators for hydromorphone and by 70.0% for oxycodone. Mean investigator global evaluation scores at end point were similar between groups (3.00 [0.95] and 3.10 [1.08]). At end point, the mean (SD) change in WOMAC total score was -2.00 (1.90) points in the hydromorphone group and -1.80 (2.14) points in the oxycodone group (P value not reported). Mean changes in WOMAC pain scale scores were -2.10 (1.96) in the hydromorphone and -2.00 (2.03) in the oxycodone group (P value not reported). The mean changes in WOMAC stiffness and physical function scale scores were not significantly different between the two groups (P values not reported). At end point, scores on the MOS Sleep Problem Index I indicated significantly less sleep disruption and daytime somnolence in the hydromorphone group compared to the oxycodone group (mean [SD], 25.70 [17.82] and 35.30 [22.56], respectively; P<0.012). Both agents were associated with numerical improvements, the change from baseline was significantly greater for hydromorphone (-13.30 [21.10] vs -5.20 [22.09]; P<0.045). Changes on the MOS Sleep Problems Index II were comparable in the two groups.
Quigley et al[50] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting or placebo or non-opioids	MA (48 RCTs) Patients of any age suffering from any illness with either acute or chronic pain, including cancer pain and postoperative pain	N=3,293 Duration not reported	Primary: Pain relief and safety Secondary: Not reported	Primary: Overall, studies varied in quality and methodology. The review did not demonstrate any clinically significant difference between hydromorphone and other strong opioids. Compared to meperidine, hydromorphone appeared more effective in achieving acute pain relief without an increase in adverse events. For the treatment of chronic pain, two studies showed that hydromorphone ER and morphine ER achieved similar pain relief; however, one of the studies showed that patients taking hydromorphone ER required more doses of rescue medication and were more likely to experience withdrawal compared to morphine. Diarrhea was more commonly seen with hydromorphone. No significant differences were seen in other adverse events. In studies comparing hydromorphone to morphine for the treatment of acute pain, hydromorphone-to morphine equianalgesic ratio was shown to vary from 7:1 to 5:1 for parenteral and spinal administration. Both drugs were associated with nausea, sleepiness and pruritus. Less anger and anxiety but lower cognitive function was

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				associated with hydromorphone compared to morphine. One study comparing patient-controlled hydromorphone, morphine and sufentanil showed that morphine was superior with regard to time to treatment failure and was associated with the lowest incidence of adverse events. No significant differences were seen in chronic pain relief between hydromorphone ER and oxycodone SR. One study showed that transmucosal fentanyl led to greater improvement in pain and anxiety compared to hydromorphone. Studies comparing different formulations and/or routes of administration of hydromorphone found no differences in chronic pain relief between IR vs ER tablets, subcutaneous bolus vs subcutaneous infusion, intravenous vs subcutaneous and oral vs intramuscular. For the treatment of acute pain, epidural hydromorphone was associated with higher incidence of pruritus compared to intravenous or intramuscular hydromorphone. For the treatment of acute pain, hydromorphone IR was associated with greater pain relief compared to placebo, and there were no significant differences in adverse events between hydromorphone and placebo. One study showed that subcutaneous hydromorphone and intravenous indomethacin were equally effective in pain relief, although the duration of nausea and vertigo was longer following hydromorphone. Secondary: Not reported
Felden et al[51] Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; P=0.006). No differences were observed for the treatment of chronic pain relief (P=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (P=0.005) and vomiting (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported.
Pigni et al[52] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting	Systematic review (9 RCTs, 4 non-RCTs) Patients ≥18 years of age with chronic cancer pain who had not taken a strong opioid in the past	N=1,208 Duration not specified	Primary: Pain relief and safety Secondary: Not reported	Primary: MA was not performed due to study heterogeneity. Overall, the review supported the use of hydromorphone in the treatment of moderate to severe cancer pain as an alternative to morphine and oxycodone. There was no clinically significant difference between hydromorphone and morphine. The majority of the studies showed similar safety and efficacy in pain relief between hydromorphone and morphine or oxycodone. The following agents of different formulations were found comparable in safety and efficacy: hydromorphone IR vs morphine IR; hydromorphone CR or SR vs morphine CR or SR, hydromorphone IR vs intramuscular morphine and hydromorphone SR vs oxycodone SR. In one non-RCT, hydromorphone SR was shown to have similar analgesia with more vomiting and less constipation compared to transdermal fentanyl and buprenorphine. Two studies comparing hydromorphone IR to SR demonstrated similar pain relief and safety profile between the two formulations. Other studies comparing different routes of administration of hydromorphone also showed similar safety and efficacy between the following routes: intravenous vs subcutaneous, intravenous vs oral and intramuscular vs oral. Secondary: Not reported
Morley et al[53] Methadone 10 to 20 mg/day vs placebo In Phase 1 of the	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum PI by 16.00 (P=0.013) and VAS average PI by 11.85 (P=0.020) and increased VAS pain relief by 2.16 (P=0.015). Analgesic effects, by lowering VAS maximum PI and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (P=0.065 and P=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum PI by 12.02 (P=0.010), a lowering of VAS

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study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total). In Phase 2 of the study, patients were instructed to take methadone 10 mg BID or placebo on odd days and to take no medication on even days (20 days total).	caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous drug regimens			average PI by 10.46 (P=0.026), and an increase in VAS pain relief by 0.94 (P=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who completed the trial. Secondary: Not reported
Bruera et al[54] Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for breakthrough pain vs slow-release morphine 15 mg BID, in addition to IR morphine 5 mg every 4 hours as needed for	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed	N=103 4 weeks	Primary: Difference in PI Secondary: Change in toxicity and patient-reported global benefit	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; P=0.50). Secondary: The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; P=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI, 38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
breakthrough pain	consent			
Musclow et al (abstract)[55] Morphine long acting 30 mg BID for 3 days vs placebo	DB, PC, RCT Patients undergoing total hip or knee replacement surgery	N=200 3 days	Primary: Decrease in pain scores by 2 points on a 10 point rating scale Secondary: Acute confusion, pain-related interferences in function and sleep, length of stay, patient satisfaction, safety	Primary: Most pain scores did not reach the predetermined improvement for clinical significance. Secondary: There was an increase in opioid usage (P<0.0001) and over sedation (P=0.08). There were no significant changes in function or sleep. Improved satisfaction with pain management was minimal (P=0.052). There was an increase in vomiting (P=0.0148).
Caldwell et al[56] Morphine ER (Avinza®) 30 mg in the morning plus placebo in the evening vs placebo in the morning plus morphine ER (Avinza®) 30 mg in the evening vs morphine CR (MS Contin®) 15 mg BID	DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with both a clinical diagnosis and grade II-IV radiographic evidence of OA of the hip and/or knee; have had prior suboptimal analgesic response to treatment with NSAIDs and acetaminophen or had previously	N=295 4 weeks	Primary: Analgesic efficacy of morphine ER QD compared to placebo and safety of morphine ER QD compared to morphine CR BID Secondary: Physical functioning; stiffness; sleep measures; and analgesic efficacy of morphine ER in the morning, morphine ER in the evening and morphine CR	Primary: Overall, a statistically significant reduction in pain from baseline was demonstrated by morphine ER in the morning (17%; P≤0.05) and in the evening (20%; P≤0.05), and morphine CR BID (18%; P≤0.05), as compared to placebo (4%). Morphine ER in the morning (26%) and in the evening (22%) and morphine CR BID (22%) reduced overall arthritis PI as compared to placebo (14%), but these differences were not statistically significant. PI (measured on a 100-mm scale) was reduced by approximately 20 to 23 mm in the morphine ER and CR groups compared to 14 mm in the placebo group. Decreases in PI were apparent in all treatment groups by week one and further reductions in pain throughout the four week period were observed as compared to baseline. Secondary: Statistically significant differences in physical function were not achieved among the treatment groups. Mean improvements in physical function (total score, 0 to 1,700 mm) at Week four were as follows: morphine ER in the morning (207 mm, 18%) and in the evening (205 mm, 19%), morphine CR (181 mm, 14%) and placebo (97 mm, 8%). Reductions in stiffness were also observed for all treatment groups. The changes were not large enough to achieve statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	received intermittent opioid analgesic therapy; and have a baseline VAS PI score of ≥40 mm in the index joint			Active treatment groups provided greater improvements in all sleep measures compared to placebo. Morphine ER in the morning provided statistically significant improvements compared to placebo for overall quality of sleep, less need for sleep medication, increases hours of sleep and less trouble falling asleep because of pain (P values not reported). Morphine ER in the evening provided statistically significant improvements compared to placebo for overall quality of sleep and duration of sleep each night. Relative to placebo, morphine CR provided statistically significant improvements in overall quality of sleep and patients had less trouble falling asleep because of pain (P values not reported). Morphine ER in the morning demonstrated a statistically significant improvement in overall quality of sleep compared to morphine CR (P value not reported) and no significant differences were observed between morphine ER in the morning and the evening (P value not reported). A total of 197 patients (67%) experienced at least one adverse event during this trial, with constipation and nausea reported most frequently. Adverse events were higher in all active treatment groups compared to the placebo group. Among the 33 pair-wise comparisons the only significant differences observed were a higher rate of constipation with morphine ER in the morning (49%) vs morphine CR (29%), a higher rate of vomiting with morphine ER in the evening (16%) vs morphine ER in the morning (6%) and a higher rate of asthenia with morphine CR (9%) vs morphine ER in the morning (1%).
Allan et al[57] Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	MC, OL, RCT, XO Patients >18 years of age with chronic non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate pain	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment assessment, rescue drug use, SF-36 quality of life, and safety	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; P<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief. Secondary: Patients treated with fentanyl reported on average lower PI scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; P<0.001), irrespective of the order of treatment. More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; P=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (P<0.001). The corresponding percentages from the patient assessments were 60% for

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	control with a stable dose of oral opioid for seven days before the trial			fentanyl and 36% for morphine (P<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; P<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (P<0.001), vitality (P<0.001), social functioning (P=0.002), and mental health (P=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
Wiffen et al[58] Morphine, long- or short-acting vs Opioids or non-opioid analgesics	MA (54 RCTs) Adults and children with cancer pain requiring opioid treatment	N=3,749 3 days to 6 weeks	Primary: Pain relief and adverse events Secondary: Not reported	Primary: The review showed that morphine was comparable to other opioids in achieving cancer pain relief, and different formulations of morphine were effective. Limited evidence suggested that transmucosal fentanyl may provide more rapid pain relief for breakthrough pain compared to morphine. Thirteen studies (n=939) compared long-acting morphine to other opioids of either long- or short-acting formulation. There were no significant differences in pain relief and adverse events between long-acting morphine and long- or short-acting oxycodone, long-acting hydromorphone or tramadol. Pain relief was similar between morphine and transdermal fentanyl, though patients in the transdermal fentanyl group required more rescue medication and reported less sedation and constipation. Compared to methadone, morphine was associated with similar pain relief and fewer adverse events. Six studies (n=973) compared short-acting morphine to other opioids. One study comparing morphine to transmucosal fentanyl for breakthrough pain showed that PI scores were significantly lower with transmucosal fentanyl at all time points compared to morphine. No differences in pain relief were seen between morphine and methadone,

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				short-acting oxycodone or tramadol. Compared to methadone, morphine was associated with more dry mouth and fewer headaches. Morphine was also associated with more nausea than oxycodone. Fifteen studies (n=460) compared long- to short-acting morphine and demonstrated that the two formulations were comparable in pain relief and adverse events. No carry-over effects were observed with long-acting morphine. One study showed long-acting morphine was associated with greater improvement in sleep quality. Twelve studies (n=1,010) compared long-acting morphine of different dosage strengths, dosing intervals or dosage formulations. Results from these studies showed no significant differences in pain relief or adverse events between the following comparisons: 12-hourly vs eight-hourly dosing, 12-hour-release capsule (M-Eslon®†) vs tablet (MS Contin®), 24-hour-release capsule or tablet (Kadian®, Kapenol®†, Morcap®† or MXL®†) vs 12-hour-release tablet (MS Contin®) and long-acting tablet vs long-acting suspension. One study showed that long-acting morphine suppository caused less nausea compared to long-acting morphine oral tablet. Another study showed rectal administration of morphine solution led to faster and greater pain relief compared to oral solution. In one study, oral and epidural morphine achieved similar pain relief. Patients on epidural morphine reported significantly fewer adverse events Secondary: Not reported
Caraceni et al[59] Morphine, long- or short-acting vs opioids	MA (16 RCTs and 1 MA) Patients ≥18 years of age with chronic cancer pain	N=2,487 Duration not reported	Primary: Pain relief and adverse events Secondary: Not reported.	Primary: No significant differences in pain relief were observed when long- and short-acting morphine was compared to diamorphine†, hydromorphone, methadone, oxycodone or transdermal fentanyl. No clinically significant differences were observed between morphine and other opioids; however, transdermal fentanyl was associated with a lower incidence of constipation, and patients on methadone were more likely to withdraw from the study due to sedation. Secondary: Not reported

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Katz et al (abstract)[60] Morphine/ naltrexone vs placebo All patients received morphine/ naltrexone, titrated to 20/160 mg/day, prior to randomization. Patients randomized to placebo were tapered off morphine/ naltrexone over a two week period.	DB, MC, RCT Patients with chronic, moderate to severe, OA (hip or knee) pain	N=547 12 weeks	Primary: Change from baseline in diary average-pain scores to the last seven days of the trial Secondary: Remaining BPI scores, WOMAC OA index, opioid withdrawal symptoms	Primary: Combination therapy maintained pain control better than placebo (mean change from baseline dairy average-pain score: -0.2±1.9 vs ±0.3±2.1; P=0.045). Change from baseline for combination therapy pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks two to 12 (P<0.05). Secondary: WOMAC composite score change from baseline was superior at most visits. Combination therapy was generally well tolerated, with a typical morphine safety profile. No patient taking combination therapy as directed experienced withdrawal symptoms.
Gimbel et al[61] Oxycodone ER (OxyContin®) 10 to 60 mg BID vs placebo	DB, MC, PC, PG, RCT Adult diabetic patients with a history of stable diabetes mellitus and a HbA1c ≤11.0%, painful symmetrical distal	N=159 6 weeks	Primary: Average daily PI during the past 24 hours obtained during the study period from days 28 to 42 Secondary: Patient reported scores for average PI from days one	Primary: In the ITT cohort, the efficacy analysis of the primary endpoint showed that oxycodone provided “superior” analgesia compared to placebo (P=0.002). Least squares mean scores for overall average daily PI from days 28 to 42 were 4.1 and 5.3 for the oxycodone and placebo groups. The primary efficacy results from the per protocol cohort confirmed these results: least squares mean scores for overall average daily PI from days 28 to 42 in this cohort was 4.2 and 2.3 for the oxycodone and placebo groups (P=0.009). Secondary: Oxycodone produced significant improvements in overall scores for average PI from days one to 27 (P<0.001), pain right now (P=0.002), worst pain (P=0.001), satisfaction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	polyneuropathy, a history of pain in both feet for more than half the day for ≥3 months prior to enrollment, and at least moderate pain in the absence of any opioid analgesic therapy for three days before receiving the study treatment		to 27, current and worst pain, satisfaction, and sleep quality from days one to 42; total and subscale scores from the 14-item BPI; scores for validated measures of psychological state, physical functioning, and general health status; the proportion of patients who discontinued study medication due to lack of efficacy; and time to mild pain, number of days with mild pain and proportion of days with mild pain	with study medication (P<0.001) and sleep quality from days one to 42 (P=0.024). Significant improvements in all pain measurements (except worst pain) and in sleep quality were observed within one week of initiation of oxycodone therapy. An improvement from baseline in nine out of 14 items (average PI [P=0.004], pain right now [P<0.001], worst pain [P=0.001], least pain [P=0.004], pain relief [P<0.001], interference score [P=0.015], relations with other people [P=0.023], sleep [P<0.001] and enjoyment of life [P=0.016]) were significant and improved in the oxycodone group compared to placebo. No significant improvements occurred for the five remaining items which included physical function score, general activity, mood, walking ability and normal work. There were no significant differences between treatments in physical functioning, general health and mental health subscales of the SF-36 Health Survey or in the seven subscales of the Rand Mental Health Inventory. A significant difference in ambulation, a subscale of the Sickness Impact Profile, was observed between oxycodone and placebo at the final visit. Of the 12 patients discontinuing study medication due to inadequate pain control, one patient was in the oxycodone group and 11patients were in placebo group (P=0.002). The median time to achieve mild pain was shorter for the patients treated with oxycodone (six days) compared to placebo-treated patients (17 days; P=0.017). Patient treated with oxycodone had more days with mild pain: mean (SD) of 20.0 (16.6) days vs 12.5 (16.0) days for the placebo (P=0.007). Oxycodone-treated patients reported a higher mean (±SD) percentage of days with mild pain (47%±39%) compared to placebo-treated patients (29%±37%; P=0.006).
Ma et al[62] Oxycodone ER 5 to 10 mg or larger dosages every 12 hours vs	DB, PRO, RCT Patients 40 to 70 years of age with a history of chronic refractory neck pain for >6 months, a MRI	N=116 4 weeks	Primary: Frequency of pain flares, PI, quality of life, quality of sleep, adverse events and SF-36 Secondary: Not reported	Primary: Compared to the pretreatment and placebo group, the frequency of acute pain flares (>3 times/day) in the oxycodone group decreased significantly on day three and day seven (P<0.05). Only 20.7% of patients (12/58) continued to have acute flare pain (>3 times/day) on day seven, and 21 days later no patient complained of acute flare pain in the oxycodone group (P<0.01). Patients treated with oxycodone had a stepwise reduction in PI during the first week compared to their baseline. The VAS decreased from 6.82±1.83 to 3.35±1.57 on day

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	or computer topography scan suggesting a degenerative disease process, with a frequency of acute pain flares occurring >3 times/day that are VAS >4 for 3 days			three, and to 3.24±0.92 on day seven (P<0.05). Patients in the oxycodone group had lower scores for PI compared to patients in the placebo group (P<0.05). The oxycodone group had dramatic improvements in performance status and performance status scale scores after seven days of treatment. Compared to pretreatment levels and the placebo group, performance status decreased from 2.74±1.01 to 1.25±0.42 on day seven, and to 0.28±0.07 on day 28, respectively (P<0.05). Similarly, performance status scale increased from 3.21±0.68 to 4.74±0.95 on day seven and to 7.23±1.44 on day 28 (P<0.05). Bad quality of sleep was 63.8% before treatment and was decreased to 15.5% on day three, 8.6% on day seven, and 5.6% on day 14 in patients treated with oxycodone. Additionally, there was significant improvement in the quality of sleep, with 13.8% as the baseline for good quality of sleep, rising to 46.6%, 50.0%, and 58.3% on day three, seven and 14 respectively after oxycodone treatment (P<0.01). Adverse events, including mild-to-moderate nausea (31.0%) constipation (22.4%), pruritus (18.9%) and dizziness (27.6%) were only seen on day seven of the treatment in oxycodone patients (P<0.05). However, events diminished starting from day 14 of the treatment until day 28; only two patients had persistent constipation. Most domains of SF-36 were effective positively in patients treated with oxycodone. The score for physical functioning, pain index, vitality, social functioning, emotional role and mental health index were significantly better in the oxycodone group compared to placebo at the end of the study (P<0.05). Secondary: Not reported
Watson et al[63] Oxycodone ER (OxyContin®) 10 to 40 mg BID vs	DB, RCT, XO Adult diabetic patients in stable glycemic control; with painful symmetrical	N=36 8 weeks	Primary: PI, SF-36 and PDI Secondary: Not reported	Primary: Oxycodone resulted in significantly lower VAS (P=0.0001) and ordinal (P=0.0001) pain scores and better pain relief (P=0.0005) compared to placebo during the last week of treatment assessed in patients' daily diaries. There was no evidence of sequence effect (P=0.2098). Steady (P=0.0001), brief (P=0.0001) and skin pain (P=0.0001) were significantly reduced with oxycodone treatment compared to placebo. For the SF-36, results were significantly better during the oxycodone treatment phase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
active placebo (Benztropine® 0.25 to 1 mg BID)	distal sensory neuropathy; at least moderate pain in the lower extremities; a medical history of moderate daily pain for previous three months; one or more symptoms of diabetic neuropathy; and signs of reduced sensation, strength or tendon reflexes not attributable to any other cause			compared to active placebo for Physical Functioning (P=0.0029), Pain Index (P=0.0001), Vitality (P=0.0005), Social Functioning (P=0.0369) and Mental Health Index (P=0.0317) domains. All variables in the PDI were significantly better in the oxycodone treatment phase (P≤0.0005 and P≤0.05) with the exception of sexual behavior, which showed no difference between the two treatments. Secondary: Not reported
Bruera et al[64] Oxycodone ER (OxyContin®) and placebo every 12 hours for 7 days vs morphine ER (MS Contin®) and placebo every 12 hours for 7 days	DB, DD, PC, RCT, XO Patients ≥18 years of age who had cancer pain and who were receiving treatment with an oral opioid analgesic during study entry and who gave informed consent	N=32 2 weeks	Primary: PI, overall effectiveness, and adverse events Secondary: Not reported	Primary: There were no significant differences between treatments in pain-intensity VAS scores when tested by day of treatment, time of day, or overall (P=0.43) or between categorical scores pain-intensity scores by day of treatment, time of day, or overall (P=0.36). For both formulations, there was a significant (P=0.02) difference in rescue use with respect to doses taken during the night (2 to 6 AM) as compared to the remainder of the 24-hour day. The rate of rescue use during the night was 55 and 67% of that used during the daytime in the oxycodone and morphine groups, respectively. The average daily number of rescue doses in a 24-hour period was 2.3±2.3 for oxycodone and 1.7±2.1 for morphine (P=0.01). There were no significant differences in sedation or nausea between oxycodone ER and morphine. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
King et al[65] Oxycodone vs strong opioids	Systematic Review (14 RCTs, 1 MA, 10 OS) Patients ≥18 years of age with moderate to severe cancer pain	N=3,875 3 days to 3 months	Primary: Pain relief and adverse events Secondary: Not reported	Primary: This review found no significant differences in safety and cancer pain relief between oxycodone and hydromorphone, morphine or oxymorphone. The MA included in this review showed no difference in analgesia and safety between oxycodone and morphine or hydromorphone (pooled standardized mean difference, 0.04; 95% CI, -0.29 to 0.36; P=0.8). Similarly, results from RCT and PRO OS also showed no difference between oxycodone and hydromorphone, morphine or oxymorphone. Studies that compared short- to long-acting oxycodone showed similar pain relief and safety profile between the two formulations. Studies comparing intravenous vs rectal and intramuscular vs oral oxycodone also demonstrated similar safety and efficacy between different routes of administration. Secondary: Not reported
Slatkin et al[66](abstract) Oxymorphone ER Patients who had been taking oxymorphone ER continued the dose established in a previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of oxymorphone ER.	Post-hoc analysis of 2 ES, OL Patients with cancer	N=80 12 months	Primary: Current, average, worst and least pain scores normalized to a 100-point scale Secondary: Patients rated global assessment of study medication and adverse events	Primary: Of the 80 patients who were entered into the ES, 26 patients completed 52 weeks, seven patients discontinued owing to loss of effectiveness, and 20 patients discontinued owing to adverse events (most unrelated to the study drug). No significant increase in mean (SD) average PI was observed from baseline (30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; P=0.37). Secondary: The most common adverse events were concomitant disease progression (28.8%; n=23), nausea (22.5%; n=18), dyspnea (16.3%; n=13), fatigue (16.3%; n=13) and edema of the lower limb (15%; n=12). Patient rated global assessment of study medication was not reported in the abstract.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sloan et al[67] Oxymorphone ER Patients were stabilized for ≥3 days on morphine CR (MS Contin®) or oxycodone ER (OxyContin®), and then treated for 7 days at their stabilized dose (Period 1). Patients were then crossed over for 7 days of treatment at an estimated equianalgesic dosage of oxymorphone ER (Period 2).	MC, MD, OL, PRO, XO Patients 18 to 80 years of age with a history of chronic cancer pain requiring ≥20 mg of oxycodone or the analgesic equivalent of ≥30 mg of oral morphine per day	N=63 7 days (Period 2)	Primary: Efficacy Secondary: Not reported	Primary: Mean daily PI scores were comparable during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain was achieved with oxymorphone as with oxycodone. The average scheduled daily dose of study medication and the average total daily dose decreased after XO to oxymorphone. There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for the treatment groups. Secondary: Not reported
Kivitz et al[68] Oxymorphone ER 10 mg every 12 hours for 2 weeks vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER	DB, DR, MC, PG, RCT Patients ≥18 years of age with OA (defined by the presence of typical knee or hip joint symptoms [pain, stiffness, and disability] and signs [bony	N=370 2 weeks	Primary: Mean change in arthritis PI Secondary: Change in pain, stiffness, and physical function subscales of WOMAC OA index and WOMAC composite index;	Primary: In the ITT population, the least squares mean change in arthritis PI from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for oxymorphone 10, 40 and 50 mg; and placebo, respectively. The least squares mean differences in change from baseline compared to placebo were -4.3 (95% CI, -12.8 to -4.3; P value not significant), -11.1 (95% CI, -19.7 to -2.5; P=0.012) and -12.2 (95% CI, -20.9 to -3.5; P=0.006) for oxymorphone 10, 40 and 50 mg, respectively. Compared to placebo, arthritis PI scores were improved by 62.8% and 70.9% after treatment with oxymorphone 40 or 50 mg every 12 hours, respectively (P=0.012 and P=0.006). Secondary: Overall, improvements in WOMAC scores were two- to three-fold greater in oxymorphone compared to placebo. From baseline to the final visit, two-fold greater

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40 mg every 12 hours for 1 week vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 50 mg every 12 hours for 1 week vs placebo	crepitus], and radiographic evidence of OA [grade II-IV in the index joint on the Kellgren-Lawrence scale]); who are regularly taking acetaminophen, NSAIDs or opioid analgesics for 90 days before the screening visit with suboptimal analgesic response		SF-36 quality of life, CPSI and tolerability	decreases in WOMAC pain subscale scores were found in all three oxymorphone groups compared to the placebo group (P≤0.025). Improvements in WOMAC physical function subscale scores also were significantly greater for each of the oxymorphone groups compared to the placebo group (P≤0.025). Improvements in the WOMAC stiffness subscale score were significant compared to placebo only for the oxymorphone 40 and 50 mg groups (P≤0.001). With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone groups found significantly greater improvements in each oxymorphone group (P≤0.025). All patients who received oxymorphone, irrespective of the dose, had significant improvements in the SF-36 quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with oxymorphone 10, 40 and 50 mg; and placebo, respectively (P<0.001). Improvements in the CPSI scores for overall sleep quality were two-fold greater in patients who received oxymorphone 40 and 50 mg than in the placebo group (P≤0.05). The most frequently reported adverse event in the oxymorphone groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%) and headache (14.7%).
Schwartz et al[69] Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3	DB, PC, PG, RCT Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with the following: HbA1c ≤11.0%, ≥3-month history of analgesic use	N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (main-tenance phase after	Primary: The change from baseline in average PI over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in PI of at least 30% and 50% at week 12 (i.e., responder	Primary: The least square mean change in average PI from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in PI, and 0.0 in the tapentadol ER group, indicating no change in PI. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P<0.001). Secondary: The mean changes in average PI scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in PI was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg increments every 3 days (within dose range of 100 to 250 mg BID). Acetaminophen ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.	for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average PI score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)	a 3-week titration phase)	rate), PGIC at weeks two, six, and 12, and safety measures	At least a 50% improvement in PI from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032). Of the patients who achieved ≥ 30% improvement in PI (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in PI (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period. Of those patients who were randomized to placebo after achieving ≥30%improvement in PI (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in PI during the maintenance phase. Among patients who achieved ≥50% improvement in PI (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in PI (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.
Afilalo et al[70] Tapentadol ER 100 mg BID vs placebo vs oxycodone ER 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone ER 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone ER	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current	N=1,030 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change in average PI at week-12 of the maintenance period compared to baseline Secondary: Change in average PI over the entire 12-week maintenance period compared to baseline	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (P-values not reported). The average PI rating with oxycodone ER was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average PI at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone ER compared to placebo (24.9 vs 35.9%; P=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone ER resulted in a significantly lower percentage of patients achieving at least

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20mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone ER 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone ER 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3 consecutive days) was permitted.	analgesic regimen, and had a baseline PI score ≥5 during the 3 days prior to randomization			a 50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023). Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone ER and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P<0.001) compared to the least square mean difference between oxycodone ER and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051). The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone ER and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019). The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone ER. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al[71] Tapentadol ER 100 mg BID	AC, DB, MC, PC, PRO, RCT Patients ≥18	N=981 12 weeks (main-	Primary: Change from baseline in mean PI at week-12 of	Primary: Throughout the 12-week maintenance period, average PI scores improved in both the tapentadol ER and oxycodone ER groups relative to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs oxycodone ER 20 mg BID vs placebo Initial treatment with tapentadol ER 50 mg BID or oxycodone Er 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone ER 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone ER 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone ER 50 mg BID). Acetaminophen ≤1,000 mg/day	years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses, if applicable, were equivalent to ≤160 mg of oral morphine	tenance phase after a 3-week titration phase)	the maintenance period Secondary: Change from baseline in mean PI over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in PI at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P<0.001). The mean change in PI from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P<0.001). Secondary: The mean PI was also reduced for the oxycodone ER group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P<0.001). Reductions in mean PI were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline PI. Significantly greater reductions in mean PI with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline PI and severe baseline PI. Reductions in mean PI were also significantly greater with oxycodone ER than with placebo for patients with moderate and severe baseline PI at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (P=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone ER group, however, was not significantly different from the placebo group (P=0.090). A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in PI at week-12 compared to baseline (P<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(max of 3 consecutive days) was permitted.				treated with placebo responded with 50% improvement in PI at week-12 compared to baseline (P<0.016). The percentage of patients in the oxycodone ER group with ≥30% improvement in PI at week-12 compared to baseline was 30.4% (P=0.365) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone ER group with ≥50% improvement in PI at week-12 compared to baseline was 23.3% (P=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (P<0.001) and oxycodone ER (P<0.001) compared to placebo. Compared to placebo, both tapentadol ER and oxycodone ER showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score. The percentage of patients with “any pain today other than everyday kinds of pain” on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone ER group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone ER group. The percentage of patients who reported “at least 50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone ER significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly

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				improved in the tapentadol ER group compared to the placebo group. The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone ER group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone ER groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone ER group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.
Imanaka et al[72] Tapentadol ER 25 to 200 mg BID vs oxycodone ER 5 to 40 mg BID Treatment was initiated with either tapentadol ER 25 mg BID or oxycodone ER 5 mg BID with dose escalation allowed on treatment day three based upon	AC, DB, MC, PRO, RCT Men and women ≥20 years of age experiencing chronic malignant tumor-related pain that had an average PI score over the past 24 hours ≥4 on an 11 point numerical rating scale in Japan and South Korea.	N=343 4 weeks	Primary: Mean change in the average PI score from baseline to the last 3 days of study drug administration Secondary: PGIC, rescue medication use and responder rates achieving at least 30% and at least 50% decreases in PI score from baseline	Primary: Mean change from baseline in PI scores for oxycodone ER was -2.69 and -2.57 for tapentadol ER. The least squares mean difference between tapentadol ER and oxycodone ER was -0.06, 95% CI, -0.506 to 0.383. The efficacy of tapentadol ER was shown to be non-inferior to oxycodone ER based upon the upper limit of the 95% CI of <1 (predefined non-inferiority threshold). Secondary: The percentage of subjects reporting “very much improved,” “much improved,” or “minimally improved” on the PGIC was 89.7% (N=113/126) for tapentadol ER and 82.7% (N=115/139) for oxycodone ER. The percentage of subjects reporting at least a 30% improvement in PI scores from baseline for tapentadol ER was 63.5% (N=80/126) and 59.0% (N=82/139) for the oxycodone ER group. The percentage of subjects reporting at least a 50% improvement in PI scores from baseline for tapentadol ER was 50.0% (N=63/126) and 42.4% (N=59/139) in the oxycodone ER group.

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24-hour PI scores and the need for rescue medication at least three times per day. The maximum doses were tapentadol ER 200 mg BID and oxycodone ER 40 mg BID.	Patients must not have taken opioid analgesics (other than codeine or dihydrocodeine for cough) within 28 days before screening, patients must have had pain requiring an opioid analgesic and patients must have been dissatisfied with the pain relief experienced with their current pain regimen.			The mean (SD) of the average number of doses of morphine IR 5 mg per day used for breakthrough pain in the tapentadol ER group was 1.4 (0.46) compared to 1.4 (0.43) for oxycodone ER. The mean (SD) of the average total daily dose of morphine IR used was 7.0 mg (2.30) for tapentadol ER compared to 6.7 mg (2.15) for oxycodone ER. Morphine IR was used by 74.6% (N=94/126) of subjects treated with tapentadol ER compared to 74.1% (N=103/139) of subjects in the oxycodone ER group.
Wild et al[73] Tapentadol 100 to 250 mg BID vs oxycodone ER 20 to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone ER 10 mg BID for 3 days;	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or low back pain (non-malignant) with a ≥ 3 month history of pain,	N=1,121 51 weeks (main-tenance phase)	Primary: Safety and tolerability Secondary: Change in mean PI score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone ER groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone ER group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone ER group, respectively. The incidence of pruritis was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then doses were increased to tapentadol ER 100 mg BID or oxycodone ER 20 mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone ER 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone ER 50 mg BID). Occasional pain relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and acetaminophen ≤1,000 mg/day (up to a max of 7 consecutive days and no more that 14 out of 30 days) were permitted.	who were dissatisfied with current analgesic therapy, and had a PI score ≥4 on an 11-point rating scale after therapy washout			related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone ER group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone ER group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone ER groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone ER group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean PI scores at endpoint among the tapentadol ER and oxycodone ER groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of “excellent,” “very good,” or “good” among the tapentadol ER and oxycodone ER groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was “much improved” for both the tapentadol ER and oxycodone ER groups (35.7 and 32.8%, respectively). A rating of “very much improved” or “much improved” was reported by 48.1 and 41.2%, respectively.
Bekkering et al (2011)[74] Strong opioids	Systematic review (56 RCTs)	N=not reported ≥24 hours	Primary: Change of PI Secondary:	Primary: Morphine vs another strong opioids One trial favored other opioids, one trail favored morphine, and the remaining eight trials did not find any difference between the two treatments. In the subgroup of trials with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or strong opioids	Patients ≥18 years of age with cancer-related or non-cancer-related chronic pain		Safety	duration between one week and one month, morphine was more effective than other opioids (eight trials: weighted mean difference, -5.8; 95% CI, -9.5 to -2.1). Other differences were not significant. Network analyses showed that fentanyl (weighted mean difference, 6.3; 95% CI, 1.8 to 10.9) and hydromorphone (weighted mean difference, 5.1; 95% CI, 0.5 to 9.6) were less effective compared to morphine. Also placebo was less effective (weighted mean difference, 10.7; 95% CI, 7.2 to 14.1). No differences with morphine were found for oxycodone (weighted mean difference, 2.9; 95% CI, -0.4 to 6.2), methadone (weighted mean difference, 3.3; 95% CI, -4.6 to 11.3), oxymorphone (weighted mean difference, 0.4; 95% CI, -5.5 to 6.3) and buprenorphine (weighted mean difference, 3.0; 95% CI, -3.0 to 9.0). Differences between morphine and fentanyl and between morphine and hydromorphone were not significant (3.6; 95% CI, -2.0 to 9.3 and 4.8; 95% CI, -0.1 to 9.8). No differences were found when excluding trials examining opioids in neuropathic pain. Secondary: No difference between morphine and other strong opioids were found for risk of treatment discontinuation due to any reasons (ten trials: RR, 1.06; 95% CI, 0.88 to 1.29), treatment discontinuation due to lack of efficacy (nine trials: RR, 0.83; 95% CI, 0.55 to 1.25), or treatment discontinuation due to adverse events (nine trials: RR, 1.05; 95% CI, 0.67 to 1.65). Network analyses showed no difference between morphine and any other strong opioid or placebo in treatment discontinuation when all reasons for discontinuation were pooled. Patients using buprenorphine and those using placebo are more likely to discontinue treatment due to lack of efficacy (OR, 2.32; 95% CI, 1.37 to 3.95; OR, 4.12; 95% CI, 2.66 to 6.38). Patients using methadone are more likely to discontinue due to adverse events (OR, 3.09; 95% CI, 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR, 0.29; 95% CI, 0.17 to 0.50), buprenorphine (OR, 0.30; 95% CI, 0.16 to 0.53), and placebo (OR, 0.12; 95% CI, 0.08 to 0.18). After excluding trials with reversed design, oxymorphone showed increased risk for treatment discontinuation for any reason (OR, 2.32; 95% CI, 1.49 to 3.63) whereas this was nonsignificant in the overall analysis (OR, 1.00; 95% CI, 0.70 to 1.44).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No differences were found when excluding trials examining opioids in neuropathic pain. Three trials comparing morphine to another strong opioid reported serious adverse events; no differences in risk was found in the pair-wise MA (RR, 1.15; 95% CI, 0.79 to 1.67). The network analysis also found no difference in risk of serious adverse events for patients using morphine compared to those using oxycodone, fentanyl, placebo, buprenorphine, oxymorphone, and hydromorphone. Limitations: Patients with non-cancer pain and cancer pain were included; therefore, differences in patient populations exist among included trials. Some trials included patients with moderate pain which may not require a strong opioid. Use of RCTs is less suitable for evaluating adverse events, and the majority of trials were industry funded. Conclusion: Current evidence is moderate, both in respect to the number of directly comparative trials and in the quality of reporting of these trials. No clear superiority in efficacy and tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.
Whittle et al[75] Opioids vs placebo, opioids or NSAIDs	MA (11 RCTs) Patients ≥18 years of age with a diagnosis of rheumatoid arthritis	N=672 <24 hours (four studies) 1 to 6 weeks (seven studies)	Primary: Percentage of patients with pain relief ≥30% and number of withdrawals due to adverse events Secondary: Percentage of patients with pain relief ≥50%, changes in function, quality of life, withdrawals due to inadequate	Primary: Data from the four single-dose studies were not included in the MA. A review of these studies showed that single-dose aspirin, acetaminophen, caffeine/phenacetin/ isopropylantipyrine†, codeine, codeine/aspirin, codeine/aspirin/phenacetin†, dextropropoxyphene/acetaminophen†, pentazocine and propoxyphene† were all associated with greater pain relief compared to placebo. No significant differences in efficacy were found between these agents. Five of the remaining seven studies that were at least one week in duration compared codeine/acetaminophen, morphine CR, pentazocine, tilidine/naloxone† and tramadol/ acetaminophen to placebo. One study compared dextropropoxyphene/aspirin† to aspirin, and one study compared codeine/acetaminophen plus diclofenac to diclofenac. None of these studies reported data on percentage of patients with pain relief of ≥30%. The rate of withdrawal due to adverse events was higher with opioids but not significantly different from placebo (RR, 2.67; 95% CI, 0.52 to 13.75).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			analgesia and adverse events	Secondary: One study showed that 60% of patients receiving codeine/acetaminophen achieved ≥50% pain relief compared to 26% with placebo (RR, 2.28; 95% CI, 0.99 to 5.25). Three studies showed that opioids were associated with greater improvement in CGI within the first six weeks compared to placebo (RR, 1.44; 95% CI, 1.03 to 2.03; NNT, 6). There were no significant differences between opioids and placebo with regard to changes in function, as measured by HAQ (weighted mean difference, -0.10; 95% CI, -0.33 to 0.13). One study showed that codeine/acetaminophen led to a greater improvement in self-reported disability scale compared to placebo (P=0.04). The number of withdrawals due to inadequate analgesia was similar between opioids and placebo (RR, 0.82; 95% CI, 0.34 to 2.01).The risk of adverse events was higher in patients receiving opioids compared to patients receiving placebo (OR, 3.90; 95% CI, 2.31 to 6.56; NNH, 4). The most commonly reported adverse events were nausea, vomiting, dizziness, lightheadedness and constipation.When a net efficacy was adjusted for risk, opioids provided no additional benefit compared to placebo (RR, 1.20; 95% CI, 0.89 to 1.61). Moreover, there were no significant differences in efficacy and safety between opioids and NSAIDs.
Eisenberg et al[76] Opioids vs placebo, opioids or non-opioid analgesics	MA (23 RCTs) Patients ≥18 years of age with neuropathic pain	N=727 Short-term: <24 hours (14 RCTs) Intermediate-term: 8 to 70 days (nine RCTs)	Primary: Change in PI Secondary: Safety	Primary: Among the 14 short-term studies (n=267), the following opioids were compared to placebo: morphine, alfentanil, fentanyl, meperidine and codeine. Six trials showed greater pain relief with opioids compared to placebo; five trials showed equivalent efficacy between opioids and placebo; two trials demonstrated mixed efficacy and one trial showed a reduction in the affective but not the sensory component of pain. MA was performed on six trials and showed that opioids were associated with a lower PI score by 16 points on a 100-point VAS compared to placebo (95% CI, -23 to -9; P<0.001). When analyzed separately for peripheral and central pain, the differences in PI between opioids and placebo were 15 (95% CI, -23 to -7; P<0.001) and 18 points (95% CI, -30 to -5; P=0.006), respectively. MA on two trials using percentage of pain reduction showed an additional 26% reduction in pain with opioids vs placebo (95% CI, 17 to 35; P<0.00001). Among the nine intermediate-term studies (n=460), the following opioid analgesics were compared to placebo: morphine, oxycodone, methadone and levorphanol. Three of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				trials also compared opioids to carbamazepine, nortriptyline, desipramine and gabapentin. Two of the trials compared different dosages of the same opioid, including methadone and levorphanol. MA of seven studies showed PI score was 13 points lower with opioids than placebo (95% CI, -16 to -9; P<0.00001). Evoked PI was measured in two studies, which showed that PI was 24 points lower with opioids than placebo (95% CI, -33 to -15). Two studies showed a 6-point reduction in PI with morphine or methadone compared to non-opioid analgesics (95% CI, -12 to 0). A dose-dependent analgesic effect was found with methadone and levorphanol (P values not reported). Secondary: When comparing opioids to placebo, there was a higher incidence of nausea (33 vs 9%; NNH, 4.2; 95% CI, 3.2 to 5.6), constipation (33 vs 10%; NNH, 4.2; 95% CI, 3.3 to 5.9), drowsiness (29 vs 12%; NNH, 6.2; 95% CI, 4.3 to 10.0), dizziness (21 vs 6%; NNH, 7.1; 95% CI, 5.0 to 11.1) and vomiting (15 vs 3%; NNH, 8.3; 95% CI, 5.6 to 14.3). In four intermediate-term studies, 11 and 4% of patients in the opioid and placebo groups withdrew due to adverse events (NNH, 16.7; 95% CI, 9.1 to 100.0).
Acute Pain				
Singla et al[77] Oxycodone/ acetaminophen ER every 12 hours vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age scheduled to undergo bunionectomy surgery considered healthy or with mild systemic disease states	N=303 48 hours	Primary: SPID over the first 48 hours after bunionectomy surgery Secondary: SPID from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours; TOTPAR from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36	Primary: The mean SPID from baseline to 48 hours was significantly higher in the oxycodone/acetaminophen ER (114.9) group compared to placebo (66.9), resulting in a treatment difference of 48.0 (95% CI, 27.3 to 68.6; *P*<0.001) Secondary: The mean SPID from baseline (0 hours) to 4 hours for the oxycodone/acetaminophen ER group was 8.1 versus 1.7 for placebo, resulting in a treatment difference of 6.5 (95% CI, 4.4 to 8.6; *P*<0.001). The mean SPID from 0 to 12 hours for oxycodone/acetaminophen ER was 15.5 versus 2.5 for placebo, resulting in a treatment difference of 13.0 (95% CI, 7.7 to 18.2; *P*<0.001). Mean SPID scores for oxycodone/acetaminophen ER and placebo from 0 to 24 hours were 41.0 and 13.2, respectively, for a treatment difference of 27.7 (95%CI, 17.2 to 38.2; *P*<0.001). The mean SPID score from 0 to 36 hours was 76.0 for oxycodone/acetaminophen ER versus 36.2 for placebo, which resulted in a treatment difference of 39.7 (95% CI, 24.1 to 55.3; *P*<0.001). The mean SPID score from 12 to 24 hours was 25.5 for oxycodone/acetaminophen ER versus 10.7 for placebo, which resulted in a treatment difference of 14.8 (95% CI, 8.3 to 21.3; *P*<0.0001). Mean SPID scores for oxycodone/acetaminophen ER and placebo for 24 to 36 hours were 35.0 versus 23.0,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hours and 36 to 48 hours; time to perceptible, meaningful and confirmed pain relief; percentage of patients with a 30% or greater reduction in PI scores	respectively, which results in a treatment difference of 12.0 (95% CI, 5.8 to 18.3; *P*=0.0002). The mean SPID from 36 to 48 hours for the oxycodone/acetaminophen ER group was 38.9 versus 30.7 for placebo, resulting in a treatment difference of 8.3 (95% CI, 1.8 to 14.7; *P*=0.0118). From 0 to 4 hours, oxycodone/acetaminophen ER had a mean TOTPAR value of 6.8 versus 3.4 for placebo, resulting in a treatment difference of 3.4 (95% CI, 2.4 to 4.4; *P*<0.001). Mean TOTPAR values from 0 to 12 hours for oxycodone/acetaminophen and placebo were 16.5 and 11.2, respectively, which resulted in a treatment difference of 5.3 (95% CI, 2.9 to 7.7; *P*<0.001). The mean TOTPAR value for oxycodone/acetaminophen ER from 0 to 24 hours was 38.4 versus 26.8 for placebo, resulting in a treatment difference of 11.6 (95% CI, 7.1 to 16.2; *P*<0.001). From 0 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 64.2 versus 47.5 for placebo, which resulted in a treatment difference of 16.8 (95% CI, 9.8 to 23.8; *P*<0.001). Mean TOTPAR values for oxycodone/acetaminophen ER and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). From 12 to 24 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 21.9 versus 15.6 for placebo, resulting in a treatment difference of 6.3 (95% CI, 3.4 to 9.2; *P*<0.0001). From 24 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 25.8 versus 20.7 for placebo, which resulted in a treatment difference of 5.2 (95% CI, 2.1 to 8.2; *P*=0.0009). The mean TOTPAR value for oxycodone/acetaminophen ER from 36 to 48 hours was 27.1 versus 23.4 for placebo, resulting in a treatment difference of 3.7 (95% CI, 0.4 to 7.0; *P*=0.0276). The median time to perceptible pain relief for oxycodone/acetaminophen ER was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen ER group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/acetaminophen ER versus 27.2% for placebo (*P*<0.0001).
Detoxification				
Madlung-Kratzer et al[78] Morphine slow-release	DB, MC, PG, RCT Patients ≥18 years of age	N=202 22 days	Primary: Non-inferiority of dose reduction regimens	Primary: Completion rate per treatment group was 51 and 49% in the morphine and methadone groups, resulting in a difference in completion rates between treatment groups of 2% (95% CI, -12 to 16). According to the prior-defined non-inferiority margin of -15%, morphine is non-inferior to methadone for detoxification.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs methadone Patients continued their previous maintenance treatment for 3 consecutive days and then were randomized to treatment based on previous drug for maintenance treatment and dose level. Dose reduction regimens were started and maintained for 3 consecutive days under DB conditions. Thereafter, detoxification was initiated by tapered dose reductions over a period of 16 days in order to reach abstinence for 3 days.	with a confirmed diagnosis of opioid addiction, who have received maintenance treatment with either morphine slow-release or methadone at constant doses for ≥1 month		Secondary: Patient-reported outcomes and safety	Secondary: At study entry, signs and symptoms of withdrawal were mild but deteriorated steadily over time (day 0 vs day 22; P<0.001). Craving for opiates varied considerably but was generally rated as moderate. No changes became evident during the detoxification phase and there were no significant differences between treatment groups over time, respectively (morphine: day 0, 35.4±35.1 mm; day 22, 32.0±35.1 mm; P=0.442; and methadone: day 0; 38.7±38.6 mm, day 22; 36.8±36.5 mm; P=0.813). Cravings for alcohol, cocaine and cannabis were low throughout detoxification without any significant differences between groups or over time (P values not reported). The proportion of patients reporting at least one adverse event was 16 and 13% in the morphine and methadone groups (P=0.586). The majority of adverse events were gastrointestinal system disorders (nausea, vomiting, and dentalgia), followed by psychiatric disorders (dysphoria, agitation, depression and panic attacks).

*Synonym for acetaminophen.
†Agent not available in the United States.
Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, ITT=intention-to-treat, LS=least square, MA=meta-analysis, MC=multicenter, MD=multi-dose, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single-arm, XO=crossover

Miscellaneous abbreviations: ACR=American College of Rheumatology, $AUCMB_{avg}$=average area under the curve of VAS scores overtime between baseline and end of study, BDI=Beck depression inventory, BPI=Brief Pain Inventory, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, CPSI=Chronic Pain Sleep Inventory, CRPS=Complex Regional Pain Syndrome, ECG=electrocardiogram, EORTC=European Organization for Research and Treatment of Cancer, HAQ=Health Assessment Questionnaire, HbA1c=glycosylated hemoglobin, MOS=Medical Outcomes Study, MOS Sleep-R= Medical Outcome Study Sleep Scale – Revised, MPI=multidimensional pain inventory, MRI=magnetic resonance imaging, NNH=number needed to harm, NNT=number needed to treat, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, OR=odds ratio, PDI-Pain Disability Index, PGIC=Patient's Global Impression of Change, PI=Pain Intensity, PPS=Play Performance Scale, SF-36=short form 36 health assessment questionnaire, RMDQ=Roland Morris Disability Questionnaire, RR=relative risk, SGAM=Subject global assessment of medication, SD=standard deviation, SPID= summed pain intensity difference, TOTPAR=total pain relief, VAS=visual analog scale, WOMAC index=Western Ontario and McMaster Universities Index

Special Populations

Table 5. Special Populations[1-18]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in severe hepatic dysfunction.	C	Yes (% low); breast-feeding is not advised.
Fentanyl	Use with caution in the elderly. Approved for use in opioid-tolerant children ≥2 years of age.	Insufficient information exists; use with caution.	Insufficient information exists; use with caution.	C	Yes (% not reported); do not use in nursing women.
Hydrocodone	It is recommended that elderly patients start at lower doses and be closely monitored. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal impairment can increase hydrocodone concentra-tions. ER capsule: Lower initial doses are recommended with close monitoring for patients with mild to severe renal impairment or end-stage renal disease. ER tablet: Initiate therapy with one-half of the starting dose in patients with moderate to severe renal impairment or end-stage renal disease.	No adjustment in initial dose is necessary for patients with mild or moderate hepatic impairment. ER capsule: Patients with severe hepatic impairment should start at the lowest dose (10 mg) and be monitored closely. ER tablet: Patients with severe hepatic impairment should start at one-half of the starting dose.	C	Yes (% low); risk vs benefit should be weighed in order to either discontinue the medication or nursing, taking into account the importance of the medication to the mother.
Hydromorphone	Use with caution in	Renal dose	Hepatic dose	C	Yes

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	the elderly. Safety and efficacy in pediatric patients ≤17 years of age have not been established.	adjustment is required in moderate renal impairment.	adjustment is required in moderate and severe hepatic impairment.		(% not reported); breast-feeding is not advised.
Methadone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Morphine sulfate	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required.	Hepatic dose adjustment is required.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Oxycodone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required and dose titration should follow a conservative approach.	Hepatic dose adjustment is required and careful dose titration is warranted.	B	Yes (% not reported); breast-feeding is not advised.
Oxymorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Caution should be used in patients with moderate to severe renal impairment, starting with lower doses and titrating the dosage	Caution should be used in patients with mild hepatic impairment; starting with the lowest dose and titrating the dosage slowly.	C	Unknown; caution should be exercised.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		slowly.	Contra-indicated in moderate and severe hepatic impairment.		
Tapentadol	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Not recommended in patients with severe renal impairment.	Use with caution in patients with moderate hepatic impairment; not recommended in patients with severe hepatic impairment.	C	Insufficient/ limited information on the excretion of tapentadol in human breast milk; should not be used during breast feeding.
Combination Products					
Morphine sulfate/ naltrexone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required in severe renal impairment.	Hepatic dose adjustment is required in severe hepatic impairment.	C	Yes (morphine sulfate; % variable); benefits and risks should be evaluated before use in nursing women.
Oxycodone/ acetaminophen	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required due to higher plasma oxycodone concentrations.	Start with one tablet dose for hepatic impairment and adjust as needed.	C	Yes (both; oxycodone % not reported, acetamino-phen 1 to 2%)

ER=extended release

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-18]

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Central Nervous System											
Abnormal gait	-	a	-	-	-	<5	<1	-	-	-	-
Agitation	-	a	-	-	a	<5	<1	<1	-	-	-
Anxiety	a	3 to 10	≥1 to <10	0 to 4	-	<5 to 6	1 to 5	≥1 to <10	2	2.2	-
Aphasia	-	<1	-	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	<5	-	-	-	-	-
Balance disorder	-	-	-	<2	-	-	-	-	-	-	-
Central nervous system depression	-	-	-	-	-	-	-	<1	-	-	-
Cognitive disorder	-	-	-	<2	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<5	-	-	-	-	-
Convulsions	-	a	-	<2	-	<5	-	-	-	-	-
Coordination abnormal	-	a	-	<2	-	-	-	-	-	<1	-
Depressed level of consciousness	-	-	-	<2	-	-	-	<1	-	<1	-
Depression	a	3 to 10	≥1 to <10	3	-	<3 to 10	<1	≥1 to <10	1	≥1 to <10	-
Difficulty in walking	-	-	-	<2	-	-	-	-	-	-	-
Disturbance in attention	-	-	-	<2	-	-	-	-	1	<1	-
Dizziness	2 to 16	3 to 10	2 to 7	2 to 11	a	6	13	4.8 to 17.8	17	1.2 to 7.7	13
Drowsiness	-	-	-	-	-	9	-	-	-	-	-
Dysarthria	-	-	-	<2	-	-	-	-	-	-	-
Dysgeusia	-	-	-	<2	-	-	-	-	-	-	-
Dyskinesia	-	-	-	<2	-	-	-	-	-	-	-
Encephalopathy	-	-	-	<2	-	-	-	-	-	-	-
Foot drop	-	-	-	-	-	<3	-	-	-	-	-
Headache	5 to 16	3 to 10	2 to 7	5 to 12	a	<3 to >10	7	2.9 to 12.2	15	2.3 to 6.9	-
Hostility	-	<1	-	-	-	-	-	-	-	-	10
Hyperesthesia	-	-	-	<2	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	<1	-	-	-	-
Hyperreflexia	-	-	-	<2	-	-	-	-	-	-	-
Hypertonia	-	<1	-	-	-	-	-	-	-	-	-
Hypoesthesia	2	-	-	<2	-	-	<1	-	-	-	-
Hypotonia	-	<1	-	-	-	-	<1	-	-	-	-
Irritability	-	-	-	-	-	-	-	-	-	≥1 to <10	-
Loss of concentration	-	-	-	-	-	<3	-	-	-	-	-
Memory impairment	-	-	-	<2	-	-	-	-	a	<1	-
Mental impairment	-	-	-	-	-	-	-	<1	-	<1	-
Migraine	a	-	≥1 to <10	-	-	-	<1	-	-	-	-
Myoclonus	-	-	-	<2	-	<3	-	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Paresthesia	2	a	≥1 to <10	<2	-	<3 to 10	<1	-	-	<1	-
Psychomotor hyperactivity	-	-	-	<2	-	-	-	-	-	-	-
Sedation	-	-	≥1 to <5	<2	a	-	-	5.9	-	≥1 to <10	-
Seizures	-	-	-	-	a	<3	<1	-	-	-	-
Somnolence	2 to 14	>10	1 to 5	1to 15	-	>10	23	1.9 to 19.1	12	1.2 to 13.9	4
Stupor	-	<1	-	-	-	-	<1	-	-	<1	-
Speech disorder	-	a	-	-	-	<3	<1	-	-	-	-
Tremor	2	a	3	<2	-	<5	<1	-	1	≥1 to <10	-
Vertigo	-	<1	-	<2	-	<5	<1	-	2	-	-
Visual disturbances	-	-	-	-	a	-	<1	-	1	-	-
Dermatological											
Application site reaction	2 to 15	a	-	-	-	-	-	-	-	-	-
Blister	-	-	-	-	-	-	-	-	-	-	1
Clamminess	-	-	-	-	-	-	-	<1	-	-	-
Cold sweat	-	-	-	-	-	-	-	-	-	<1	-
Decubitus ulcer	-	-	-	-	-	<3	-	-	-	-	-
Dermatitis	-	-	-	-	-	-	-	<1	-	-	-
Dry skin	-	-	-	-	-	<5	<1	-	-	-	-
Edema	-	a	1 to 3	-	a	<5	<1	≥1 to <10	-	-	-
Erythema	-	a	-	<2	-	-	-	-	-	-	1
Excoriation	-	-	-	-	-	-	-	-	-	-	1
Exfoliative dermatitis	-	<1	-	-	-	-	<1	-	-	-	-
Hemorrhagic urticaria	-	-	-	-	a	-	-	-	-	-	-
Hyperhidrosis	4	-	≥1 to <10	1 to 6	-	-	-	-	5	3.4	-
Itching	-	a	-	-	-	-	-	-	-	-	-
Night sweats	-	-	≥1 to <10	-	-	-	-	-	-	<1	-
Other skin rashes	-	-	-	-	a	-	-	-	-	-	-
Papules	-	a	-	-	-	-	-	-	-	-	-
Piloerection	-	-	-	-	-	-	-	-	-	<1	-
Pruritus	4	3 to 10	0 to 3	1 to 8	a	<3	-	0 to 15.2	5	5.6 to 6.2	1
Pustules	-	<1	-	-	-	-	-	-	-	-	-
Rash	2	a	≥1 to <10	3	-	<3 to 10	1 to 5	-	1	<1	2
Skin reaction localized	-	a	-	-	-	-	-	-	-	-	-
Skin laceration	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Sweating	-	>10	-	-	a	5 to 10	5	8.6 to >10.0	-	-	-
Urticaria	-	-	-	-	a	<5	<1	<1	-	-	-
Gastrointestinal Disorders											
Abdominal distention	-	<1	-	<2	-	-	-	<1	-	<1	-
Abdominal discomfort	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Abdominal pain	-	3 to 10	≥1 to <5	2 to 5	a	<3 to 10	1 to 5	≥1 to <10	-	-	-
Abdominal pain; lower	-	-	-	-	-	-	-	-	-	<1	-
Abdominal pain; upper	-	-	≥1 to <5	-	-	-	-	-	-	1.1 to 2.3	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Abdominal tenderness	-	-	-	-	-	-	-	-	-	<1	-
Abnormal feces	-	-	-	<2	-	-	-	-	-	-	-
Anal fissure	-	-	-	<2	-	-	-	-	-	-	-
Anorexia	2	3 to 10	-	1 to 6	a	<3 to 10	1 to 5	-	-	≥1 to <10	-
Bezoar	-	-	-	<2	-	-	-	-	-	-	-
Biliary colic	-	-	-	-	-	<3	-	-	-	-	-
Biliary pain	-	-	-	-	-	<5	-	-	-	-	-
Biliary tract spasm	-	-	-	-	a	a	-	-	-	-	-
Constipation	3 to 14	>10	3 to 12	7 to 31	a	9 to >10	23	5.7 to 27.6	17	7.0 to 31.2	4
Cramps	-	-	-	-	-	a	-	-	-	-	-
Decreased appetite	-	-	1 to 2	-	-	-	-	≥1 to <10	2	≥1 to <10	-
Delayed gastric emptying	-	-	-	-	-	<3	-	-	-	-	-
Diarrhea	3	3 to 10	≥1 to <5	3 to 8	-	<3 to 10	1 to 5	≥1 to <10	-	1.1 to 7.0	≥1
Diverticulum	-	-	-	<2	-	-	-	-	-	-	-
Dry mouth	7	>10	≥1 to <5	1 to 5	a	<3 to 10	6	≥1 to <10	7	1.8 to 5.7	≥1
Duodenitis	-	-	-	<2	-	-	-	-	-	-	-
Dyspepsia	3	3 to 10	≥1 to <5	4	-	<5	1 to 5	≥1 to <10	3	≥1 to <10	≥1
Dysphagia	-	-	-	<2	-	<5	<1	-	-	-	-
Eructation	-	-	-	<2	-	-	<1	-	-	-	-
Fecaloma	-	-	-	-	-	-	-	-	-	<1	-
Flatulence	-	a	-	<2	-	-	<1	-	-	≥1 to <10	-
Gastritis	-	-	-	-	-	-	1 to 5	-	-	-	-
Gastroenteritis	-	-	≥1 to <5	<2	-	<5	-	-	-	-	-
Gastro-esophageal reflux	-	-	≥1 to <10	-	-	<3	-	-	-	-	-
Gastrointestinal motility disorder	-	-	-	<2	-	-	<1	-	-	-	-
Glossitis	-	-	-	-	a	-	-	-	-	-	-
Hematochezia	-	-	-	<2	-	-	-	-	-	-	-
Hemorrhoids	-	-	-	<2	-	-	-	-	-	-	-
Ileus	-	-	-	<2	-	-	<1	<1	-	-	-
Increased appetite	-	-	-	<2	-	-	<1	-	-	-	-
Intestinal obstruction	-	-	-	<2	-	-	-	-	-	-	-
Large intestine perforation	-	-	-	<2	-	-	-	-	-	-	-
Nausea	8 to 23	>10	7 to 16	9 to 28	a	7 to >10	23	2.9 to 33.1	21	11.1 to 22.2	31
Pancreatitis	-	-	-	-	-	-	-	-	-	<1	-
Painful defecation	-	-	-	<2	-	-	-	-	-	-	-
Rectal disorder	-	-	-	-	-	<5	-	-	-	-	-
Stomach atony disorder	-	-	-	-	-	<3	-	-	-	-	-
Stomach discomfort	2	-	-	-	-	-	-	-	-	≥1 to <10	-
Stomatitis	-	-	-	-	-	-	<1	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Thirst	-	-	-	-	-	<5	<1	-	-	-	-
Vomiting	2 to11	>10	3 to 7	6 to 14	a	<3 to >10	12	0 to 15.6	8	4.1 to 8.4	9
Weight gain	-	-	-	-	a	-	-	-	-	-	-
Weight loss	-	a	-	1 to 3	-	<5	-	≥1 to <10	a	-	-
Laboratory Values											
Abnormal liver function tests	-	-	-	-	-	<5	-	-	-	-	-
Alanine aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Anemia	-	-	-	-	-	<5	-	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Blood amylase increased	-	-	-	<2	-	-	-	-	-	-	-
Blood potassium decreased	-	-	-	<2	-	-	-	-	-	-	-
Blood testosterone decreased	-	-	-	<2	-	-	-	-	-	-	-
Gynecomastia	-	-	-	-	-	<3	-	-	-	-	-
Hepatic enzyme increased	-	-	-	<2	-	-	-	-	-	-	≥1
Hypokalemia	-	-	≥1 to <10	-	a	-	-	-	-	-	-
Hypomagnesemia	-	-	-	-	a	-	-	-	-	-	-
Hyponatremia	-	-	-	-	-	<3	<1	-	-	-	-
Increased blood cholesterol	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Increased gamma-glutamyltransferase	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	<3	-	-	-	-	-
Oxygen saturation decreased	-	-	-	<2	-	-	-	<1	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	-	-	-	-	-	-	<1	-	-	-	-
Thrombocytopenia; reversible	-	-	-	-	a	<5	-	-	-	-	-
Psychiatric Disorders											
Abnormal dreams	-	a	-	<2	-	<5	1 to 5	-	1	<1	-
Aggression	-	-	-	<2	-	-	-	-	-	-	-
Amnesia	-	a	-	-	-	<5	<1	-	-	-	-
Apathy	-		-	-	-	<3	-	-	-	-	-
Confusional state	2	>10	-	<2	a	<5	1 to 5	≥1 to <10	-	<1	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Crying	-	-	-	<2	-	-	-	-	-	-	-
Delirium	-	-	-	-	-	<5	-	-	-	-	-
Depersonalization	-	<1	-	-	-	-	<1	-	-	-	-
Disorientation	-	-	-	-	a	-	-	≥1 to <10	-	<1	-
Dysphoria	-	-	-	<2	a	-	-	<1	-	-	-
Emotional lability	-	-	-	-	-	-	<1	-	-	-	-
Euphoric mood	-	3 to 10	-	<2	a	<5	1 to 5	<1	a	<1	-
Hallucination	-	3 to 10	-	<2	a	<5	<1	<1	-	<1	-
Insomnia	3	3 to 10	≥1 to <10	3 to 7	a	<3 to 10	1 to 5	≥1 to <10	4	1.3 to 2.9	≥1
Listless	-	-	-	<2	-	-	-	-	-	-	-
Mental status changes	-	-	-	-	-	-	-	<1	-	<1	-
Mood altered	-	-	-	<2	-	-	-	-	-	-	-
Mood swings	-	-	-	-	-	-	-	-	-	<1	-
Nervousness	-	3 to 10	-	<2	-	<5	1 to 5	≥1 to <10	-	<1	-
Panic attack	-	-	-	<2	-	-	-	-	-	-	-
Paranoid reaction	-	a	-	<2	-	-	-	-	-	-	-
Restlessness	-	-	-	<2	-	-	-	≥1 to <10	-	≥1 to <10	-
Suicide ideation	-	-	-	<2	-	-	-	-	-	-	-
Thinking abnormal	-	a	-	-	-	<5	1 to 5	-	a	<1	-
Other											
Abnormal ejaculation	-	-	-	-	-	<5	-	-	-	-	-
Accidental injury	-	a	-	-	-	<3 to 10	<1	-	-	-	-
Allergic reaction	-	a	-	-	-	-	-	<1	-	-	-
Amblyopia	-	<1	-	-	-	<5	-	-	-	-	-
Amenorrhea	-	-	-	-	a	<3	<1	-	-	-	-
Anaphylactic reaction	-	-	-	-	-	-	<1	-	-	-	-
Anorgasmia	-	a	-	-	-	-	-	-	-	-	-
Apnea	-	3 to 10	-	-	-	-	-	-	-	-	-
Arrhythmia	-	a	-	-	a	-	-	-	-	-	-
Arthralgia	2	-	≥1 to <10	2 to 6	-	<3	-	-	-	≥1 to <10	-
Asthenia	-	>10	-	1 to 11	a	<3 to 10	6	-	2	<1	-
Asthma	-	<1	-	-	-	<3	-	-	-	-	-
Atelectasis	-	-	-	-	-	<3	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	<3	-	-	-	-	-
Back pain	3	3 to 10	1 to 4	3 to 4	-	<3 to 10	-	-	-	-	-
Bladder pain	-	<1	-	-	-	-	-	-	-	-	-
Bone pain	-	-	-	-	-	<3	-	-	-	-	-
Bradycardia	-	<1	-	<2	a	<5	-	<1	-	-	-
Bronchitis	-	a	≥1 to <5	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	<2	-	-	-	-	-	-	-
Cardiomyopathy	-	-	-	-	a	-	-	-	-	-	-
Chest discomfort	-	-	-	2	-	-	-	-	-	-	-
Chest pain	-	a	≥1 to <5	-	-	<3	<1	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Chills	-	-	≥1 to <5	<2	-	<3	1 to 5	-	1	≥1 to <10	-
Conjunctivitis	-	-	-	-	-	<3	-	-	-	-	-
Contusion	-	-	≥1 to <10	<2	-	-	-	-	-	-	-
Coughing	-	a	≥1 to <10	-	-	-	<1	-	-	-	≥1
Decreased libido	-	a	-	<2	a	<5	<1	-	-	-	-
Dehydration	-	-	≥1 to <10	<2	-	-	<1	≥1 to <10	-	-	-
Depressed cough reflex	-	-	-	-	-	<3	-	-	-	-	-
Diaphoresis	-	-	-	-	-	<3	-	-	-	-	-
Difficult micturition	-	-	-	-	-	-	-	<1	-	-	-
Drug withdrawal syndrome	-	-	-	2 to 10	-	<5	<1	-	-	<1	-
Diplopia	-	-	-	<2	-	<3	-	-	-	-	-
Dry eye	-	-	-	<2	-	-	-	-	-	-	-
Dyspnea	3	3 to 10	≥1 to <10	3	-	<3 to 10	1 to 5	≥1 to <10	1	<1	-
Dysuria	-	-	-	<2	-	<5	<1	-	-	<1	1
Electrocardiogram abnormalities	-	-	-	-	a	-	-	-	-	-	-
Edema peripheral	7	-	≥1 to <5	2 to 5	-	<3 to 10	<1	-	-	≥1 to <10	1
Ejaculatory difficulty	-	a	-	-	-	-	-	-	-	-	-
Erectile dysfunction	-	-	-	<2	-	-	-	-	1	<1	-
Extrasystoles	-	-	-	<2	a	-	-	-	-	-	-
Eye pain	-	-	-	-	-	<5	-	-	-	-	-
Facial edema	-	-	-	-	-	-	<1	-	-	-	-
Facial flushing	-	-	-	-	-	<3	-	-	-	-	-
Fall	4	-	≥1 to <10	2	-	-	-	-	-	-	-
Fatigue	5	3 to 10	1 to 4	-	-	-	-	≥1 to <10	9	4.1	≥1
Feeling abnormal	-	-	-	<2	-	-	-	-	-	-	-
Feeling drunk	-	-	-	<2	-	-	-	-	-	-	-
Feeling hot and cold	-	-	-	<2	-	-	-	-	-	-	-
Feeling jittery	-	-	-	<2	-	-	-	<1	-	<1	-
Foot fracture	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Fever	-	3 to 10	-	-	-	<3 to 10	1 to 5	-	-	-	-
Flu syndrome	-	-	-	-	-	<3 to 10	-	-	-	-	-
Fluid retention	-	-	-	<2	-	-	-	-	-	-	-
Flushing	-	a	-	<2	a	<3	-	≥1 to <10	-	<1.0 to 2.3	-
Hangover	-	-	-	<2	-	-	-	-	-	-	-
Heart failure	-	-	-	-	a	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	<1	-	-	-	-
Hemoptysis	-	a	-	-	-	-	-	-	-	-	-
Hiccups	-	a	-	-	-	<5	1 to 5	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	<1	-	-	1
Hot flush	-	-	≥1 to <10	-	-	-	-	-	2	≥1 to <10	-
Hypersensitivity	-	-	-	-	-	-	-	<1	a	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Hypertension	a	a	≥1 to <5	<2	-	<5	-	≥1 to <10	-	-	-
Hyperuricemia	-	-	-	<2	-	-	-	-	-	-	-
Hyperventilation	-	-	-	<2	-	-	-	-	-	-	-
Hypogonadism	-	-	-	<2	-	-	-	-	-	-	-
Hypotension	-	-	-	<2	a	<5	-	<1	-	<1	-
Hypothermia	-	-	-	<2	-	-	-	-	-	-	-
Hypoventilation	-	3 to 10	-	-	-	<5	-	-	-	-	-
Hypoxia	-	-	-	<2	-	<3	-	<1	-	-	-
Impotence	-	-	-	-	-	<5	<1	-	-	-	-
Infection	-	-	-	-	-	5 to 10	-	-	-	-	-
Influenza-like symptoms	a	3 to 10	1 to 3	-	-	-	-	-	-	-	-
Joint injury	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint sprain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint swelling	3	-	-	-	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	a	a	-	-	-	-	-
Lethargy	-	-	≥1 to <10	-	-	<5	-	≥1 to <10	1	≥1 to <10	-
Lymphadenopathy	-	-	-	-	-	-	<1	-	-	-	-
Malaise	-	-	-	<2	-	<5	<1	-	-	<1	-
Micturition disorder	-	-	-	<2	-	-	-	-	-	-	-
Miosis	-	-	-	<2	-	<3	-	<1	-	-	-
Muscle spasms	-	-	≥1 to <5	1 to 3	-	-	-	-	-	≥1 to <10	-
Muscle strain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	-	<1	-
Musculoskeletal pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Myalgia	a	-	≥1 to <10	<2	-	-	-	-	-	<1	-
Neck pain	a	-	≥1 to <10	-	-	-	<1	-	-	-	-
Non-cardiac chest pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Non-cardiogenic pulmonary edema	-	-	-	-	-	<3	-	-	-	-	-
Nystagmus	-	-	-	-	-	<3	-	-	-	-	-
Oliguria	-	<1	-	-	-	<5	-	-	-	-	-
Orthostatic hypotension	-	-	-	-	-	-	-	-	-	<1	-
Osteoarthritis	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Overdose	-	-	-	<2	-	-	-	-	-	-	-
Pain	a	3 to 10	≥1 to <10	2	-	<3	<1	-	-	-	-
Pain in extremity	3	-	≥1 to <10	3	-	-	-	-	-	-	-
Pallor	-	-	-	-	-	<3	-	-	-	-	-
Palpitations	-	-	-	<2	a	<5	-	<1	-	-	-
Pharyngitis	-	3 to 10	-	-	-	-	<1	-	-	-	-
Polyuria	-	-	-	-	-	-	<1	-	-	-	-
Postural hypotension	-	-	-	-	-	-	1 to 5	<1	-	-	-
Pulmonary edema	-	-	-	-	a	-	-	-	-	-	-
Pyrexia	-	-	≥1 to <10	2	-	-	-	≥1 to <10	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
QT interval prolongation	-	-	-	-	a	-	-	-	-	-	-
Respiratory depression	-	a	-	<2	a	-	-	<1	-	-	-
Respiratory disorder	-	<1	-	-	-	-	-	-	-	-	-
Respiratory distress	-	-	-	<2	-	-	-	<1	-	-	-
Respiratory insufficiency	-	-	-	-	-	<3	-	-	-	-	-
Respiratory rate decreased	-	-	-	-	-	-	-	<1	a	-	-
Rhinorrhea	-	-	-	<2	-	-	-	-	-	<1	-
Rhinitis	-	a	-	-	-	<3	-	-	-	-	-
Rigors	-	a	-	-	-	-	-	-	-	-	-
Sexual dysfunction	-	-	-	<2	-	-	-	-	a	-	-
Sinusitis	-	a	≥1 to <5	-	-	-	-	-	-	-	-
Skeletal muscle rigidity	-	-	-	-	-	<5	-	-	-	-	-
Sneezing	-	-	-	<2	-	-	-	-	-	-	-
ST depression	-	-	-	-	-	-	<1	-	-	-	-
Stertorous breathing	-	<1	-	-	-	-	-	-	-	-	-
Syncope	-	a	-	<2	a	<5	<1	<1	-	-	-
T-wave inversion	-	-	-	-	a	-	-	-	-	-	-
Tachycardia	-	a	-	<2	a	<5	-	<1	-	-	-
Taste perversion	-	-	-	-	-	<5	<1	-	-	-	-
Tinnitus	-	-	0 to 2	<2	-	-	<1	-	-	-	-
Torsade de pointes	-	-	-	-	a	-	-	-	-	-	-
Twitching	-	-	-	-	-	-	1 to 5	-	-	-	-
Upper respiratory tract infection	a	3 to 10	1 to 3	-	-	-	-	-	-	-	-
Urinary abnormality	-	-	-	-	-	<3	-	-	-	-	-
Urinary frequency	-	<1	-	<2	-	-	-	-	-	-	-
Urinary hesitancy	-	-	-	<2	a	<3	-	-	a	-	-
Urinary retention	-	-	-	<2	a	<5	<1	<1	-	<1	-
Urinary tract infection	3	-	1 to 5	-	-	5 to 10	-	-	-	-	-
Urination impaired	-	-	-	-	-	-	<1	-	-	-	-
Vasodilation	-	-	-	-	-	<5	<1	-	-	-	-
Ventricular fibrillation	-	-	-	-	a	-	-	-	-	-	-
Ventricular tachycardia	-	-	-	-	a	-	-	-	-	-	-
Vision blurred	-	a	-	<2	-	<3	-	≥1 to <10	-	<1	-
Voice alteration	-	-	-	-	-	<5	<1	-	-	-	-
Weakness	-	-	-	-	-	a	-	≥1 to <10	-	-	-

APAP=Acetaminophen
*During dosage titration and maintenance therapy.
†At least one dosage formulation.
a Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-18]

Contraindication(s)	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Bronchial asthma or hypercarbia, acute or severe	a	a	a	a	a	a	a	a	a	a	a
Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days	-	-	-	-	-	-	-	-	a	-	-
Hypersensitivity reactions including anaphylaxis have been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	a
Hypersensitivity to any components or the active ingredient	a	a	a	a	a	a	a	a	a	a	a
Management of acute pain or in patients who require opioid analgesia for a short period of time	-	a	-	-	-	-	-	-	-	-	-
Management of intermittent pain (e.g., use on an as-needed basis)	-	a	-	-	-	-	-	-	-	-	-
Management of mild pain	-	a	-	-	-	-	-	-	-	-	-
Management of postoperative pain, including use after out-patient or day surgeries	-	a	-	-	-	-	-	-	-	-	-
Moderate and severe hepatic impairment	-	-	-	-	-	-	-	a	-	-	-
Opioid non-tolerant patients	-	a	-	a	-	-	-	-	-	-	-
Preexisting gastrointestinal surgery or narrowing of gastrointestinal tract	-	-	-	a	-	-	-	-	-	-	-
Respiratory depression, significant	a	a	a	a	a	a	a	a	a	a	a
Suspected or documented paralytic ileus	a	a	a	a	a	a	a	a	a	a	a

APAP=Acetaminophen

Boxed Warnings

Boxed Warning for Butrans® (buprenorphine)[1]

WARNING

Addiction, Abuse, and Misuse
Butrans® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Butrans®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Butrans®. Monitor for respiratory depression, especially during initiation of Butrans® or following a dose increase. Misuse or abuse of Butrans® by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.

Accidental Exposure
Accidental exposure to even one dose of Butrans®, especially by children, can result in a fatal overdose of buprenorphine.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Butrans® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Duragesic® (Fentanyl)[2]

WARNING

Addiction, Abuse, and Misuse
Duragesic® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Duragesic®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Duragesic®, even when used as recommended. Monitor for respiratory depression, especially during initiation of Duragesic® or following a dose increase. Because of the risk of respiratory depression, Duragesic® is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain.

Accidental Exposure
Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to Duragesic®. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.

Neonatal Opioid Withdrawal Syndrome

WARNING
Prolonged use of Duragesic® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Cytochrome P450 3A4 Interaction The concomitant use of Duragesic® with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving Duragesic® and any CYP3A4 inhibitor or inducer. Exposure To Heat Exposure of the Duragesic® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl and death. Patients wearing Duragesic® systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of Duragesic® to avoid overdose and death.

Boxed Warning to Zohydro® (hydrocodone ER)[3]

WARNING
Addiction, Abuse, and Misuse Zohydro ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Zohydro ER®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Zohydro ER®. Monitor for respiratory depression, especially during initiation of Zohydro ER® or following a dose increase. Instruct patients to swallow Zohydro ER® capsules whole; crushing, chewing, or dissolving Zohydro ER capsules can cause rapid release and absorption of a potentially fatal dose of hydrocodone. Accidental Exposure Accidental consumption of even one dose of Zohydro ER®, especially by children, can result in a fatal overdose of hydrocodone. Neonatal Opioid Withdrawal Syndrome For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Zohydro ER®. The co-ingestion of alcohol with Zohydro ER® may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

Boxed Warning for Hysingla ER® (hydrocodone ER)[4]

WARNING
Addiction, Abuse, and Misuse Hysingla ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Hysingla ER®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Hysingla ER®. Monitor for respiratory depression, especially during initiation of Hysingla ER® or following a dose increase. Instruct patients to swallow Hysingla ER® tablets whole; crushing, chewing, or dissolving Hysingla ER® tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone. Accidental Ingestion Accidental ingestion of even one dose of Hysingla ER®, especially by children, can result in a fatal overdose of hydrocodone. Neonatal Opioid Withdrawal Syndrome Prolonged use of Hysingla ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Cytochrome P450 3A4 Interaction The concomitant use of Hysingla ER® with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving Hysingla ER® and any CYP3A4 inhibitor or inducer.

Boxed Warning for Exalgo® (hydromorphone)[5]

WARNING
Addiction, Abuse, and Misuse Exalgo® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing EXALGO, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Exalgo®. Monitor for respiratory depression, especially during initiation of Exalgo® or following a dose increase. Instruct patients to swallow Exalgo® tablets whole; crushing, chewing, or dissolving Exalgo® tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone. Accidental Ingestion

WARNING
Accidental ingestion of even one dose of Exalgo®, especially by children, can result in a fatal overdose of hydromorphone. Neonatal Opioid Withdrawal Syndrome Prolonged use of Exalgo® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Dolophine®, Methadose® tablet, solution (methadone)[6-8]

WARNING
Addiction, Abuse, and Misuse Dolophine®/Methadose® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Dolophine®/Methadose®, and monitor all patients regularly for the development of these behaviors or conditions Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Dolophine®/Methadose®. Monitor for respiratory depression, especially during initiation of DOLOPHINE or following a dose increase. Accidental Ingestion Accidental ingestion of even one dose of Dolophine®/Methadose®, especially by children, can result in a fatal overdose of methadone. Life-threatening QT Prolongation QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients for changes in cardiac rhythm during initiation and titration of Dolophine®/Methadose®. Neonatal Opioid Withdrawal Syndrome Prolonged use of Dolophine®/Methadose® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration.

Boxed Warning for Methadose® concentrate, dispersible tablet (methadone)[9,10]

WARNING
Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have

WARNING
been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8: Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8:
Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Boxed Warning for Avinza®, Kadian® (morphine sulfate ER capsules)[11,12]

WARNING
Addiction, Abuse, and Misuse Avinza®/Kadian® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Avinza®/Kadian®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Avinza®/Kadian®. Monitor for respiratory depression, especially during initiation of

WARNING
Avinza®/Kadian® or following a dose increase. Instruct patients to swallow Avinza®/Kadian® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving Avinza®/Kadian® can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of even one dose of Avinza®/Kadian®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of Avinza®/Kadian® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Avinza®/Kadian®. The co-ingestion of alcohol with AVINZA may result in increased plasma levels and a potentially fatal overdose of morphine.

Boxed Warning for MS Contin® (morphine sulfate controlled-release)[13]

WARNING
Addiction, Abuse, and Misuse MS Contin® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS Contin®, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of MS Contin®. Monitor for respiratory depression, especially during initiation of MS Contin® or following a dose increase. Instruct patients to swallow MS Contin® tablets whole; crushing, chewing, or dissolving MS Contin® tablets can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of even one dose of MS Contin®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of MS Contin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning to OxyContin® (oxycodone ER)[14]

WARNING
Addiction, Abuse, and Misuse

WARNING

OxyContin® exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OxyContin® and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of OxyContin®. Monitor for respiratory depression, especially during initiation of OxyContin® or following a dose increase. Instruct patients to swallow OxyContin® tablets whole; crushing, chewing, or dissolving OxyContin® tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Ingestion
Accidental ingestion of even one dose of OxyContin®, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of OxyContin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of OxyContin® with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OxyContin® and any CYP3A4 inhibitor or inducer .

Boxed Warning for Opana ER® (oxymorphone ER)[15]

WARNING

Addiction, Abuse, and Misuse
Opana ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Opana ER®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Opana ER®. Monitor for respiratory depression, especially during initiation of Opana ER® or following a dose increase. Instruct patients to swallow Opana ER® tablets whole; crushing, chewing, or dissolving Opana ER® tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental Ingestion
Accidental ingestion of even one dose of Opana ER®, especially by children, can result in a fatal overdose of oxymorphone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Opana ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and

WARNING
requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Opana ER®. The co-ingestion of alcohol with Opana ER® may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Boxed Warning for Nucynta ER® (tapentadol ER)[16]

WARNING
Addiction, Abuse, and Misuse NUCYNTA® ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing NUCYNTA® ER, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA® ER. Monitor for respiratory depression, especially during initiation of NUCYNTA® ER or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole; crushing, chewing, or dissolving NUCYNTA® ER tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol. Accidental Ingestion Accidental ingestion of even one dose of NUCYNTA® ER, especially by children, can result in a fatal overdose of tapentadol. Neonatal Opioid Withdrawal Syndrome Prolonged use of NUCYNTA® ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA® ER. The co-ingestion of alcohol with NUCYNTA® ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Boxed Warning for Embeda® (morphine sulfate/naltrexone)[17]

WARNING
Abuse Potential Embeda® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Embeda®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Embeda® for signs of misuse, abuse, and addiction during treatment.

WARNING

Life-threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with use of Embeda®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Embeda® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Embeda® or following a dose increase. Instruct patients to swallow Embeda® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure
Accidental consumption of Embeda®, especially in children, can result in a fatal overdose of morphine.

Interaction with Alcohol
The co-ingestion of alcohol with Embeda® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Embeda® therapy.

Boxed Warning for Xartemis XR® (oxycodone/acetaminophen)[18]

WARNING

Addiction, Abuse, and Misuse
XARTEMIS XR® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing XARTEMIS XR®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMIS XR®. Monitor for respiratory depression, especially during initiation of XARTEMIS XR® or following a dose increase. Instruct patients to swallow XARTEMIS XR® tablets whole; crushing, chewing, or dissolving XARTEMIS XR® can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure
Accidental ingestion of XARTEMIS XR®, especially in children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of XARTEMIS XR® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Hepatotoxicity
XARTEMIS XR® contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limit, and often involve more than one acetaminophen-

WARNING
containing product.

Warnings and Precautions

Table 8. Warnings and Precautions[1-18]

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Accidental exposure; can result in a fatal overdose, especially in children	a	a	a	-	-	a	a	-	a	-	-
Acute abdominal conditions; administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions	-	-	a	-	a	-	a	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule III controlled substance.	a	-	-	-	-	-	-	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule II controlled substance.	-	a	a	a	a	a	a	a	a	a	a
Ambulatory surgery and postoperative use; not indicated for pre-emptive analgesia and only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time	-	-	-	-	-	-	-	a	-	-	-
Anaphylaxis have been reported	a	-	a	-	-	a	-	-	-	a	-
Application of external heat; avoid exposing the application site and surrounding area to direct external heat sources	a	a	-	-	-	-	-	-	-	-	-
Application site skin reactions	a	-	-	-	-	-	-	-	-	-	-
Cardiac disease; may produce bradycardia	-	a	-	-	-	-	-	-	-	-	-
Central nervous system depression; may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma	a	a	a	-	-	-	-	-	a	-	-
Coadministration of anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone; dose should be adjusted accordingly	-	-	-	-	a	-	-	-	-	-	-
Cordotomy	-	-	-	-	-	a (Kadian®)	-	-	-	a	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Cytochrome P450 inducers; should be monitored for evidence of withdrawal effects	-	a	a	-	a	-	a	-	-	-	a
Cytochrome P450 inhibitors; may result in an increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression	-	a	a	-	a	-	a	-	-	-	a
Difficulty swallowing, including esophageal obstruction, dysphagia, and choking.			a (tablet)								
Difficulty in swallowing and risk for obstruction in patients at risk for a small gastrointestinal lumen	-	-	-	-	-	-	a	a	-	-	a
Driving and operating machinery	a	a	a	a	-	a	a	a	a	a	a
Gastrointestinal obstruction; do not administer to patients with gastrointestinal obstruction, especially paralytic ileus	a	a	a	a	a	a	a	a	a	a	a
Head injury and increased intracranial pressure	a	a	a	a	a	a	a	a	a	a	a
Hepatic or renal disease; clearance may be reduced in patients with hepatic dysfunction, while the clearance of its metabolites may be decreased in renal dysfunction	-	a	-	-	-	a	a	a	a	-	-
Hepatotoxicity	a	-	-	-	-	-	-	-	-	-	a
Hypotensive effect; may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs	a	a	a	a	a	a	a	a	a	a	a
Impaired respiration/respiratory depression	a	a	a	a	a	a	a	a	a	a	a
Interactions with alcohol and drugs of abuse; additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression	a	a	a	a	a	a	a	a	a	a	a
Interactions with mixed agonist/antagonist opioid analgesics; may reduce the analgesic effect and/or may precipitate withdrawal symptoms	a	a	a	a	a	a	a	a	a	a	-
Interactions with other central nervous system depressants; may result in	a	a	a	a	a	a	a	a	a	a	a

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
respiratory depression, hypotension, and profound sedation or coma											
Monoamine oxidase inhibitors; not recommended for use in patients who have received monoamine oxidase inhibitors within 14 days	-	-	-	a	a	-	-	-	-	-	-
Neonatal opioid withdrawal syndrome; prolonged maternal use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts	a	a	a	a	a	a	a	a	a	a	a
Pancreatic/biliary tract disease; use with caution in patients with biliary tract disease, including acute Pancreatitis	-	a	-	a	-	a	a	a	a	a	-
Patients with fever; patients should be monitored for opioid adverse events and the dose should be adjusted if necessary	a	a	-	-	-	-	-	-	-	-	-
Precipitation of withdrawal; mixed agonist/antagonist analgesics should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic	-	a	a	a	a	a	-	-	a	a	-
QTc prolongation	a	-	-	-	a	-	-	-	-	-	-
Seizures	a	-	-	a	a	a	a	a	a	a	-
Risk of relapse; abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms	-	-	-	-	a	-	-	-	-	-	-
Skin reactions, serious have rarely been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	a
Serotonin syndrome risk	-	-	-	-	-	-	-	-	a	-	-
Special risk groups; should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients; caution should be exercised in the administration to patients with central nervous system depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure disorders	a	-	a	a	a	a	a	a	a	a	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Sulfites; contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes	-	-	-	a	-	-	-	-	-	-	-
Tolerance and physical dependence may develop	-	a	a	-	a	a	a	-	-	a	-
Use in addiction treatment; has not been studied and is not approved for use in the management of addictive disorders	a	-	-	-	-	-	-	-	-	-	-
Use in elderly, cachectic and debilitated patients; life-threatening respiratory depression is more likely to occur in these patient populations; monitor these patients closely, especially when initiating and titrating doses	a	a	a	a	a	a	a	a	a	a	a
Use in patients with chronic pulmonary disease; monitor patients for respiratory depression, particularly when initiating therapy and titrating therapy	a	a	a	a	a	a	a	a	a	a	a
Use with other acetaminophen-containing products should not be used if total acetaminophen dose is ≥4,000 mg/day	-	-	-	-	-	-	-	-	-	-	a

Drug Interactions

Table 9. Drug Interactions[1-18,31]

Drug	Interacting Medication	Potential Result
All long-acting opioids	Mixed agonist/antagonist and partial agonists	Effects of long-acting opioid may be reduced
All long-acting opioids	CNS depressants (alcohol, benzodiazepines)	Increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients carefully.
Buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone oxycodone/ acetaminophen, oxymorphone, tapentadol	Anticholinergics	May result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Burenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 Inducers (amiodarone, phenytoin, carbamazepine, diltiazem St. John's wort, etc.)	May cause increased clearance of oxycodone/acetaminophen, leading to decreased concentrations and lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. Monitor and adjust dose as needed.
Buprenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 inhibitors (azole antifungals, macrolides, protease inhibitors, etc.)	The pharmacologic effects and adverse reactions of certain opioid analgesics may be increased.
Buprenorphine, methadone	Arrhythmogenic Agents (class I and III anti-arrhythmics, some neuroleptics and tricyclics, calcium channel blockers)	Cardiac conduction changes when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Monitor closely when used together.
Buprenorphine morphine, morphine/ naltrexone, oxycodone, oxycodone/ acetaminophen, oxymorphone,	Neuromuscular blocking agents	May enhance the effects of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Drug	Interacting Medication	Potential Result
tapentadol		
Fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone/ acetaminophen	Monoamine Oxidase Inhibitors (MAOIs)	Enhanced effects of at opioid drugs causing anxiety, confusion, and significant depression of respiration or coma. Avoid use during and 14 days after stopping MAOIs.
Morphine, morphine/ naltrexone, oxymorphone	Cimetidine	Cimetidine can potentiate opioid-induced respiratory depression.
Morphine, morphine/ naltrexone, oxymorphone	Diuretics	Reduced efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.
Morphine, morphine/ naltrexone	P-Glycoprotein Inhibitors	PGP inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.
Oxycodone, Tapentadol	Serotonergic Drugs SSRIs and SNRIs).	The risk of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may be increased.

Dosage and Administration

When selecting an individualized initial dose for any of the long-acting opioids, taking into account the patient's prior opioid and non-opioid analgesic treatment, consideration should be given to the general condition and medical status of the patient, the daily dose, potency and kind of analgesic(s) the patients has been taking, the reliability of the conversion estimate used to calculate the dose of the new long-acting opioid, the patient's opioid exposure and opioid tolerance (if any), any safety issues associated with the specific long-acting opioid, and the balance between pain control and adverse outcomes. The specific dosing for each of long-acting opioids are listed in Table 10 below.[1-18]

Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven.[1-2] Buprenorphine patches are applied for a 7-day cycle on the right or left outer arm, upper chest, upper back or side of chest. The same location for application should not be reused within 21 days.[1] Each fentanyl system may be worn continuously for 72 hours on areas such as the chest, back, flank or upper arm and then removed and disposed of immediately. The next fentanyl transdermal system should be applied to a different skin site.[2] Buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1] If problems with adhesion to either occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, waterproof or semipermeable adhesive dressings or transparent adhesive film dressing may be used on buprenorphine patches or fentanyl transdermal systems respectively.[1-2]

Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian® and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to give only one Zohydro ER®

(hydrocodone) capsule, or one Hysingla ER (hydrocodone) ®, OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,4,14-16]

Almost all oral, long-acting opioids are dosed twice daily. Exalgo® ER (hydromorphone) tablets, Hysingla ER® (hydrocodone) tablets and Avinza® (morphine) capsules, however, are dosed once daily.[4,5,11] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (OxyContin® [oxycodone], Opana ER® [oxymorphone], Nucynta ER® [tapentadol], Xartemis XR® [oxycodone/acetaminophen]).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]

Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

Methadone differs from many of the other long-acting opioids due to pharmacokinetic properties; high interpatient variability in absorption, metabolism, and relative analgesic potency. For these reasons, it is necessary that a cautious and highly individualized approach to prescribing methadone is practiced.[6-10] The concentrate and dispersible tablets are only indicated for the detoxification treatment or maintenance treatment of opioid addiction.[9,10] When methadone is used for the treatment of opioid addiction in detoxification or maintenance programs, it is only to be dispensed by opioid treatment programs certified by the Substance Abuse and Mental Health Service Administration and approved by the designated state authority. Also, these programs must only dispense oral formulations of methadone according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12).[6-10] The methadone solution and concentrate are for oral administration only and should never be injected.[8,9]

Table 10. Dosing and Administration[1-18]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Transdermal patch: initial (opioid-naïve)†, 5 µg/hour; maintenance and titration, titrate only after 72 hours of continuous exposure to current dose; maximum, 20 µg/hour Application sites: Right or left outer arm, upper chest, upper back or side of chest	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are	Approved for use in opioid-tolerant children ≥2 years of age.	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour

Generic Name	Adult Dose	Pediatric Dose	Availability
	inadequate*: Transdermal system: initial, dose conversion instructions should be consulted; maintenance/titration, titrate after three days based on the daily dose of supplemental opioid analgesics required in the second or third day of application; maximum, no maximum Application sites: Right or left chest, back, flank or upper arm	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*: Transdermal system: initial, dosage is based upon oral morphine sulfate dose; maintenance, dose may be increased after three days based on the daily dose of supplemental opioid analgesics required by the patients in the second or third day of initial application	75 µg/hour 100 µg/hour
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER capsule: initial (opioid-naïve or no opioid tolerance)†, 10 mg every 12 hours; maintenance/titration, titrate 10 mg every 12 hours every three to seven days as necessary; maximum, no maximum dose. ER tablet: initial (opioid-naïve or no opioid tolerance) †, 20 mg every 24 hours; maintenance/titration, titrate 10 mg to 20 mg every three to five days as needed to achieve adequate analgesia; maximum, no maximum dose	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release (Zohydro ER®): 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate*: ER tablets: initial, once daily, dose conversion instructions should be consulted ; maintenance/titration,	Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡

Generic Name	Adult Dose	Pediatric Dose	Availability
	titrate every three to four days; maximum, no maximum		
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Oral solution, ER tablet: initial (opioid-naïve)†, 2.5 to 10 mg every eight to 12 hours; maintenance/titration, titrate every 24 to 48 hours; maximum, no maximum For detoxification treatment of opioid addiction (heroin or other morphine-like drugs): Oral concentrate solution, dispersible tablet for oral suspension, oral solution, ER tablet (first day of treatment): initial, single 20 to 30 mg dose to suppress withdrawal symptoms; maintenance, an additional 5 to 10 mg may be provided if withdrawal symptoms have not been suppressed; maximum, 40 mg/day Oral concentrate solution, dispersible tablet for oral suspension, oral solution, ER tablet (short-term detoxification): titrate total daily dose to 40 mg administered in divided doses; maintenance, stabilization should be continued for two to three days after which the dose should be gradually decreased For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services: Oral concentrate solution, dispersible tablet for suspension, oral solution, ER tablet: maintenance, 80 to 120 mg/day	Safety and efficacy in pediatric patients <18 years of age have not been established.	Concentrate solution, oral (sugar-free available): 10 mg/mL Dispersible tablet for oral suspension: 40 mg Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Biphasic ER biphasic capsule (Avinza®): initial (opioid-naïve or no opioid tolerance)†, 30 mg once daily;	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡

Generic Name	Adult Dose	Pediatric Dose	Availability
	maintenance/titration, titrate every three to four days; maximum, 1,600 mg/day ER capsule (Kadian®): initial (opioid-naïve)†, not recommended, start with instant release morphine and convert to once daily dose after; initial (no opioid tolerance)†, 30 mg once daily; maintenance/titration, dose conversion instructions should be consulted for once or twice daily dose; maximum, no maxium ER tablet (MS Contin®): initial (opioid-naïve or no opioid tolerance)†, 15 mg every eight to 12 hours; maintenance/titration, titrate every one to two days for every eight to 12 hour dose; maximum, no maximum		Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER tablet: initial (opioid naïve or no opioid tolerance)†, 10 mg every 12 hour dose; maintenance/titration, titrate every one to two days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER tablet: initial (opioid-naïve or no opioid tolerance)†, 5 mg every 12 hours; maintenance/titration, titrate five to 10 mg every 12 hours every three to seven days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to three days; maximum, 500 mg/day Neuropathic pain associated with diabetic peripheral neuropathy (DPN)	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to three days; maximum, 500 mg/day		
Combination Products			
Morphine sulfate/ naltrexone	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: ER capsule: initial (opioid-naïve)†, 20 mg/0.8 mg once or twice daily; maintenance/titration, titrate every one to two days for once or twice daily dose; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡
Oxycodone/ Acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate: ER capsule: initial (opioid-naïve), 15/650 mg every 12 hours; maximum, 15/650 mg every 12 hours	Safety and efficacy in pediatric patients <18 years of age have not been established.	Biphasic tablet, extended release: 7.5 mg/325 mg

ER=extended release
*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†For patients already taking opioids, initial dose should be calculated by consulting dose conversion instructions.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.

Clinical Guidelines

The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole. In terms of specific etiologies of pain, opioids are recognized as a possible treatment option for the treatment of noncancer pain, osteoarthritis pain, lower back pain, gout pain and neuropathic pain. Only weak opioids are recommended for the treatment of pain associated with fibromyalgia; strong opioids are not recommended in these patients.

Specific to the long-acting opioids, proposed benefits of these agents when administered around-the-clock include more consistent control of pain, improved adherence, and lower risk of abuse or addiction; however, to date, no well-conducted clinical trials have clearly proven these benefits.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Treatment Guidelines from The Medical Letter: **Drugs for Pain**	· Nociceptive pain can be treated with nonopioid analgesics or opioids. · Neuropathic pain is less responsive to opioids and is often treated with adjuvant drugs such as antidepressants and antiepileptics.

Clinical Guideline	Recommendations
(2013)[24]	· Combining different types of analgesics may provide an additive analgesic effect without increasing adverse events. · Nonopioid analgesics such as aspirin, acetaminophen and NSAIDs are preferred for initial treatment of mild to moderate pain. · For moderate acute pain, most NSAIDs are more effective than aspirin or acetaminophen and some have shown equal or greater analgesic effect than an oral opioid combined with acetaminophen, or even injected opioids. The selective cyclooxygenase-2 inhibitor celecoxib appears to cause less severe gastrointestinal toxicity compared to non-selective NSAIDs. · Moderate pain that does not respond to nonopioids can be treated with a combination of opioid and nonopioid analgesics. · For treatment of most types of severe pain, full opioid agonists are the drugs of choice. Unlike NSAIDs, morphine and the other full agonists generally have no dose ceiling for their analgesic effectiveness except that imposed by adverse events. · Patients who do not respond to one opioid may respond to another. Meperidine use should be discouraged because of the high rate of central nervous system (CNS) toxicity and the availability of less toxic, longer-acting alternatives. · Tolerance to most of the adverse events of opioids, including respiratory and CNS depression, develops at least as rapidly as tolerance to the analgesic effect; tolerance can usually be surmounted and adequate analgesia restored by increasing the dose. · When frequent dosing becomes impractical, long-acting opioids may be helpful.
National Comprehensive Cancer Network: **Adult Cancer Pain (2014)**[80]	· Pain is one of the most common symptoms associated with cancer. · The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine. · This guideline is unique it that it contains the following components: o In order to maximize patient outcomes, pain is an essential component of oncology management. o There is an increasing amount of evidence that survival is linked to effective pain control. o Analgesic therapy must be administered in conjunction with management of multiple symptoms or symptom clusters and complex pharmacologic therapies that patients with cancer are generally prescribed. o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect. o Persistent cancer pain often requires treatment with regularly scheduled analgesics with supplemental doses of analgesics provided as needed to manage breakthrough pain. o A multidisciplinary team may be needed for comprehensive pain

Clinical Guideline	Recommendations
	management. o Psychosocial support must be available. o Specific educational material must be provided to the patient. · The pain management algorithm distinguishes three levels of pain intensity, based on a zero to 10 numerical rating scale: severe pain (seven to 10), moderate pain (four to six) and mild pain (one to three). · Pain associated with oncology emergency should be addressed while treating the underlying condition. · Patients considered to be opioid tolerant are those who are taking >60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer. Patients not meeting this definition are considered opioid naïve. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as patient and family education. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. · Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. · Opioid-naïve patients experiencing mild pain intensity should receive nonopioids analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids. · Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration as preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. · Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). · In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice at an initial oral dose of 5 to 15 mg. · Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. · Pure agonists (fentanyl, morphine, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. · Due to the ease of titration, opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. · Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. · Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of

Clinical Guideline	Recommendations
	around-the-clock opioid. · Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. Methadone use should be initiated by physicians with experience and expertise in its use. · At a maximum dose of 400 mg/day, tramadol is less potent than other opioids and is approximately 1/10 as potent as morphine. · Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration. · The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. · The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” · “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. · For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate, 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended. · Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. · If the pain decreases to 4 to 6, the same dose of opioid is repeated and reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered “as needed” over the initial 24 hours before proceeding to subsequent management strategies.

Clinical Guideline	Recommendations
	· No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse events, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. · For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new "rescue dose" must be increased by 10 to 20%. · Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families. · Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. · Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. · If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an ER oral medication (if feasible) or another ER formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by ER opioids. · Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. · Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. · Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. · The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. · Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant to opioids. · Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. · Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic

Clinical Guideline	Recommendations
	interventions. Attention should also be focused on psychosocial support and providing education to patients and families.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[81]	· Comprehensive assessment and documentation is recommended prior to initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. · Screening for opioid use is recommended, despite limited evidence for reliability and accuracy, as it will identify opioid abusers and reduce opioid abuse. · Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. · Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. · Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. Use caution in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. · Patients should be stratified as low, medium, or high risk. · A pain management consult may assist non-pain physicians, if high-dose opioid therapy is utilized. · Establish medical necessity prior to initiation or maintenance of opioid therapy. · Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. · Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain not amenable to short-acting or moderate doses of long-acting opioids, as there is no difference between long-acting and short-acting opioids for their effectiveness or adverse events. · An agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. · Opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid adverse events. · Up to 40 mg of morphine equivalent is considered as low dose, 41 to 90 mg of morphine equivalent as a moderate dose and greater than 91 mg of morphine equivalence as high dose. · In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. · Methadone is recommended for use after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. · Monitoring recommendation for methadone include electrocardiogram prior to initiation, at 30 days and yearly thereafter. · In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT and prescription drug monitoring programs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. · Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary.

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	· Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse events.
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[82]	· Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. · Clinicians may consider a trial of chronic opioid therapy as an option for chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. · A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during chronic opioid therapy. · When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy. · Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education. · Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate. · Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids. · Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics, and should be initiated and titrated cautiously, by clinicians familiar with its use and risks. · Clinicians should reassess patients on chronic opioid therapy periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies. · In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. · In patients on chronic opioid therapy not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. · Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultations with a mental health or addiction specialist. · Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management, or

Clinical Guideline	Recommendations
	discontinuation of chronic opioid therapy. · When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and reassess benefits relative to harms. · In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits. · Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse events or inadequate benefit despite dose increases. · Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse events. · Clinicians should anticipate, identify, and treat common opioid-associated adverse events. · As chronic non-cancer pain is often a complex biopsychosocial condition, clinicians who prescribe chronic opioid therapy should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies. · Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment. · Patients on chronic opioid therapy should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe chronic opioid therapy, but should coordinate consultation and communication among all clinicians involved in the patient's care. · Clinicians should pursue consultation, including interdisciplinary pain management, when patients with chronic non-cancer pain may benefit from additional skills or resources that they cannot provide. · In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk. · Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of chronic opioid therapy during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn. · Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of chronic opioid therapy for chronic non-cancer pain.
	·
A Joint Clinical Practice Guideline from the American College of Physicians and the American	· Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms. · The potential interventions for low back pain are outlined below: Interventions for the Management of Low Back Pain

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td>Pain Society: Diagnosis and Treatment of Low Back Pain (2007)[83]</td><td>
<table>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td rowspan="3">Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Book, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="6">Pharmacologic Therapy</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="9">Non-pharmacologic Therapy</td><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

· Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
· In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first-line options.
· Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
· Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution.
· Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
· Opioid analgesics and tramadol are options for patients with severe,
</td></tr>
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Clinical Guideline	Recommendations
	disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another. · Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution.
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[84]	Nonpharmacologic recommendations for the management of hand osteoarthritis · It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. Pharmacologic recommendations for the initial management of hand osteoarthritis · It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. · It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. · It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. Nonpharmacologic recommendations for the management of knee osteoarthritis · It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed.

Clinical Guideline	Recommendations
	o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> · It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. · No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> · It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions.

Clinical Guideline	Recommendations
	o Be instructed in the use of thermal agents. o Receive walking aids, as needed. · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> · It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. · No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
American Academy of Orthopaedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[85]	<u>Nonpharmacological/surgical therapy</u> · Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. · Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. · Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. · Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. · It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. · Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. <u>Pharmacological therapy</u> · Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol.

Clinical Guideline	Recommendations
	· There is a lack of compelling evidence to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. · There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[86]	<u>Painful polyneuropathy</u> · Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. · Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). · Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. · Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. · In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <u>PHN</u> · Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. · Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. · Strong opioids and capsaicin cream are recommended as second-line therapies. <u>Trigeminal neuralgia</u> · Recommended first-line treatments include carbamazepine and oxcarbazepine. · Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable adverse events may be prescribed lamotrigine but should also be considered for a surgical intervention. <u>Central pain</u> · Recommended first-line treatments include amitriptyline, gabapentin or pregabalin. · Tramadol may be considered second-line. · Strong opioids are recommended as second- or third-line if chronic treatment is not an issue. · Lamotrigine may be considered in central post-stroke pain or spinal cord injury pain with incomplete cord lesion and brush-induced allodynia and cannabinoids in multiple sclerosis only if all other treatments fail.

Clinical Guideline	Recommendations
American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[87]	Anticonvulsants · If clinically appropriate, pregabalin should be offered for treatment. · Gabapentin and sodium valproate should be considered for treatment. · There is insufficient evidence to support or refute the use of topiramate for treatment. · Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants · Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. · Venlafaxine may be added to gabapentin for a better response. · There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids · Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options · Capsaicin and isosorbide dinitrate spray should be considered for treatment. · Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. · Lidocaine patch may be considered for treatment. · There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options · Percutaneous electrical nerve stimulation should be considered for treatment. · Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. · Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[88]	Neuropathy · All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. · Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. · Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. · Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. · Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy.

Clinical Guideline	Recommendations
	· When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. · Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. · Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. · Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[89]	Algorithm for the management of symptoms diabetic polyneuropathy · Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[90]	· Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. · There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. · Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. · Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. · In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. · Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. · The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. · There is insufficient evidence to make any recommendations on the long-term effects of these treatments.
European League Against Rheumatism: **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[91]	· Tramadol is recommended for the management of pain in fibromyalgia. · Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. · Corticosteroids and strong opioids are not recommended. · Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. · Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.

Conclusions

Opioids have been the mainstay of pain treatment for a number of years and there is well documented evidence of their effectiveness. Oral morphine sulfate is the standard for comparison for all other opioid agents currently available. Starting in March 2014, all long-acting opioid labels were updated with an indication change. Long-acting opioids are now indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[19] Methadone is the only long-acting opioid to also be FDA-approved for the treatment of opioid addiction (maintenance or detoxification treatment).[6-10]

The current formulations of OxyContin® (oxycodone ER), Opana® ER (oxymorphone), Hysingla ER® (hydrocodone) and Embeda® (morphine sulfate/naltrexone) were developed to deter abuse; however, there is no well-documented clinical evidence to demonstrate these formulations prevent abuse.[4,14,15,17]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which is a Schedule III controlled substance.[1-18] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy for all long-acting opioids which includes the availability of training regarding proper prescribing practices by manufacturers, as well as the distribution of educational materials on the safe use of these agents.[23]

In general, all of the long-acting opioids are similar in terms of associated effectiveness, adverse events, warnings, and contraindications.[1-18] Head-to-head trials demonstrate similar efficacy among the agents in the class, and current clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain.[80-91] Main differences among the individual agents and formulations are due to dosing requirements and generic availability. Several generic long-acting opioids exist, including fentanyl transdermal systems; hydromorphone ER tablets; methadone ER tablets, oral solution, and oral concentrate solution; morphine sulfate ER tablets and capsules; oxycodone ER tablets; and oxymorphone ER tablets. Unlike other non-opioid analgesics, full opioid agonists generally have no ceiling for their analgesic effectiveness, except that imposed by adverse events.[21] Even though no true ceiling dose exists, dosing intervals are important with these agents; mainly due to their associated adverse events and risks.[22]

Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) tablets, Hysingla ER (hydrocodone) tablets, and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]

Most solid, long-acting opioid formulations (tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, Embeda®), which can all be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER® capsule, or one Hysingla ER (hydrocodone), OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,4,14-16]

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