## *Therapeutic Class Overview*
## *Tramadol and Related Products*

**Therapeutic Class**

- **Overview/Summary:** Tramadol (Ultram®) and tapentadol (Nucynta®) are both centrally-acting opioid analgesics that exert their analgesic effects through binding to μ opioid receptors and through the weak inhibition of norepinephrine reuptake. Tramadol also has an inhibitory effect on serotonin reuptake.[1,2] Tapentadol is approved by the Food and Drug Administration for the relief of moderate-to-severe acute pain, while tramadol is approved for the management of moderate-to-moderately severe pain. Extended-release (ER) formulations are available for both tramadol (ConZip®, Ryzolt® and Ultram ER®) and tapentadol (Nucynta ER®).[3-6] These products are approved for use in adult patients with moderate-to-moderately severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In August 2012 tapentadol ER was approved for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[6] Tapentadol ER should not be used in the treatment of acute or postoperative pain. Tramadol is also available as an orally disintegrating tablet (Rybix ODT®) and in combination with acetaminophen (Ultracet®).[7,8] The combination of tramadol/acetaminophen is indicated for the short-term (five days or less) management of acute pain.[8] Tramadol is available generically in immediate-release (IR) and ER formulations, as well as in combination with acetaminophen.[9]

  The prescribing information for both tramadol and tapentadol contain warnings regarding the risk of seizures and serotonin syndrome in patients using concomitant serotonergic drugs; however, the risk is believed to be higher with tramadol.[1-8,10] Both tapentadol products are classified as Schedule II controlled substance; tramadol is not currently a scheduled agent. Tapentadol ER carries a Black Box Warning regarding the risk of abuse and adverse events associated with its use.[6] Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products.[2,6] Tramadol is associated with minimal cardiovascular and respiratory side effects when compared to opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. Cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing the tramadol containing products long term.[11]

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

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Single-Entity Products** | | | |
| Tapentadol (Nucynta®) | Relief of moderate to severe acute pain | Tablet:<br>50 mg<br>75 mg<br>100 mg | - |
| Tapentadol extended-release (Nucynta ER®) | Management of moderate to moderately severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time | Extended-release tablet:<br>50 mg<br>100 mg<br>150 mg<br>200 mg<br>250 mg | - |
| Tramadol (Rybix | Management of moderate to moderately | Orally | a * |


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| | | | |
|---|---|---|---|
| ODT®, Ultram®*) | severe pain | disintegrating tablet:<br>50 mg<br><br>Tablet:<br>50 mg | |
| Tramadol extended-release (ConZip®, Ryzolt®*, Ultram ER®*) | Management of moderate to moderately severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time | Extended-release capsule:<br>100 mg<br>150 mg<br>200 mg<br>300 mg<br><br>Extended-release tablet:<br>100 mg<br>200 mg<br>300 mg | a * |
| **Combination Products** | | | |
| Tramadol/acetaminophen (Ultracet®*) | Short term management (five days or less) of acute pain | Tablet:<br>37.5 mg/325 mg | a * |

*Generic available in at least one dosage form or strength.

**Evidence-based Medicine**

- Several clinical studies have demonstrated the superior analgesic efficacy of tapentadol compared to placebo in the treatment of moderate to severe pain.[12-16] In addition to reducing pain intensity and providing pain relief, therapy with tapentadol is associated with a shorter time to 50% pain relief, a longer time to first dose of rescue medication, a decrease in the use of rescue medications and a greater number of treatment responders compared to placebo.[13,14,16]
- The safety and efficacy of tapentadol ER was evaluated in three placebo-controlled and active-controlled comparator trials against oxycodone controlled-release (CR). Tapentadol significantly improved pain scale scores, responder rates and quality of life compared to placebo. Although not directly compared for most endpoints, tapentadol ER demonstrated a similar improvement in analgesia compared to oxycodone CR while be associated with significantly fewer adverse events.[17-20]
- Treatment with tramadol IR has not consistently been demonstrated to be more effective compared to nonsteroidal antiinflammatory drugs (NSAIDs).[21,22]
- Tramadol ER formulations have consistently demonstrated significant improvements in pain scores compared to placebo in patients with moderate-to-moderately severe chronic pain.[23-27]
- In patients with mild low back pain or those who were undergoing minor surgical procedures, short-term treatment with the combination of tramadol/acetaminophen was significantly more effective compared to placebo with regard to improvements in pain scores, and provided similar analgesia compared to NSAIDs.[28-31]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - For the treatment of cancer pain, patients should be started on acetaminophen or an NSAID and escalated to a “weak opioid” and then to a “strong opioid”, such as morphine if sufficient analgesia is not obtained.[32]
  - In general, opioid selection, 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 versus long-acting opioids, or as needed versus around-the-clock dosing of opioids.[33]


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- Opioid analgesics and tramadol are effective treatments for low back pain in patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs alone.[34]
- Tramadol may be considered an initial treatment option for patient with osteoarthritis as an alternative to topical capsaicin and topical or oral NSAIDs.[15]
- According to the American Academy of Neurology, tramadol or other opioids should be considered for the treatment of painful diabetic neuropathy.[16]

· Other Key Facts:

- Tramadol IR and ER formulations are available generically as is the combination with acetaminophen.[9]
- A tramadol ER formulation, Ryzolt®, was discontinued by the manufacturer in June 2012.[9]
- No head-to-head studies are available comparing tramadol and tapentadol for the management of moderate-to-severe pain.
- Tapentadol ER is the first opioid approved for the management of neuropathic pain associated with diabetic peripheral neuropathy.[37]

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# *Therapeutic Class Review*
# *Tramadol and Related Products*

## Overview/Summary

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] Moreover, pain is a subjective experience that is unique to the individual and is difficult to identify or quantify by any observer. The type of pain being experienced is often classified by its pathophysiologic etiology. Somatic pain results from the activation of pain receptors in cutaneous or deep tissues (skin, bone, joint or connective tissues) and is generally localized and is described as sharp in nature. Visceral pain involves internal areas of the body (organs) and may be poorly localized and described as an aching pain. Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system.[2] An individual's reaction or response to treatment of pain can be highly variable. Pain thresholds are highly individualized among patients and responses to therapy will vary between persons and may vary within the same patient from day to day. Pain management is multifaceted and should incorporate both pharmacological and non-pharmacological measures.

Tramadol (Ultram®) and tapentadol (Nucynta®) are both centrally-acting opioid analgesics that exert their analgesic effects through binding to μ opioid receptors and through the weak inhibition of norepinephrine reuptake. Tramadol also has an inhibitory effect on serotonin reuptake.[3,4] Tapentadol is approved by the Food and Drug Administration (FDA) for the relief of moderate-to-severe acute pain, while tramadol is approved for the management of moderate-to-moderately severe pain. Extended-release (ER) formulations are available for both tramadol (ConZip®, Ryzolt® and Ultram ER®) and tapentadol (Nucynta ER®).[5-8] These products are approved for use in adult patients with moderate-to-moderately severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In August 2012 tapentadol ER was approved by the FDA for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[8] Tapentadol ER should not be used for the treatment of acute or postoperative pain. Tramadol is also available as an orally disintegrating tablet (Rybix ODT®) and in combination with acetaminophen (Ultracet®).[9,10] The combination of tramadol/acetaminophen is indicated for the short-term (five days or less) management of acute pain.[5] Tramadol is available generically in immediate-release (IR) and ER formulations as well as in combination with acetaminophen.[11] A tramadol ER formulation, Ryzolt®, was discontinued by the manufacturer in June 2012.[12]

The prescribing information for both tramadol and tapentadol contain warnings regarding the risk of seizures and serotonin syndrome in patients using concomitant serotonergic drugs; however, the risk is believed to be higher with tramadol.[2-10] Tapentadol is a Schedule II controlled substance and the ER formulation carries a Black Box Warning regarding the risk of abuse associated with its use.[8] Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products.[4,8] Tramadol is associated with minimal cardiovascular and respiratory side effects when compared to opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. Cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing the tramadol containing products long term.[13]

Current consensus guidelines for the management of low back pain recommend the use of opioids or tramadol in patients with severe pain that has not responded to treatment with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs).[14] Tramadol may be an initial treatment option along with topical capsaicin and topical or oral NSAIDs for osteoarthritis of the hand, knee or hips.[15] Guidelines established by the European Federation of Neurological Societies and the American Academy of Neurology generally recommend the use of tramadol as a second-line therapy for the treatment of various polyneuropathies.[16,17] The specific role immediate- or extended-release tapentadol has not been


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incorporated into currently available treatment guidelines; however, in most cases no preference is given to one single opioid over another.

## Medications

**Table 1. Medications Included Within Class Review**

| Generic Name (Trade Name) | Medication Class | Generic Availability |
|---|---|---|
| **Single-Entity Products** | | |
| Tapentadol (Nucynta®) | Synthetic opioid analgesic | - |
| Tapentadol extended-release (Nucynta ER®) | Synthetic opioid analgesic | - |
| Tramadol (Rybix ODT®, Ultram®*) | Synthetic opioid analgesic | a * |
| Tramadol extended-release (ConZip®, Ryzolt®*, Ultram ER®*) | Synthetic opioid analgesic | a * |
| **Combination Products** | | |
| Tramadol/acetaminophen (Ultracet®*) | Synthetic opioid analgesic/non-opioid, non-salicylate analgesic | a * |

*Generic available in at least one dosage form or strength.

## Indications

**Table 2. Food and Drug Administration-Approved Indications[3-12]**

| Generic Name | Management of Moderate to Moderately Severe Pain | Management of Moderate to Moderately Severe Chronic Pain | Management of Neuropathic Pain Associated with Diabetic Peripheral Neuropathy | Relief of Moderate to Severe Acute Pain | Short Term Management (Five Days or Less) of Acute Pain |
|---|---|---|---|---|---|
| **Single-Entity Products** | | | | | |
| Tapentadol | | a (ER)* | a (ER)* | a | |
| Tramadol | a | a (ER)* | | | |
| **Combination Products** | | | | | |
| Tramadol/ acetaminophen | | | | | a |

*In adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

## Pharmacokinetics

**Table 3. Pharmacokinetics[3-12]**

| Generic Name | Bioavailability (%) | Absorption (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|---|
| **Single-Entity Products** | | | | | |
| Tapentadol | 32 | Not reported | 99 (IR) | None | 4 to 5 |
| Tramadol | 75 (IR)<br>85 to 90 (ER) | Not reported | 90 | Yes, O-desmethyl-tramadol (M1) | 6.3 (IR)<br>7.9 (ER) |
| **Combination Products** | | | | | |
| Tramadol/ acetaminophen | 75/60 to 98 | Not reported | 90/9 | O-desmethyl-tramadol (M1) | 5 to 6/2 to 3 |

## Clinical Trials

The clinical trials demonstrating the safety and efficacy of the tramadol and tapentadol products in their respective Food and Drug Administration approved indications are described in Table 4.[18-46]


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Several clinical studies have demonstrated the superior analgesic efficacy of tapentadol compared to placebo in the treatment of moderate to severe pain.[26,27,30,32,35] In addition to reducing pain intensity and providing pain relief, therapy with tapentadol is associated with a shorter time to 50% pain relief, a longer time to first dose of rescue medication, a decrease in the use of rescue medications and a greater number of treatment responders compared to placebo.[27,30,32] In one study of patients who were candidates for joint replacement surgery, tapentadol significantly reduced pain intensity scores compared to placebo, and was noninferior to analgesia provided by oxycodone. In addition, the incidence of gastrointestinal-related adverse events was significantly lower with tapentadol compared to oxycodone ($P$<0.001).[26] In a short-term (four day) study of postoperative pain in patients who had undergone bunionectomy, both tapentadol and oxycodone significantly lowered summed pain intensity scores after three days of treatment compared to placebo ($P$≤0.05 for all); however, only the tapentadol 100 mg doses demonstrated statistically significant differences compared to placebo on day four ($P$=0.0284). Tapentadol treatment was associated with a reduction in nausea, dizziness, vomiting and constipation compared to oxycodone ($P$ values not reported).[27] Another three month safety study by Hale et al demonstrated a lower incidence of treatment-related adverse events with tapentadol compared to oxycodone, while also significantly lowering the incidence of withdrawal symptoms (17 vs 29%; $P$≤0.05).[35]

In a 12-week trial of adults with osteoarthritis (OA) of the knee, significant pain relief was achieved with tapentadol extended-release (ER) compared to placebo (Least Squares Mean (LSM) difference, -0.7; 95% CI, -1.04 to -0.33). Oxycodone controlled-release (CR) reduced the average pain intensity compared to placebo for the overall maintenance period (LSM difference vs. placebo: -0.3), but was not statistically significantly lower at week 12 of the maintenance period (LSM of -0.3; $P$ value not reported). More patients treated with tapentadol ER achieved a ≥30% reduction in average pain intensity at week 12 of the maintenance period; however, the difference was not statistically significant (43.0 vs 35.9%; $P$=0.058). Significantly fewer patients in the oxycodone CR group achieved this improvement compared to placebo (24.9 vs 35.9%; $P$=0.002). A higher percentage of patients achieved a ≥50% reduction in average pain intensity from baseline at week 12 with tapentadol ER compared to placebo (32.0 vs 24.3%; $P$=0.027), while significantly fewer oxycodone CR-treated patients achieved this improvement compared to placebo (17.3 vs 24.3% ($P$=0.023).[36]

Buynak et al evaluated tapentadol ER compared to oxycodone ER and placebo in adults with moderate to severe lower back pain. The mean change in pain intensity from baseline to week 12 was significantly greater for tapentadol ER (LSM difference, -0.8; $P$<0.001) and oxycodone CR (LSM difference, 0.9; $P$<0.001) compared to placebo. 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 (LSM difference, -0.7; $P$<0.001).[23] Schwartz et al evaluated tapentadol ER over 12 weeks in adults with painful diabetic peripheral neuropathy. The LSM change in average pain intensity from the start of double-blind treatment period to 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 (LSM difference, -1.3; 95% CI, -1.70 to -0.92; $P$<0.001). 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). A ≥50% improvement in pain intensity was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients.[18]

In a pooled analysis of three studies of patients with pain due to OA or nonmalignant lower back pain, tapentadol was significantly more effective compared to placebo over a three week treatment phase (LSM difference, -0.6; 95% CI, -0.80 to -0.39; $P$<0.001) and for the overall 12 week maintenance period (-0.5; 95% CI, -0.73 to -0.34; $P$<0.001). A similar analgesic effects was reported in patients receiving oxycodone CR; however, the responder rate was higher with tapentadol ER ($P$<0.001). Moreover, a significantly higher proportion of patients receiving tapentadol ER achieved a ≥30% and ≥50% improvement in pain intensity from baseline compared to oxycodone CR and placebo ($P$<0.001 for both).[24]

Tramadol has been evaluated in various settings for the management of moderate-to-moderately severe pain. In patients with symptomatic OA, tramadol (up to 400 mg daily) did not significantly improve the

mean final pain intensity score compared to placebo when administered over three months (*P*=0.082); however, both patient and investigator assessment of treatment favored tramadol over placebo (*P*=0.038 and *P*=0.001, respectively).[19]

Treatment with tramadol has not consistently been demonstrated to be more effective compared to nonsteroidal antiinflammatory drugs (NSAIDs). In a two studies by O'Donnell et al, a significantly greater proportion of patients receiving celecoxib 200 mg twice-daily achieved a ≥30% improvement from baseline in NRS-pain scale scores compared to tramadol 50 mg administered four times daily (63.2 vs 49.9%; *P*<0.001 in study I and 64.1 vs 55.1%; *P*=0.008 study II).[38] In patients with post-tonsillectomy pain, there was no statistically significant difference in visual analog scale (VAS) pain scores between tramadol and diclofenac over two weeks of treatment (*P*=0.66).[39]

Tramadol ER formulations have consistently demonstrated significant improvements in pain scores compared to placebo in patients with moderate-to-moderately severe chronic pain.[21,28,29] In one study, tramadol ER 300 mg significantly improved patient global assessment scores compared to placebo (*P*≤0.05); however, no improvements in WOMAC pain subscale scores were reported for tramadol ER 100 mg, 200 mg or 300 mg after 12 weeks of treatment.[31] Compared to tramadol alone, tramadol ER was associated with a significant reduction in VAS scores in an eight-week crossover study of patients with chronic pain (29.9 vs 36.2; *P*<0.001).[46]

In a 12-week study comparing tramadol ER to the buprenorphine transdermal patch, the LSM change from baseline in Box Scale-11 pain score between treatments was -0.17 (95% CI, -0.89 to 0.54; *P* value not reported), which was within the non-inferiority margin, demonstrating that buprenorphine was non-inferior to tramadol ER in patients with OA of the hip or knees.[40] In patients undergoing elective hallux valgus surgery, etoricoxib significantly reduced VAS pain scores compared to tramadol ER when administered for seven days (12.5±8.2 vs 17.3±11.0; *P*<0.05).[41]

In patients with low back pain (N=318), the combination of tramadol/acetaminophen (APAP) was significantly more effective compared to placebo with regard to changes in VAS pain scores over three months (44.4 vs 52.3 mm; *P*=0.015).[22] In a study by Fricke et al comparing tramadol/APAP to hydrocodone/APAP in patients undergoing molar removal, both treatments provided statistically significant pain relief compared to placebo (*P*≤0.024); however, the differences were not significantly different from one another during the eight hour evaluation period.[25] In an eight-week study comparing tramadol/APAP to meloxicam in patients with OA, there was a similar improvement in WOMAC pain scores between the treatment arms (6.75 vs 6.51, respectively; *P* value not reported). Similarly, there was no statistically significant difference in the percentage of patients who reported pain relief with tramadol/APAP compared to meloxicam (68.2 vs 78.7%; *P*>0.05).[42] Alfano et al reported that tramadol/APAP was associated with significantly lower visual rating scale pain scores compared to codeine/APAP (1.40±0.76 vs 2.52±0.86; *P*<0.001) in patients undergoing surgical procedures; however, the trial was only two days in duration.[43] The results of a four-week trial in patients with low back pain demonstrated similar improvements in pain scores between these two treatments.[44]


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**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Schwartz et al[18]<br><br>Tapentadol ER 100 to 250 mg BID<br><br>vs<br><br>placebo<br><br>Initial treatment with tapentadol ER 50 mg BID for three days then titrated to tapentadol ER 100 mg BID for three days; subsequent titration in 50 mg increments every three days (within dose range of 100 to 250 mg BID). APAP ≤ 2,000 mg/day was permitted during the OL phase, except during the last four days. | DB, PC, PG, RCT<br><br>Adults ≥18 years with Type 1 or 2 diabetes and DPN for ≥6 months with an: $HbA_{1c}$ ≤11%, ≥3-month history of analgesic use for DPN and dissatisfaction with current treatment (opioid daily doses equivalent to <160 mg of oral morphine) and an average pain intensity score of ≥5 on an 11-point rating scale | N=395*<br><br>12 weeks (maintenance phase after a 3-week titration phase)<br><br>*A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study | Primary:<br>The change from baseline in average pain intensity over the last week (week-12) of the maintenance phase<br><br>Secondary:<br>Proportion of patients with improvements in pain intensity of ≥30% and 50% at week 12, PGIC at weeks 2, 6, and 12, and safety measures | Primary:<br>The LSM change in average pain intensity from the start of double-blind treatment to 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. The LSM difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; *P*<0.001).<br><br>Secondary:<br>The mean changes in average pain intensity 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, those >65 years who received tapentadol ER and those who were opioid-naïve and opioid-experienced.<br><br>From pre-titration to week 12 of maintenance treatment, 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).<br><br>At least a 50% improvement in pain intensity from pre-titration to week 12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients.<br><br>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).<br><br>Of the patients who achieved ≥30% improvement in pain intensity (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 achieve ≥30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER reached ≥ 30% improvement from pre-titration by week 12 of the maintenance period.<br><br>Of those patients who were randomized to placebo after achieving |


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| | | | | ≥30%improvement in pain intensity (titration phase), 48.7% 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 pain intensity during the maintenance phase.<br><br>Among patients who achieved ≥50% improvement in pain intensity (titration phase) and were randomized to treatment with tapentadol ER, 59.1% 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.<br><br>Among patients who were randomized to placebo after achieving ≥ 50% improvement in pain intensity (titration phase), 36.4% 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.<br><br>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).<br><br>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.<br><br>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.<br><br>Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase and among 5.1% of patients in the |


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| | | | | tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase. |
| Fleishmann et al[19]<br><br>Tramadol up to 400 mg/daily<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients aged 35 to 75 with symptomatic (painful) osteoarthritis of the knee for ≥1 year and had used NSAIDs for ≥3 months | N=129<br><br>3 months | Primary:<br>Efficacy (as measured by pain intensity, relief, patient and investigator overall assessments, discontinuation, time to failure, and WOMAC OA index scores)<br><br>Secondary:<br>Tolerability and adverse events | Primary:<br>The mean final pain intensity score was not statistically different between treatment groups (*P*=0.082). Pain intensity scores improved progressively from baseline through day 91 for patients in both groups, and the mean final pain intensity score was 15% lower in the tramadol group (2.10) than in the placebo group (2.48; *P*=0.045).<br><br>The mean final pain relief score for tramadol patients was significantly higher compared to patients receiving placebo (0.43 vs -0.57; *P*=0.004).<br><br>The patient overall assessment score was significantly higher for tramadol compared to placebo (*P*=0.038). The investigator overall assessment was also significantly more positive for tramadol than for placebo (*P*=0.001).<br><br>A total of 26 tramadol-treated patients (41.3%) and 43 placebo patients (65.2%) discontinued the study due to lack of effect.<br><br>Time to failure of effectiveness was substantially shorter for the placebo group (median=19 days) compared to the tramadol group (median=57 days; *P*=0.042).<br><br>Patients who received tramadol had significantly better WOMAC scores for pain (*P*=0.012), stiffness (*P*=0.028), and physical function (*P*=0.033) compared to patients who received placebo. The mean final overall score was 17.5% lower in the tramadol group compared to the placebo group (4.16 vs 5.04; *P*=0.015).<br><br>Secondary:<br>No clinically significant trends in vital signs were noted among tramadol patients. The most common adverse events were nausea, constipation, dizziness, pruritus and headache. |


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| Stoop et al[20]<br><br>Tramadol ODT 50 mg prior to procedure<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Women undergoing hysterosalpingo-graphy with either a metal cannula or balloon catheter | N=128<br><br>Single-dose | Primary:<br>VAS score<br><br>Secondary:<br>Adverse events and investigator assessed pain | Primary:<br>Tramadol was associated with a statistically significant improvement compared to placebo in self-reported VAS (difference, -0.91; 95% CI, -1.35 to -0.47) and -33% (95% CI, -48 to -17) on the relative, scale in favor of tramadol.<br><br>Secondary:<br>During the surgical procedure, one patient reported nausea following tramadol administration, and one patient reported dizziness. No other adverse events were reported.<br><br>There was a significant benefit for tramadol compared to placebo for physician-perceived VAS pain scores (39% relative reduction; *P*<0.001). |
| Burch et al[21]<br><br>Tramadol ER 200 mg to 300 mg QD<br><br>vs<br><br>placebo | DB, MC, OL, RCT<br><br>Patients 40 to 80 years of age with pain due to OA of the knee who were taking NSAIDs, COX-2 inhibitors, or tramadol on a regular basis for OA pain during the previous 30 days, a score of ≥4 on the 11-point PI-NRS at screening, with an increase of ≥2 points after analgesic washout | N=646<br><br>12 weeks | Primary:<br>Score on the PI-NRS after 12 weeks<br><br>Secondary:<br>Responders rates, PGIC, CGIC and safety | Primary:<br>Patients treated with tramadol ER experienced a statistically significant improvement on the PI-NRS from baseline compared to the placebo group (2.9 vs 2.4; *P*<0.0001) after 12 weeks of treatment.<br><br>Secondary:<br>There was a significantly greater percentage of responders in the tramadol ER group compared to placebo irrespective of the magnitude of response (*P*<0.05 for all levels of improvement).<br><br>The median number of days required for patients to achieve a two-point improvement in PI-NRS scores was similar between the treatment tramadol ER and placebo treatment groups (14 vs 15 days, respectively). It took more than twice as long for placebo-treated patients to achieve a three-point improvement in the PI-NRS score (39 days) compared to those receiving tramadol ER (16 days; *P*<0.0001).<br><br>After 12-weeks, 80% of patients who received tramadol ER rated their condition as “improved” compared to 69% of the patients randomized to placebo (*P*=0.0002). Similar results were obtained with the PGIC (*P*=0.0042).<br><br>The most commonly reported adverse events in the active-treatment group were nausea, constipation, dizziness/vertigo, somnolence, vomiting, and |


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| | | | | headache. During the double-blind phase, 59% of patients receiving tramadol ER experienced ≥1 adverse event and 10% withdrew because due to an adverse event. The majority of adverse events reported by patients receiving tramadol ER were mild or moderate during the double-blind phase (88%). |
| Ruoff et al[22]<br><br>Tramadol 37.5 mg/ APAP 325 mg up to eight tablets daily<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Men and non-pregnant women age 25 to 75, in general good health, ambulatory, and with lower back pain such that daily medication was needed for ≥3 months | N=318<br><br>3 months | Primary:<br>PVA score at final visit<br><br>Secondary:<br>Scores on the PRRS, SF-MPQ, RDQ, SF-36, discontinuation due to insufficient pain relief, and overall assessments of medication by patients and investigators | Primary:<br>The tramadol/APAP group had a significantly lower final mean PVA score compared to the placebo group (*P*=0.015). The mean final PVA score was 44.4 mm in the tramadol/APAP group and 52.3 mm in the placebo.<br><br>Secondary:<br>The tramadol/APAP group exhibited a significantly higher mean PRRS score compared to the placebo group (1.8 vs 1.1; *P*<0.001).<br><br>The tramadol/APAP group exhibited greater improvement from baseline on every category of the SF-MPQ compared to the placebo group. The mean change was statistically significant for the sensory component (*P*=0.011), present pain index (*P*=0.011) and total score (*P*=0.021).<br><br>In the categorical responder analysis, 54.7% of the tramadol/APAP group had ≥30% reduction in PVA scores compared to 39.5% of the placebo group (*P*=0.011), and 44.1% of the tramadol/APAP group had ≥50% reduction in PVA scores compared to 32.5% of the placebo group (*P*=0.044).<br><br>The tramadol/APAP group had a significantly greater improvement in bothersome score (RDQ; *P*=0.027) and total score (RDQ; *P*=0.023) compared to the placebo group.<br><br>For every subcategory of the SF-36, mean improvements from baseline were greater in the tramadol/APAP group than in the placebo group. These changes were statistically significant for the subcategories of role-physical (*P*=0.005), bodily pain (*P*=0.046), role-emotional (*P*=0.001), mental health (*P*=0.026), reported health transition (*P*=0.038) and mental component summary (*P*=0.008).<br><br>The overall assessments of study medication by patients (*P*<0.001) and |


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| | | | | investigators (*P*=0.002) were significantly more positive for the tramadol/APAP group than for the placebo group.<br><br>The incidence of treatment failure was significantly lower in the tramadol/APAP group compared to the placebo group (19.3 vs 37.6%; *P*<0.001). |
| Buynak et al[23]<br><br>Tapentadol ER 100 mg BID<br><br>vs<br><br>oxycodone CR 20 mg BID<br><br>vs placebo<br><br>Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for three days then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20mg BID; at three-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR | AC, DB, IN, MC, PC, PRO, RCT<br><br>Patients ≥18 years with a history of non-malignant LBP for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity of ≥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 | N=981<br><br>12 weeks (maintenance phase after a 3-week titration phase) | Primary:<br>Change from baseline in mean pain intensity at week 12 of the maintenance period<br><br>Secondary:<br>Change from baseline in mean pain intensity over the entire 12 week maintenance period, proportion of patients with ≥ 30% and ≥50% reduction in pain intensity at week 12 of maintenance, PGIC score, BPI survey and SF-36 health survey | Primary:<br>Throughout the 12 week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo.<br><br>The mean change in pain intensity from baseline to week 12 was -2.9 for tapentadol ER and -2.1 for placebo (*P*<0.001).<br><br>The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for tapentadol ER and -2.1 for placebo, corresponding to a LSM difference of -0.7 (95% CI, -1.06 to -0.35; *P*<0.001).<br><br>Secondary:<br>The mean pain intensity was also reduced for the oxycodone CR group compared to placebo at week 12 (LSM difference, -0.9; 95% CI, -1.24 to -0.49; *P*<0.001) and over the entire maintenance period (LSM difference, -0.8; 95% CI, -1.16 to -0.46; *P*<0.001).<br><br>Reductions in mean pain intensity were significantly greater with tapentadol ER compared to placebo at week 12 for patients with moderate and severe baseline pain intensity. Significantly greater reductions in mean pain intensity with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline pain intensity and severe baseline pain intensity.<br><br>Reductions in mean pain intensity were also significantly greater at both week 12 of the maintenance period and for the overall maintenance period with oxycodone CR compared to placebo for patients with moderate and severe baseline pain intensity. |


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| 50 mg BID). APAP ≤1,000 mg/day (max of three consecutive days) was permitted. | | | | Tapentadol ER treatment was associated with a significantly higher proportion of responders at week 12 compared to placebo (*P*=0.004). Overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from placebo (*P*=0.090).<br><br>A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo experienced a ≥30% improvement in pain intensity at week 12 compared to baseline (*P*<0.001).<br><br>A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo experienced a ≥50% improvement in pain intensity at week 12 compared to baseline (*P*<0.016).<br><br>The percentage of patients in the oxycodone CR group with ≥30% improvement in pain intensity at week 12 compared to baseline was 30.4% (*P*=0.365) and did not differ significantly from placebo. The percentage of patients in the oxycodone CR group with ≥ 50% improvement in pain intensity at week 12 compared to baseline was 23.3% (*P*=0.174) and did not differ significantly from placebo.<br><br>There was a significant difference in PGIC ratings for both tapentadol ER (*P*<0.001) and oxycodone CR (*P*<0.001) compared to placebo.<br><br>Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week 12 in the BPI total score, the pain interference subscale score and the pain subscale score.<br><br>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 CR group, respectively.<br><br>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 CR group. The percentage of patients who reported “≥50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, |


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| | | | | 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.<br><br>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 improved in the tapentadol ER group compared to the placebo group.<br><br>The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group (*P* value not reported).<br><br>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 CR groups, respectively.<br><br>The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence. The majority were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group. |
| Lange et al[24]<br><br>Tapentadol ER 100 mg to 250 mg BID<br><br>vs<br><br>oxycodone CR 20 mg to 50 mg BID<br><br>vs | Pooled analysis of 3 AC, DB, DD, MC, PC, PG, RCT<br><br>Patients with a diagnosis of OA knee pain or nonmalignant LBP for ≥3 months who had been taking analgesics for the | N=2,974<br><br>15 weeks (3 week treatment and 12 week maintenance phase) | Primary:<br>Change from baseline in 11-point NRS at week 12 and for the overall maintenance period, responder analyses, proportion of responders with ≥30% and ≥50% reduction in pain | Primary;<br>Patients treated with tapentadol ER experienced statistically significant reductions from baseline at both week 12 of the maintenance period (LSM difference, -0.6; 95% CI, -0.80 to -0.39; *P*<0.001) and for the overall maintenance period (-0.5; 95% CI, -0.73 to -0.34; *P*<0.001).<br><br>Statistically significant reductions from baseline in average pain intensity were also observed with oxycodone CR compared to placebo at both week 12 of the maintenance period (LSM difference, -0.3; 95% CI, -0.53 to -0.12; *P*=0.002) and for the overall maintenance period (LSM difference, -0.3; 95% CI, -0.52 to -0.14; *P*<0.001). |


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| placebo | pain condition for ≥3 months, and were dissatisfied with their current analgesic therapy (patients on opioids were required to take total daily dose equivalent to 160 mg or less of oral morphine) and an average pain intensity score at baseline of ≥5 on an 11-point NRS | | intensity at week 12 of the maintenance period, PGIC, SF-36 and EQ-5D<br><br>Secondary:<br>Not reported | There was a significantly greater responder rate with tapentadol ER compared to placebo (*P*=0.006) and oxycodone CR (*P*<0.001).<br><br>More patients treated with tapentadol ER experienced a ≥30% improvement from baseline in pain intensity at week 12 compared to placebo (41.3 vs 34.8%; *P*=0.003), while a significantly lower proportion of patients receiving oxycodone CR achieved this benchmark compared to placebo (27%; *P*<0.001).<br><br>More patients in the tapentadol ER group experienced a ≥50% improvement in pain intensity from baseline to week 12 compared to placebo (30.1 vs 23.5%; *P*<0.001); however there was no significant difference between oxycodone CR and placebo (20.8%; *P*=0.153). A significantly higher percentage of patients in the tapentadol ER group achieved ≥30% and ≥50% improvement in pain intensity from baseline to week 12 compared to the oxycodone CR group (*P*<0.001 for both comparisons).<br><br>There was a significant difference in the overall distribution of PGIC scores favoring tapentadol ER and oxycodone CR compared to placebo (*P*<0.001 for both comparisons) and favoring tapentadol ER over oxycodone CR (*P*<0.001).<br><br>Patients treated with tapentadol ER experienced statistically significant improvements in SF-36 scores from baseline compared to oxycodone CR for all individual domain scores except general health (*P*≤0.048 for all comparisons), as well as for the physical component summary (*P*<0.001) and the mental component summary (*P*<0.001).<br><br>On the EQ-5D questionnaire, significantly greater improvements from baseline occurred with tapentadol ER compared to placebo (*P*<0.001); however, the difference between oxycodone CR and placebo was not statistically significant (*P*=0.867). A significantly greater improvement was observed with tapentadol ER compared to oxycodone CR (*P*<0.001).<br><br>The most common treatment-emergent adverse events were nausea, dizziness, constipation, headache, somnolence, fatigue, vomiting, dry mouth, |


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| | | | | hyperhidrosis, pruritus, and diarrhea. Gastrointestinal disorders were significantly less frequent in the tapentadol ER compared to the oxycodone CR group (42.8 vs 65.6%; *P*<0.001). |
| Fricke et al[25]<br><br>Tramadol 37.5 mg/ APAP 325 mg<br><br>vs<br><br>tramadol 75 mg/APAP 650 mg<br><br>vs<br><br>hydrocodone 10 mg/APAP 650 mg<br><br>vs<br><br>placebo | AC, DB, PC, PG, SC<br><br>Men and women aged 16 to 75 experiencing moderate or severe pain within five hours after surgical removal of ≥2 impacted third molars and associated bone | N=200<br><br>8 hours | Primary:<br>Efficacy based on TOTPAR, SPID and SPRID measures<br><br>Secondary:<br>Efficacy measured by PAR, PID, and PRID scores; onset and duration of pain relief, time to re-medication with a supplemental analgesic agent; and patients' overall assessment of medication | Primary:<br>For TOTPAR, SPID, and SPRID, tramadol 75 mg/APAP 650 mg and hydrocodone/APAP provided statistically superior pain relief during all three intervals (zero to four hours, four to eight hours and zero to eight hours) compared to placebo (*P*≤0.024); however, the differences were not significantly different from one another.<br><br>There was a statistically significant dose response for tramadol/APAP compared to placebo (two tramadol/APAP tablets >one tablet >placebo) on all three primary efficacy variables during all three time periods (*P*≤0.018 for all)<br><br>Secondary:<br>The median times to onset of pain relief were 34.0 and 33.3 minutes in the tramadol 75 mg/APAP 650 mg and tramadol 37.5 mg/APAP 325 mg groups, respectively, and 25.4 minutes in the hydrocodone/APAP group (*P*≤0.001 compared to placebo).<br><br>There was no significant difference between tramadol 75 mg/APAP 650 mg and hydrocodone/APAP in terms of duration of pain relief as measured by the areas under the curve for PAR, PID, and PRID over the second half of the study (four to eight hours). Both treatments had significantly longer duration of activity than placebo (TOTPAR; *P*≤0.018; SPID; *P*≤0.024; SPRID; *P*≤0.019).<br><br>Fewer patients required supplemental analgesic medication during the eight-hour observation period in the tramadol 75 mg/APAP 650 mg (78%) and hydrocodone/APAP (84%) groups compared to the tramadol 37.5 mg/ APAP 325 mg (94%) and placebo (94%) groups.<br><br>The median time to remedication with a supplemental analgesic was shortest in the placebo group (78.5 minutes), followed by tramadol 37.5 mg/APAP 325 mg (113.0 minutes), tramadol 75 mg/APAP 650 mg (169.0 minutes), and hydrocodone/APAP (204.0) minutes. The time to remedication was significantly |


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| | | | | longer for all active treatments compared to placebo (tramadol 75 mg/APAP 650 mg and hydrocodone/APAP; *P*<0.001; tramadol 37.5 mg/APAP 325 mg; *P*=0.036).<br><br>Patients' mean overall assessment of study medication was statistically superior in all active-treatment groups compared to placebo (*P*<0.001). |
| Hartrick et al[26]<br><br>Tapentadol 50 mg every four to six hours<br><br>vs<br><br>tapentadol 75 mg every four to six hours<br><br>vs<br><br>oxycodone 10 mg every four to six hours<br><br>vs<br><br>placebo | AC, DB, PC, RCT<br><br>Patients 18 to 80 years of age who were candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease, requiring daily doses of analgesics, reporting a mean pain intensity score ≥5 on an 11-point NRS over three days | N=674<br><br>15 days | Primary:<br>5-day SPID<br><br>Secondary:<br>Reductions in pain intensity, reductions in pain relief, safety, and tolerability | Primary:<br>Both tapentadol treatment groups had a significant reduction in pain intensity compared to placebo (both *P*<0.0001).<br><br>Secondary:<br>Both tapentadol treatment groups had significant reductions in pain intensity, with increasing two- and 10-day SPID values (all *P*<0.001). Significant reductions in pain intensity were also reflected in two-, five- and 10-day TOTPAR and SPRID compared to placebo (all *P*<0.001).<br><br>A significant reduction in pain intensity was also seen in the oxycodone group compared to placebo (all comparisons, *P*<0.001).<br><br>Overall pain relief status was rated as "very much improved" or "much improved" by 49% and 42% of tapentadol 50 mg and 75 mg groups (*P*<0.001 for both compared to placebo).<br><br>Both tapentadol 50 mg and 75 mg provided analgesic efficacy that was noninferior to that of oxycodone.<br><br>The incidence of selected gastrointestinal adverse events was significantly lower for both doses of tapentadol compared to oxycodone (nominal *P*<0.001 for all events). Specifically, the OR for the incidence of the composite of nausea and/or vomiting for tapentadol 50 mg compared to oxycodone was 0.21 (95% CI, 0.128 to 0.339), and the OR for the incidence of constipation was 0.13 (95% CI, 0.057 to 0.302). For tapentadol 75 mg, the OR vs oxycodone was 0.32 for the composite of nausea/vomiting (95% CI, 0.204 to 0.501) and 0.20 for constipation (95% CI, 0.098 to 0.398). |


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| | | | | Rates of treatment discontinuation were 18, 26, 35 and 10% in the tapentadol 50 mg, tapentadol 75 mg, oxycodone, and placebo groups. A post hoc analysis found a significant difference in the percentage of patients who discontinued treatment between the tapentadol 50 mg group and the oxycodone group (*P*<0.001); rates of discontinuation did not differ significantly between the tapentadol 75 mg and oxycodone groups (*P* value not reported). Gastrointestinal and central nervous adverse events were the primary reason for study discontinuation. |
| Stegmann et al[27]<br><br>Tapentadol 50 mg every four to six hours<br><br>vs<br><br>tapentadol 100 mg every four to six hours<br><br>vs<br><br>oxycodone 10 mg every four to six hours<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 18 to 65 years of age who underwent a unilateral first metatarsal bunionectomy with osteotomy, with postoperative pain of ≥4 on an 11-point NRS, and an increase in pain of ≥1 on the 11-point NRS within nine hours after regional anesthesia was stopped on the first postoperative day | N=269<br><br>4 days | Primary:<br>SPI-24 on evaluation day 3<br><br>Secondary:<br>SPI-24 on evaluation days 2 and 4 (VRS), SPI-24 on evaluation days 2, 3, and 4 (NRS), TOTPAR-24 on evaluation days 2, 3, and 4, time to confirmed perceptible pain relief, time to 50% pain relief, time to first dose of rescue medication, and patient global assessment of study medication | Primary:<br>Mean (SD) SPI-24 values on evaluation day three were significantly lower for tapentadol (50 mg, 33.6 [19.7]; *P*=0.0133; 100 mg, 29.2 [15.2]; *P*=0.0001) and oxycodone (35.7 [17.2]; *P*=0.0365) compared to placebo (41.9 [17.7]).<br><br>Secondary:<br>Mean (SD) SPI-24 values on evaluation day two were significantly lower for tapentadol (50 mg, 41.2 [16.1]; *P*<0.0001; 100 mg, 36.9 [15.6]; *P*<0.0001) compared to placebo. On evaluation day four, only the tapentadol 100 mg group showed significance compared to placebo (23.4 [15.2]; *P*=0.0284). Oxycodone was associated with significantly lower SPI-24 (VRS) scores compared to placebo on evaluation day two only (*P*<0.0001).<br><br>Tapentadol 50 mg and 100 mg had significantly lower mean SPI-24 scores on evaluation days two (*P*<0.001 for both), three (*P*=0.0041 and *P*<0.0001, respectively), and four (*P*=0.0078 and *P*=0.0109, respectively) compared to placebo. Similar results were seen with oxycodone (*P*<0.0001, *P*=0.0075, and *P*=0.0062 compared placebo for all measures).<br><br>Tapentadol 100 mg had significantly higher TOTPAR-24 scores on evaluation days two, three, and four compared to placebo (*P*<0.0001, *P*=0.0009, *P*=0.0103, respectively). Tapentadol 50 mg was significant compared to placebo only on evaluation day two (*P*<0.0001). Similar to tapentadol 50 mg, oxycodone was only significant compared to placebo on evaluation day two (*P*=0.0021).<br><br>The median time to confirmed perceptible pain relief was longer for placebo- |


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| | | | | treated patients compared to all tapentadol and oxycodone groups. In addition, the median time to 50% pain relief was shorter in all of the active treatment groups compared to placebo with a significant difference for tapentadol 100 mg (*P*=0.0015) and oxycodone (*P*=0.0216).<br><br>The median times to first dose of rescue medication were significantly longer in the tapentadol 50 mg, 100 mg and oxycodone groups compared to placebo (*P*<0.0001 for all).<br><br>The distribution of responses ("good", "very good", or "excellent") on the global evaluation for tapentadol 50 mg and 100 mg was significantly different compared to placebo on evaluation days three, four, five, and at the post-treatment follow-up day (*P*≤0.05 for all).<br><br>While providing similar analgesic efficacy, tapentadol 50 mg, when compared to oxycodone, was associated with lower rates of nausea (46.3 vs 71.6%), dizziness (32.8 vs 56.7%), vomiting (16.4 vs 38.8%), and constipation (6.0 vs 17.9%), and a similar rate of somnolence (28.4 vs 26.9%; *P* values not reported). |
| Kean et al[28]<br><br>Tramadol ER 100 mg QD<br><br>vs<br><br>tramadol ER 200 mg QD<br><br>vs<br><br>tramadol ER 300 mg QD | 2 DB, DD, MC, PC, PG, RCT<br><br>Subanalysis of women aged 40 to 75 years with moderate-to-severe pain associated with OA of the knee and a WOMAC pain subscale and VAS score of above 150 mm at baseline | N=685<br><br>12 weeks | Primary:<br>Percent change in WOMAC pain and physical function subscales and patient global rating of pain<br><br>Secondary:<br>Percent change in WOMAC pain and physical function subscales at each visit | Primary:<br>The WOMAC pain scores from baseline to week 12 improved by an average of 58.8% in the 100 mg tramadol ER group (*P*=0.018), 53.0% in the 200 mg group (*P*=0.175) and 58.9% in the 300 mg group (*P*=0.023) compared to 45.2% in the placebo group.<br><br>The corresponding WOMAC physical function scores improved by a mean of 56.9% (*P*=0.009), 54.0% (*P*=0.034) and 53.4% (*P*=0.043) in the tramadol ER 100 mg, 200 mg and 300 mg groups compared to 41.9% in the placebo group.<br><br>At 12 weeks, 62 of 70 women (88.6%; *P*=0.059) in the 100 mg group, 62 of 71 women (87.3%; *P*=0.004) in the 200 mg group, and 55 of 63 women (87.3%; *P*<0.0001) in the 300 mg group rated their overall pain relief as "effective" or "very effective" compared to 134 of 177 women (75.7%) randomized to placebo. |


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| vs<br><br>placebo | | | | Secondary:<br>The mean WOMAC physical function scores for tramadol ER 100 mg, 200 mg and 300 mg doses showed statistically significant improvement with respect to placebo at all measurement periods of the study (*P*<0.05 for all comparisons). |
| Fishman et al (abstract)[29]<br><br>Tramadol ER 100 mg QD<br><br>vs<br><br>tramadol ER 200 mg QD<br><br>vs<br><br>tramadol ER 300 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients with moderate to severe pain due to OA of the knee | N=552<br><br>12 weeks | Primary:<br>Patient Global Rating of Pain Relief, WOMAC pain and functioning subscales, responders to treatment and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>There were statistically significant differences compared to placebo with regard to scores for Patient Global Rating of Pain Relief in the 200 mg and 300 mg tramadol ER treatment groups (*P*≤0.001).<br><br>Treatment was rated as “effective” or “very effective” by 75% and 80% of patients receiving tramadol ER 200 mg and 300 mg, respectively.<br><br>There was a statistically significant improvement in WOMAC scores with tramadol ER 300 mg (46%; *P*=0.016) and 200 mg (43%; *P*=0.05) compared to placebo (32%).<br><br>There was a statistically significant increase in the proportion of treatment responders (patients who achieved a ≥30% improvement in their baseline WOMAC pain score) in the tramadol ER 200 mg group (65%; *P*=0.0095) and 300 mg (65%; *P*=0.0104) compared to placebo (50%).<br><br>The most commonly reported adverse events were nausea, dizziness/vertigo, vomiting, somnolence, and constipation. Adverse events were reported as mild to moderate in intensity if 87% of patients. |
| Daniels et al[30]<br><br>Tapentadol 50 mg, frequency not specified<br><br>vs<br><br>tapentadol 75 mg, frequency not specified<br><br>vs | AC, DB, MC, PC, PG, RCT<br><br>Patients 18 to 80 years of age experiencing a pain intensity of ≥4 on an 11-point NRS following the cessation of postoperative | N=600<br><br>72 hours | Primary:<br>SPID-48<br><br>Secondary:<br>SPID-12, SPID-24, SPID-72, responder rates, TOTPAR, SPRID over the first 12, 24, 48, and 72 hours of treatment, time to first rescue | Primary:<br>All tapentadol groups showed a significant reduction in SPID-48 compared to placebo (all *P*<0.001) and increasing levels of pain relief were associated with higher doses of tapentadol.<br><br>In addition, the mean SPID-48 value for oxycodone was significantly different from placebo (nominal *P*<0.001).<br><br>Secondary:<br>Pain intensity reductions were demonstrated based on SPID over 12, 24 and 72 hours. Over each of these time periods, treatment with tapentadol resulted in |


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| tapentadol 100 mg, frequency not specified<br><br>vs<br><br>oxycodone 15 mg, frequency not specified<br><br>vs<br><br>placebo | analgesia following bunionectomy | | medication, and patient global impression of change | increased efficacy compared to placebo (*P*<0.001 for all).<br><br>A minimum of 50.0% reduction in pain intensity at 48 hours was shown by 30.0, 58.0, 56.7, 70.3 and 72.8% of the placebo, tapentadol 50 mg, tapentadol 75 mg, tapentadol 100 mg and oxycodone groups (all nominal *P*<0.001 compared to placebo).<br><br>Based on the TOTPAR scores over each time interval, pain relief was significantly greater in all of the tapentadol and oxycodone groups compared to placebo (*P*<0.001 for all). Similar results were seen with SPRID scores compared to placebo (*P*<0.001 for all).<br><br>The time to first rescue medication was significantly shorter for the placebo groups compared to all tapentadol treatment groups (*P*<0.001 for all) and oxycodone (nominal *P*<0.001). The percentage of patients who took rescue medications was highest in the placebo group (49%). A dose-response trend (19, 14 and 10%) of decreasing rescue medication with increased dose was noted in the tapentadol treatment groups (50 mg, 75 mg and 100 mg).<br><br>The percentage of patients who rated their overall status with the two highest distinctions, “much improved” or “very much improved”, was higher in the tapentadol and oxycodone groups compared to placebo (*P* values not reported). |
| DeLamos et al (abstract)[31]<br><br>Tramadol ER 100 mg QD<br><br>vs<br><br>tramadol ER 200 mg QD<br><br>vs | DB, MC, PC, RCT<br><br>Adults with knee and/or hip osteoarthritis and baseline pain intensity of ≥40 on a 100-mm VAS | N=1,001<br><br>12 weeks | Primary:<br>WOMAC pain subscale, WOMAC physical function subscale scores and patient global assessment of disease<br><br>Secondary:<br>Not reported | Primary:<br>Patients receiving tramadol ER 200 mg or 100 mg did not achieve WOMAC scores that were significantly different compared to placebo.<br><br>Tramadol ER 300 mg significantly improved patient global assessment scores compared to placebo (*P*≤0.05), but WOMAC pain or physical function subscales were not significantly different between treatments. Tramadol ER 200 and 100 mg were not significantly different from placebo with regard to WOMAC subscales.<br><br>Daily diary arthritis pain intensity scores improved significantly for tramadol ER 300 and 200 mg compared to placebo. |


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| tramadol ER 300 mg QD<br><br>vs<br><br>celecoxib 200 mg QD<br><br>vs<br><br>placebo | | | | WOMAC joint stiffness subscale, physician's global assessment, arthritis pain intensity in index and nonindex joints, and overall sleep quality scores improved significantly for tramadol ER 300 mg compared to placebo over 12 weeks.<br><br>Significant differences in efficacy between celecoxib and placebo validated the model sensitivity.<br><br>Adverse events were more common with tramadol ER compared to placebo with regard to gastrointestinal events (nausea, constipation, diarrhea) and central nervous (dizziness, headache). |
| Kleinert et al[32]<br><br>Tapentadol 25 mg, single dose<br><br>vs<br><br>tapentadol 50 mg, single dose<br><br>vs<br><br>tapentadol 75 mg, single dose<br><br>vs<br><br>tapentadol 100 mg, single dose<br><br>vs<br><br>tapentadol 200 mg, | AC, DB, MC, PC, Phase II, RCT<br><br>Patients 18 to 45 years of age undergoing mandibular third molar extraction with bone removal due to impaction, experiencing "moderate" to "severe" pain within six hours postsurgery | N=400<br><br>8 hours | Primary:<br>Mean TOTPAR-8<br><br>Secondary:<br>Mean TOTPAR-4, PID, and onset of analgesia | Primary:<br>Mean TOTPAR-8 scores were significantly improved compared to placebo for tapentadol 75 mg, 100 mg and 200 mg (all $P \leq 0.05$). Similar results were also observed with morphine sulfate ($P \leq 0.05$ vs placebo). In addition, TOTPAR-8 scores increased with tapentadol dose. Mean TOTPAR-8 scores for tapentadol 75 mg, 100 mg, and 200 mg were 9.7, 11.6, and 15.3, respectively. Mean TOTPAR-8 scores for morphine sulfate and placebo were 13.8, and 4.7, respectively<br><br>Secondary:<br>Mean TOTPAR-4 scores increased with increasing tapentadol dose, and mean TOTPAR-4 scores were higher for all tapentadol doses $\geq$50 mg, morphine sulfate 60 mg and ibuprofen 400 mg compared to placebo ($P \leq 0.05$ for all).<br><br>All efficacy variables for tapentadol 100 mg and 200 mg consistently showed greater analgesia compared to placebo ($P \leq 0.05$).<br><br>In the tapentadol 75 mg, 100 mg and 200 mg groups, mean PID scores increased from baseline until approximately two hours, then decreased gradually. The increases in mean PID were more rapid for tapentadol 200 mg compared to placebo, morphine sulfate 60 mg, and the other tapentadol doses (*P* values not reported). |


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| single dose<br><br>vs<br><br>morphine sulfate 60 mg, single dose<br><br>vs<br><br>ibuprofen 400 mg, single dose<br><br>vs<br><br>placebo | | | | All time-to-event variables were significantly shorter for tapentadol 75 mg, 100 mg, and 200 mg compared to placebo (*P*<0.05). |
| Steigerwald et al[33]<br><br>Tapentadol ER 50 mg to 250 mg BID (titrated each week to achieve ≥1 point decrease in pain intensity score)<br><br>Patients were permitted to take tapentadol IR 50 mg (BID or less frequently; ≥4 hours apart) throughout the 12-week treatment period; the maximum total daily dose of tapentadol (ER and IR) was not allowed to | MC, OL<br><br>Patients ≥18 years of age with OA of the knee for ≥3 months who had been receiving WHO Step I or II analgesic treatment for ≥2 weeks and current pain requiring WHO Step III analgesic with an average NRS-3 of ≥5 on 11 point scale, or ≥6 if no medications were being used at baseline | N=208<br><br>12 weeks | Primary:<br>Change from baseline to week six in NRS-3<br><br>Secondary:<br>Change in NRS-3 at 6, 8 and 12 weeks, , PGIC, CGIC, EQ-5D, SF-36, HADS and adverse events | Primary:<br>The mean change in pain intensity score from baseline to week six was -2.8 with tapentadol ER treatment (*P*<0.0001).<br><br>Secondary:<br>Statistically significant improvements in pain intensity scores from baseline occurred at week six (-3.2; *P*<0.0001), week eight (-3.5; *P*<0.0001) and week 12 (-3.9; *P*<0.0001).<br><br>By week six, 76.1% of patients reported “excellent”, “very good”, or “good” satisfaction with treatment. At week 12, the percentage of patients reporting “excellent”, “very good”, or “good” satisfaction with treatment was 83.5%. Overall, patient satisfaction with treatment improved from baseline for 81.9% of patients at week six and for 86.8% of patients at week 12.<br><br>A rating of “very much improved”, “much improved” or “minimally improved” was reported by 84.1% of patients at week six and 92.3% of patients at week 12 on the PGIC and by 86.2% of investigators at week six and 92.3% of investigators at week 12 on the CGIC. |


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| exceed 500 mg. | | | | Treatment with tapentadol ER was associated with statistically significant improvements in the mean EQ-5D health status at week six and week 12 compared to baseline (*P*<0.0001).<br><br>Tapentadol ER was associated with significant improvements in SF-36 domain scores at week six and week 12 compared to baseline values (*P*≤0.0002 for all comparisons).<br><br>The mean HAD anxiety score significantly decreased by week six (*P*=0.0002), week eight (*P*<0.0001), and week 12 (*P*=0.0001) of treatment. The mean HAD depression score decreased significantly at week six (*P*<0.0001), week eight (*P*<0.0001) and week 12 (*P*<0.0001).<br><br>No significant changes were observed in any standard clinical laboratory parameters or vital sign measures from screening or baseline to the end of tapentadol treatment. Overall, 84.7% of patients reported at least one treatment-related adverse event. The most commonly reported treatment-related adverse events were nausea (21.0%), dizziness (17.6%), headache (16.5%), dry mouth (15.3%), fatigue (12.5%), constipation (11.4%), diarrhea (11.4%), nasopharyngitis (11.4%), somnolence (10.2%), vomiting (6.3%), upper abdominal pain (5.1%), hyperhidrosis (5.1%), and pruritus (5.1%). The intensity of these adverse events were considered to be mild (51.3%) or moderate (42.2%). Only 6.1% were considered to be severe. |
| Steigerwald et al[34]<br><br>Tapentadol ER 50 mg to 250 mg BID (titrated each week to achieve ≥1 point decrease in pain intensity score)<br><br>Patients were permitted to take tapentadol IR | MC, OL<br><br>Patients ≥40 years of age with OA of the knee for ≥3 months who had been receiving WHO Step I or II analgesic treatment for ≥2 weeks and current pain requiring WHO | N=224<br><br>12 weeks | Primary:<br>Change from baseline to week six in NRS-3<br><br>Secondary:<br>Change in NRS-3 at 6, 8 and 12 weeks, responder rates, PGIC, WOMAC scores, EQ-5D, SF-36, HAD score and | Primary:<br>The mean pain intensity score decreased from 7.5 at baseline to 4.1 at week six (mean difference, -3.4; *P*<0.0001).<br><br>Secondary:<br>In the overall population, mean pain intensity scores improved significantly from baseline to week six (-3.8; *P*<0.0001), week eight (-4.2; *P*<0.0001) and week 12 (−4.4; *P*<0.0001).<br><br>The percentage of patients with a decrease in average pain intensity from baseline of ≥1 point was 96.9% at week six (*P*<0.0001). |


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| 50 mg (BID or less frequently; ≥4 hours apart) throughout the 12-week treatment period; the maximum total daily dose of tapentadol (ER plus IR) was not allowed to exceed 500 mg daily. | Step III analgesic with an average NRS-3 ≥5 on 11 point scale, or ≥6 if no medications were being used at baseline | | adverse events | The percentage of patients with a decrease in average pain intensity from baseline of ≥1 point and an improvement in patient-rated satisfaction with treatment [5-point VRS] of ≥1 category) was 88.8% at week six (*P*<0.0001).<br><br>On the PGIC, a rating of "very much improved" or "much improved" was reported by 9.4% of patients at week one, 55.6% of patients at week six and 69.6% of patients at week 12.<br><br>Tapentadol ER treatment was associated with statistically significant improvements in WOMAC osteoarthritis index pain, stiffness, and physical function subscale scores and the WOMAC global score at all time points evaluated (*P*<0.0001 for all comparisons).<br><br>Significant improvements from baseline in the mean EQ-5D health status index score occurred at weeks 6, 8 and 12. The mean EQ-5D health status index score was 0.42 at baseline and increased to 0.66 by week six, 0.67 by week eight and 0.69 by week 12 (*P*<0.0001 for all comparisons).<br><br>There were statistically significant improvements from baseline in the mean SF-36 physical and mental component summary scores at weeks six and 12 (*P*< 0.005 for both).<br><br>At weeks 6, 8 and 12, HAD scores for depression and anxiety were significantly lower following treatment with tapentadol ER compared to baseline values (*P*<0.0001 for all).<br><br>No clinically relevant changes were observed with regard to vital sign measures, laboratory values, or physical examination findings. In the safety population, 71.0% of patients reported a treatment-related adverse event. The most common treatment-related adverse events were nausea (13%), constipation (10.5%), dizziness (12%) and dry mouth (10%). The majority of treatment-related adverse events (95.7%) were considered to be mild to moderate in intensity. |
| Hale et al[35] | AC, DB, MC, PG, RCT | N=849 | Primary:<br>Adverse events, | Primary:<br>A smaller proportion of patients treated with tapentadol experienced treatment- |


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| Tapentadol 50 mg or 100 mg every four to six hours as needed; maximum total daily dose of 600 mg<br><br>vs<br><br>oxycodone 10 mg or 15 mg every four to six hours as needed; maximum total daily dose of 90 mg | Patients ≥18 years of age with a clinical diagnosis and a ≥3 month history of lower back pain of non-malignant origin or osteoarthritis pain of the knee or hip, with a score ≥4 on an 11-point NRS while taking non-opioid analgesics or following a 24-hour washout of opioid analgesics | 3 months | tolerability, and withdrawal symptoms<br><br>Secondary:<br>Efficacy | emergent adverse events compared to those receiving oxycodone (76.3 vs 82.9%; *P* value not reported). Gastrointestinal, nervous system, and skin adverse events were the most common treatment-emergent adverse events reported by at least 5.0% patients.<br><br>Patients in the tapentadol group experienced less nausea (10.3 vs 21.8%) and vomiting (3.5 vs 12.9%) compared to oxycodone on day two (*P* values not reported). After more than three weeks, the incidences of vomiting diminished to similar, low levels in both treatment groups, however there was a consistently higher frequency of nausea over the entire study with oxycodone.<br><br>There were no relevant changes in laboratory, urinalysis, vital sign, or ECG findings among patients in the two treatment groups.<br><br>Withdrawal symptoms, measured by the COWS, which were only of mild to moderate intensity, were detected in a significantly lower percentage of patients in the tapentadol group compared to the oxycodone group (17.0 vs 29.0%; *P*<0.05). Additionally, the mean total SOWS score in the tapentadol group was lower than in the oxycodone group which did not reach statistical significance (*P* value not reported).<br><br>Secondary:<br>Tapentadol and oxycodone demonstrated similar efficacy based on pain intensity measurements reported throughout the study. |
| Afilio et al[36]<br><br>Tapentadol ER 100 mg BID<br><br>vs<br><br>oxycodone CR 20 mg BID | AC, DB, IN, MC, PA, PC, RCT<br><br>Patients ≥40 years of age with a diagnosis of OA of the knee functional capacity class I-III, and pain at reference joint requiring | N=1,030<br><br>12 weeks (maintenance phase after a 3-week titration phase) | Primary:<br>Change in average pain intensity at week 12 of the maintenance period compared to baseline<br><br>Secondary:<br>Change in average pain intensity over the entire 12 week | Primary:<br>Significant pain relief was achieved with tapentadol ER compared to placebo at study endpoint. The LSM difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo.<br><br>Secondary:<br>The LSM difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol ER compared to placebo.<br><br>The average pain intensity rating with oxycodone CR was reduced significantly compared to placebo for the overall maintenance period (LSM difference, -0.3; |


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| Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for three days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20mg BID (minimum study doses); at three-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). APAP ≤1,000 mg/day (max of three consecutive days) was permitted. | analgesics (both non-opioid and opioid doses ≤160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current analgesic regimen, and had a baseline pain intensity score ≥5 during the three days prior to randomization | | maintenance period compared to baseline | 95% CI, -0.67 to 0.00); however, no difference was reported at week 12 of the maintenance period (LSM difference, -0.3; 95% CI, -0.68 to 0.02).<br><br>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 with oxycodone CR compared to placebo (24.9 vs 35.9%; *P*=0.002).<br><br>Treatment with 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 compared to placebo (32.0 vs 24.3%; *P*=0.027). Significantly fewer patients treated with oxycodone CR resulted achieved a ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period compared to placebo (17.3 vs 24.3%; *P*=0.023).<br><br>Tapentadol ER significantly improved WOMAC global scale scores compared to placebo (LSM difference, -0.21; 95% CI, -0.357 to -0.065; *P*=0.0047). Similarly, patients treated with oxycodone CR experienced significant improvements in WOMAC global scale scores compared to placebo (LSM difference, -0.18; 95% CI, -0.343 to -0.010; *P*=0.0381).<br><br>Tapentadol ER significantly improved subscale scores compared to treatment with placebo (LSM difference, -0.27; 95% CI, -0.422 to -0.126; *P*<0.001); however there was no difference in subscores for patients treated with oxycodone CR compared to placebo (LSM difference, -0.17; 95% CI, -0.338 to -0.000; *P*=0.051).<br><br>The physical function subscale at week 12 was significantly improved with tapentadol ER compared to placebo (LSM difference, -0.21; 95% CI, -0.357 to -0.060; *P*=0.006), whereas the difference between oxycodone CR and placebo was<br>-0.20 (95% CI, -0.373 to -0.034; *P*=0.019).<br><br>The stiffness subscale assessment was improved with tapentadol ER |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | compared to placebo (LSM difference, -0.17; 95% CI, -0.377 to -0.002; *P*=0.053); however, the difference was not statistically significant. Similarly, there was no statistically significant difference in stiffness subscale scores between oxycodone ER and placebo (LSM difference, -0.10, 95% CI, -0.292 to 0.096; *P*=0.321).<br><br>The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER and 87.4% with oxycodone CR. 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. |
| Wild et al[37]<br><br>Tapentadol ER 100 to 250 mg BID<br><br>vs<br><br>oxycodone CR 20 to 50 mg BID<br><br>Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for three days; then doses were increased to tapentadol ER 100 mg BID or | AC, MC, OL, PG, RCT<br><br>Men and women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or LBP (non-malignant) with a ≥3 month history of pain and dissatisfaction with current analgesic therapy and a pain intensity score of ≥4 on an 11-point rating scale after therapy washout | N=1,121<br><br>51 weeks (maintenance phase) | Primary:<br>Safety and tolerability<br><br>Secondary:<br>Change in mean pain intensity score | Primary:<br>The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.7% for tapentadol ER and 36.8% for oxycodone ER).<br><br>Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR 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 and fatigue.<br><br>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 compared to patients receiving oxycodone CR group. The incidence of pruritus was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed.<br><br>Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of |


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| oxycodone CR 20mg BID for four days; at three-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID. | | | | gastrointestinal events (i.e., nausea, vomiting or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively).<br><br>Serious adverse events were reported in 5.5% of patients receiving tapentadol ER and 4.0% of those treated with oxycodone CR.<br><br>Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group compared to those in the oxycodone CR group for the overall PAC-SYM score (0.3 vs 0.5, respectively), as well as for the overall rectal and overall stool subscale scores.<br><br>All COWS total scores during all time periods were <25, indicating no moderately severe or severe withdrawal in either treatment group for patients who did not take opioids after the last dose of medication.<br><br>Mean SOWS total scores from two, three, four and five or more days after discontinuation ranged from 6.9 to 9.5 for patients treated with tapentadol ER and from 7.5 to 12.3 for patients treated with oxycodone CR.<br><br>Secondary:<br>Baseline mean pain intensity scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively.<br><br>Ratings on the global assessment of study medication of “excellent,” “very good,” or “good” among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively).<br><br>The most commonly reported rating on the PGIC at endpoint was “much improved” for both the tapentadol ER and oxycodone CR 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. |
| O’Donnell et al[38] | 2 AC, DB, DD, MC, | N=796 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Tramadol 50 mg four times daily<br><br>vs<br><br>celecoxib 200 mg BID | PG, RCT<br><br>Patients ≥18 years of age with chronic LBP (≥12 weeks duration) who required regular use of analgesics (≥4 days/week), and experienced moderate to severe LBP at baseline visit (score of ≥4 on the NRS scale for pain) | (Study I)<br><br>N=802<br>(Study II)<br><br>6 weeks | Proportion of patients responding successfully to treatment (≥30% improvement from baseline on the NRS-pain scale)<br><br>Secondary:<br>Safety | The percentage of successful responders completing six weeks of treatment and having a ≥30% improvement from baseline in NRS-pain scale was significantly greater in the celecoxib group compared to the tramadol group in both study I (63.2 vs 49.9%; *P*<0.001) and study II (64.1 vs 55.1; *P*=0.008).<br><br>Secondary:<br>A significantly higher proportion of patients in the tramadol group (13.4 and 10.6% in studies I and II, respectively) withdrew due to lack of tolerability compared to the celecoxib group (1.2 and 1.0% in studies I and II, respectively; *P*<0.0001).<br><br>The most common reasons for withdrawal in the tramadol group were nausea and dizziness and dyspepsia and somnolence in the celecoxib group.<br><br>A higher percentage of gastrointestinal-related adverse events were reported in the tramadol group compared to the celecoxib group in both studies. The most common (occurring in >5% of patients) treatment-related adverse events in both study I and II were nausea, vomiting and constipation. No deaths were reported in either treatment group. |
| Courtney et al[39]<br><br>Tramadol 150 to 200 mg/daily<br><br>vs<br><br>diclofenac 100 to 150 mg/daily | PRO, RCT, SB<br><br>Patients ≥11 years of age with post-tonsillectomy pain | N=49<br><br>14 days | Primary:<br>Analgesic efficacy (measured by VAS pain scores)<br><br>Secondary:<br>Not reported | Primary:<br>The average VAS pain scores for the 14 days did not differ significantly (diclofenac group: mean [SD], 38.4 [17.5]; 95% CI, 32.0 to 45.0; tramadol group: mean [SD], 37.8 [15.6]; 95% CI, 32.0 to 43.5; *P*=0.66).<br><br>Secondary:<br>Not reported |
| Karlsson et al[40]<br><br>Tramadol ER 150 to 200 mg BID<br><br>vs | AC, MC, OL, PG, RCT<br><br>Patients ≥18 years of age with a clinical diagnosis of osteoarthritis of the | N=135<br><br>12 weeks | Primary:<br>Mean weekly Box Scale-11 pain score<br><br>Secondary:<br>Daily number of tablets of | Primary:<br>In the intent-to-treat analysis, the LSM 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 demonstrating that buprenorphine was non-inferior to tramadol ER. |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every seven days | hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before the first visit | | supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety | Secondary:<br>The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol ER. The difference between the two treatment groups did not reach statistical significance (*P* value not reported).<br><br>There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol ER groups (*P* value not reported).<br><br>There were statistically significant differences in favor of buprenorphine compared to tramadol ER with regard to patient- and investigator-rated global assessment of pain relief (*P*=0.039 and *P*=0.020, respectively).<br><br>Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for osteoarthritis pain in the future.<br><br>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%). |
| Brattwall et al[41]<br><br>Tramadol ER 100 mg BID for seven days<br><br>vs<br><br>etoricoxib 120 mg QD for four days followed by 90 mg QD for three days | AC, DB, PRO, RCT<br><br>Women undergoing an elective hallux valgus surgery | N=100<br><br>7 days | Primary:<br>VAS pain score, VAS pain relief score, treatment satisfaction and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>The mean maximum VAS was significantly lower among etoricoxib patients evaluated during the entire seven-day period (12.5±8.3 vs 17.3±11.0; *P*<0.05).<br><br>A significant difference in daily maximum pain VAS scores was observed on days three, four and seven (*P*<0.05). The relief of pain from study medication was rated as high for patients in both groups; however, pain relief was significantly higher in the etoricoxib group (*P*<0.05) on days two, three and five.<br><br>Satisfaction with pain management was significantly higher in the etoricoxib treatment group (*P*<0.05). There was no statistically significant difference in between patients in either treatment group with regard to EQ-5D scores as follow-up (*P*>0.05 for all components). |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Twenty patients in the etoricoxib group and 13 in the tramadol group, did not take any rescue medication during the seven-day follow-up period, however, the difference was not significant. Adverse events occurred more frequently in the tramadol group compared to etoricoxib (*P*<0.05). Six patients discontinued study medication because of side effects, primarily nausea, dizziness and sleepiness.<br><br>Secondary;<br>Not reported |
| Park et al[42]<br><br>Tramadol 37.5 mg/ APAP 325 mg up to eight tablets daily<br><br>vs<br><br>meloxicam 7.5 to 15 mg QD or aceclofenac 100 mg BID<br><br>Patients received combination therapy with tramadol 37.5 mg/ APAP 325 mg and NSAIDs for four weeks. Patients with an NRS score <4 continued to the maintenance phase. | AC, MC, OL,<br><br>Patients 40 to 75 years of age with symptomatic knee OA for ≥1 year and moderate OA pain (≥5 on NRS) despite treatment with stable doses of NSAIDs (meloxicam 7.5 mg or 15 mg QD or aceclofenac 100 mg BID) for ≥4 weeks | N=97<br><br>8 weeks | Primary:<br>WOMAC OA index score<br><br>Secondary:<br>Pain intensity on NRS, overall assessment by patient and investigator | Primary:<br>The WOMAC scores did not significantly increase on days 29 and 57 of monotherapy with tramadol/APAP compared to meloxicam treatment (6.75 vs 6.51, respectively; *P* value not reported).<br><br>Secondary:<br>There was no significant difference between the tramadol/APAP and meloxicam treatment groups with regard to NRS pain intensity scores over eight weeks of treatment (3.61 vs 3.51; *P* value not reported).<br><br>There was no statistically significant difference between the tramadol/APAP and meloxicam groups in the proportion of patients who reported pain relief (68.2 vs 78.7%; *P*>0.05).<br><br>Similar percentages of patients in the tramadol/APAP and meloxicam treatment groups rated medication as “good” or “very good” (44.2 vs 61.7%, respectively; *P*>0.05). There was no significant difference in the proportion of investigators rating the treatment as “good” or “very good” in the tramadol/APAP and meloxicam groups, respectively were 51.2 and 63.8%; *P*>0.05). |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Alfano et al (abstract)[43]<br><br>Tramadol/paracetamol 37.5 mg/325 mg one tablet administered after surgery followed by one tablet four times daily<br><br>vs<br><br>codeine/paracetamol 30 mg/500 mg one tablet administered after surgery followed by one tablet four times daily | AC, PRO, RCT<br><br>Patients undergoing surgical procedures (hallux valgus, haemorrhoid-ectomy, varicectomy and inguinal hernia repair) | N=122<br><br>2 days | Primary:<br>VSR, quality of life, patient assessment of surgical procedure and postoperative outcome<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with tramadol/paracetamol was associated with significantly lower VSR scores at 24 hours compared to codeine/paracetamol (1.40±0.76 vs 2.5±0.86; *P*<0.001).<br><br>Fewer patients reported adverse events with tramadol/paracetamol compared to those receiving codeine/paracetamol (36 vs 62%; *P*<0.01).<br><br>Fewer patients receiving tramadol/paracetamol required "rescue" pain medications compared to those receiving codeine/paracetamol (5.5 vs 18.2%; *P*<0.01).<br><br>Significantly more patients treated with tramadol/paracetamol rated their treatment as "excellent" compared to patients in the codeine/paracetamol treatment group (54.5 vs 16.0%; *P*<0.001).<br><br>Secondary:<br>Not reported |
| Mullican et al[44]<br><br>Tramadol 37.5 mg/ APAP 325 mg every four to six hours<br><br>vs<br><br>codeine 30 mg/APAP 300 mg every four to six hours | AC, DB, DD, PG, RCT<br><br>Men and women ≥18 years of age with chronic nonmalignant LBP, osteoarthritis pain, or both | N=462<br><br>4 weeks | Primary:<br>Efficacy (measured by patient reported pain relief and pain intensity using Likert scales, and overall efficacy as reported by investigators)<br><br>Secondary:<br>Safety | Primary:<br>Mean TOTPAR scores were comparable between the two groups at each weekly observation.<br><br>Mean SPID scores were similar for tramadol/APAP and codeine/APAP at each visit.<br><br>The maximum number of doses required in a single day for pain relief was a mean of 5.5 tablets of tramadol/APAP and 5.7 capsules of codeine/APAP.<br><br>The percentage of patients requiring supplemental ibuprofen at any point was comparable between the groups and ranged from 21 to 30% for each week of the study. The mean duration of therapy was 25.5 days for tramadol/APAP and 25.0 days for codeine/APAP.<br><br>Secondary:<br>The overall rates of treatment-emergent adverse events were comparable for |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | the two treatment groups. Seventy one percent of the tramadol/APAP and 76% of the codeine/APAP treated patients reported adverse events.<br><br>Somnolence (24% [37/153] and constipation (21% [32/153]) were significantly more common in the codeine/APAP group than in the tramadol group (17% [54/309] and 11% [35/309]; *P*=0.05 and *P*<0.01, respectively). |
| Fricke et al[45]<br><br>Tramadol 50 mg single-dose<br><br>vs.<br><br>tramadol 37.5 mg/ APAP 325 mg single-dose<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Men and women aged 18 to 75 who underwent elective outpatient surgery for extraction of at least two upper or lower impacted third molars | N=456<br><br>1 day | Primary:<br>Efficacy (measured by hourly PAR and pain intensity scores)<br><br>Secondary:<br>PID and PAR at each time point, time to onset of perceptible/ meaningful PAR, time to rescue analgesia, and adverse events | Primary:<br>Tramadol/APAP was superior to tramadol (*P*<0.001) or placebo (*P*<0.001) for all the primary efficacy endpoints, regardless of the time interval examined. Tramadol was numerically superior to placebo but was not statistically different from placebo for any of the endpoints.<br><br>Mean PAR scores were greater at all time points after a dose of tramadol/APAP compared to tramadol (*P*<0.001) or placebo (*P*<0.001). Tramadol was significantly more effective than placebo for mean PAR scores at hour two (*P*=0.022), but not at the other time points evaluated.<br><br>Mean PID scores also demonstrated greater improvement throughout the study in the tramadol/APAP group compared to the tramadol (*P*<0.001) or placebo (*P*<0.001) group.<br><br>Secondary:<br>Tramadol/APAP-treated patients reported meaningful PAR more rapidly than tramadol-treated (*P*<0.001) or placebo-treated (*P*<0.001) patients. Tramadol-treated patients reported meaningful PAR more rapidly than placebo-treated patients (*P*=0.035).<br><br>Tramadol/APAP also had significantly faster onset of action compared to tramadol (*P*<0.001) or placebo (*P*<0.001) with respect to perceptible PAR, but tramadol did not demonstrate significantly faster onset of perceptible PAR compared to placebo (*P*=0.805).<br><br>The overall incidences of adverse events were 54% in the tramadol/APAP group, 64% in the tramadol group and 39% in the placebo group. Nausea was significantly less common in the tramadol/APAP group (33%) compared to the |


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| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | tramadol group (46%; *P*=0.019). |
| Beaulieu et al[46]<br><br>Tramadol ER 200 to 400 mg/daily<br><br>vs<br><br>tramadol IR 50 to 100 mg every four to six hours<br><br>vs<br><br>placebo | DB, DD, RCT, XO<br><br>Men and women aged 18 to 75 years with chronic (>1 month) noncancerous pain | N=122<br><br>8 weeks | Primary:<br>Pain intensity (measured by VAS and ordinal scales)<br><br>Secondary:<br>Tolerability | Primary:<br>Mean pain intensity scores did not differ during the first two weeks of treatment in each phase, however, there was a significant difference between ER and IR tramadol during the last two weeks of treatment in each phase.<br><br>In the completer population, during the last two weeks of each phase, the mean (SD) VAS scores were 29.9 (20.5) and 36.2 (20.4) mm for ER and IR tramadol, respectively (*P*<0.001). The mean (SD) ordinal scores were 1.41 (0.7) and 1.64 (0.6), respectively (*P*<0.001).<br><br>In the ITT population, during the last two weeks of each phase the mean (SD) VAS scores were 32.5 (22.9) and 38.5 (21.2) mm for ER and IR tramadol, respectively (*P*<0.003). The mean (SD) ordinal scores were 1.50 (0.80) and 1.72 (0.70), respectively (*P*<0.002).<br><br>In the completer population, over the course of the entire study, the mean (SD) VAS pain intensity scores recorded in the daily diary were 34.1 (18.7) and 38.2 (20.0) mm (*P*=0.01) and the mean (SD) ordinal scores were 1.56 (0.50) and 1.72 (0.60) (*P*<0.003) during ER and IR tramadol treatment, respectively.<br><br>Secondary:<br>The most commonly reported adverse events in both treatment groups were nausea, dizziness, constipation, somnolence, asthenia, headache, sweating, and vomiting. When the most common adverse events were analyzed individually only nausea occurred significantly more often in the ER tramadol group (*P*<0.021). |

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, XO=crossover
Miscellaneous abbreviations: APAP=acetaminophen, BPI=brief pain inventory, GCIC=clinical global improvement or change, COWS=clinical opiate withdrawal scale, CR=controlled-release, DPN=diabetic peripheral neuropathy, ECG=electrocardiogram, EQ-5D=European quality of life-five dimensions, ER=extended release, HADS=hospital anxiety and depression score, HbA1c=glycosylated hemoglobin, ITT=intent-to-treat analysis, IR=immediate release, LBP=low back pain, LSM=least squares mean, NRS=numeric rating scale, NSAIDS=nonsteroidal anti-inflammatory drugs, OA=osteoarthritis, ODT=orally disintegrating tablet, OR=odds ratio, PAC-SYM=patient assessment of constipation symptoms, PAR=pain relief, PID=pain intensity difference, PGIC=patient global impression of change, PI-NRS-pain intensity numeric rating scale, PRID=combined hourly pain relief and pain intensity difference, PRRS=pain relief rating scale, PVA=pain visual analog scale, RDQ=Roland disability questionnaire, SD=standard deviation, SF-36=36-item short form health survey, SFMPQ=short form McGill pain questionnaire, SPI-24=summed pain intensity over 24 hours, SPID= pain intensity difference from baseline, SPRID=pain intensity difference from baseline, SOWS=subjective opioid withdrawal scale, TOTPAR=total pain relief, VAS=visual analogue scale, VRS=verbal rating scale, WOMAC OA=Western Ontario and McMaster Universities osteoarthritis index score.


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## Special Populations

**Table 5. Special Populations[3-12]**

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| **Single-Entity Products** | | | | | |
| Tapentadol | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in pediatric patients ≤18 years of age have not been established. | No dosage adjustment required in patients with mild to moderate renal impairment. | No dosage adjustment required in patients with mild to moderate hepatic impairment. | C | Unknown ; tapentadol should not be used during breast feeding |
| Tramadol | In patients >75 years of age, daily doses in excess of 300 mg are not recommended. Use tramadol extended-release with great caution in patients ≥75 years of age.<br><br>Safety and efficacy in patients <16 years of age have not been established. | Renal dose adjustment is required; for creatinine clearances of <30 mL/min, it is recommended that the dosing interval be increased to every 12 hours, with a maximum daily dose of 200 mg.<br><br>Tramadol extended-release should not be used in patients with severe renal impairment (CrCl <30 mL/min). | The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours.<br><br>Tramadol extended-release should not be used in patients with severe hepatic impairment. | C | Yes (0.1%) |
| **Combination Products** | | | | | |
| Tramadol/ acetaminophen | No evidence of overall differences in safety or efficacy observed between elderly | Not studied in renal dysfunction.<br><br>In patients with | Not studied in renal dysfunction.<br><br>Use in patients with hepatic | C | Yes (0.1%) |


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| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | and younger adult patients.<br><br>Safety and efficacy in pediatric patients ≤16 years of age have not been established. | creatinine clearances <30 mL/minute, it is recommended that the dosing interval be increased not to exceed two tablets every 12 hours. | impairment is not recommended | | |

**Adverse Drug Events**

**Table 6. Adverse Drug Events[3-12]**

| Adverse Event | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| **Body as a whole** | | | | | |
| Asthenia | - | 2 | 6 to 12 | 6.5 | - |
| **Cardiovascular** | | | | | |
| Postural hypotension | - | - | - | 1.7 to 5.4 | - |
| **Central Nervous System** | | | | | |
| Abnormal dreams | 1 | 1 | - | - | - |
| Anxiety | 1 | 2 | - | - | - |
| Attention disturbances | - | 1 | - | - | - |
| Central nervous system stimulation | - | - | 7 to 14 | - | - |
| Chills | - | 1 | - | - | - |
| Confused state | 1 | - | - | - | - |
| Depression | - | 1 | - | - | - |
| Disturbances in attention | - | 1 | - | - | - |
| Dizziness | 24 | 17 | 26 to 33 | 6.9 to 22.5 | 3 |
| Headache | - | 15 | 18 to 32 | 12.2 to 15.8 | - |
| Insomnia | 2 | 4 | - | 6.5 to 10.9 | 2 |
| Somnolence | 15 | 12 | 16 to 25 | 7.3 to 20.3 | 6 |
| Tremor | 1 | 1 | - | - | - |
| Vertigo | - | 2 | - | - | - |
| **Gastrointestinal** | | | | | |
| Anorexia | - | - | - | 0.7 to 5.9 | 3 |
| Constipation | 8 | 17 | 24 to 46 | 12.2 to 29.7 | 6 |
| Decreased appetite | 2 | 2 | - | - | - |
| Diarrhea | - | - | 5 to 10 | 3.7 to 8.5 | 3 |
| Dry mouth | 4 | 7 | 5 to 10 | 5.0 to 9.8 | 2 |
| Dyspepsia | 2 | 3 | 5 to 13 | - | - |
| Nausea | 30 | 21 | 24 to 40 | 15.1 to 26.2 | 3 |
| Vomiting | 18 | 8 | 9 to17 | 5.0 to 9.4 | - |


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| Adverse Event | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| **Infections and Infestations** | | | | | |
| Nasopharyngitis | 1 | - | - | - | - |
| Upper respiratory tract infection | 1 | - | - | - | - |
| Urinary tract infection | 1 | - | - | - | - |
| **Skin and Subcutaneous tissue** | | | | | |
| Flushing | - | - | - | 7.7 to 15.8 | - |
| Hyperhidrosis | 3 | 5 | - | - | - |
| Pruritus | 3 to 5 | 5 | 8 to 11 | 6.2 to 11.9 | 2 |
| Rash | 1 | - | - | - | - |
| Sweating | - | - | 6 to 9 | 1.5 to 6.4 | 4 |
| **Other** | | | | | |
| Arthralgia | 1 | - | - | - | - |
| Erectile dysfunction | - | 1 | - | - | - |
| Fatigue | 3 | 9 | - | - | - |
| Feeling hot | 1 | 2 | - | - | - |
| Lethargy | 1 | 2 | - | - | - |
| Prostatic disorder | - | - | - | - | 2 |
| Vision blurred | - | - | - | - | - |

-Event not reported.

## Contraindications

**Table 7. Contraindications[3-12]**

| Contraindication | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days | a | a | - | - | - |
| Hypersensitivity to any components or the active ingredient | a | a | a | a | a |
| Respiratory depression, significant | a | a | - | - | - |
| Acute or severe bronchial asthma | a | a | - | - | - |
| Suspected or documented paralytic ileus | a | a | - | - | - |
| Intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs | - | - | a | a | a |


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**Boxed Warning for Nucynta ER® (tapentadol)[8,12]**

| WARNING |
|---|
| Potential for Abuse: Nucynta ER® contains tapentadol, a μ-opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics.<br><br>Nucynta ER® can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when prescribing, or dispensing Nucynta ER® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.<br><br>Proper Patient Selection: Nucynta ER® is an extended-release formulation of tapentadol indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.<br><br>Limitations of Use: Nucynta ER® is not intended for use as an as-needed analgesic.<br><br>Nucynta ER® is not intended for the management of acute or postoperative pain. Nucynta ER® tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, dissolved, or crushed Nucynta ER® tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.<br><br>Patients must not consume alcoholic beverages, prescription or nonprescription medications containing alcohol. Coingestion of alcohol with Nucynta ER® may result in a potentially fatal overdose of tapentadol. |

**Boxed Warning for Ultracet® (tramadol/acetaminophen)[10,12]**

| WARNING |
|---|
| These products contain 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 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. |

**Warnings/Precautions**

**Table 8. Warnings and Precautions[3-12]**

| Warning/Precaution | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| Accidental exposure; can result in a fatal overdose, especially in children | a | a | - | - | - |
| Acute abdominal conditions; tramadol use may complicated clinical assessment | - | - | a | a | - |
| Central nervous system depression; may cause somnolence, dizziness, alterations in judgment and alterations in levels | a | a | - | - | - |


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| Warning/Precaution | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| of consciousness, including coma | | | | | |
| Excessive doses either alone or in combination with central nervous system depressants are a cause of drug-related deaths | - | - | a | a | - |
| Driving and operating machinery | a | a | - | - | - |
| Gastrointestinal obstruction; do not administer to patients with gastrointestinal obstruction, especially paralytic ileus | a | a | - | - | - |
| Head injury and increased intracranial pressure | 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 | - |
| 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 | - | - | - |
| Impaired respiration/respiratory depression | 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 | - | - | - |
| Misuse, abuse and diversion | a | a | a | a | - |
| Pancreatic/biliary tract | a | a | - | - | - |


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| Warning/Precaution | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| disease; use with caution in patients with biliary tract disease, including acute Pancreatitis | | | | | |
| 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 | - |
| Seizures | a | a | a | a | - |
| Serotonin syndrome risk | a | a | a | 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 | - |
| Use in patients with chronic pulmonary disease; monitor patients for respiratory depression, particularly when initiating therapy and titrating therapy | a | a | - | a | - |
| Use is suicidal patients or patients who are addiction prone is not recommended | - | - | a | a | - |
| Drug and alcohol addiction; not approved | - | - | a | a | - |

| Warning/Precaution | Tapentadol | Tapentadol Extended-Release | Tramadol | Tramadol Extended-Release | Tramadol/ acetaminophen |
|---|---|---|---|---|---|
| for the management of addiction disorders | | | | | |
| Phenylketonurics; patients with a history of sensitivity to phenylketones may be at increased risk | - | - | a | a | - |

## Drug Interactions

**Table 9. Drug Interactions[3-12,47]**

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Tapentadol, tramadol, tramadol/acetaminophen | Monoamine oxidase Inhibitors | Concomitant administration may lead to an increased risk of seizures or serotonin syndrome. |
| Tapentadol, tramadol | Serotonin reuptake Inhibitors | Additive serotonergic effects of tramadol when co-administered with serotonin reuptake inhibitors may result in serotonin syndrome. |
| Tapentadol, tramadol | Central nervous system depressants | Concomitant administration may increase the risk for central nervous system and respiratory depression. |
| Tramadol, tramadol/acetaminophen | CYP 3A4 inhibitors (e.g., erythromycin, ketoconazole) | Strong CYP 3A4 inhibitors may increase tramadol concentrations increasing the risk for serious adverse events. |
| Tapentadol | Anticholinergic agents | Concomitant administration may increase the risk of urinary retention and severe constipation. |
| Tramadol | CYP 3A4 inducers (e.g., phenytoin, rifampin) | Concomitant use may decrease the clearance of tramadol. |
| Tramadol | Carbamazepine | Carbamazepine increases tramadol metabolism possibly resulting in significantly reduced analgesic effect. Due to the seizure risk associated with tramadol, concomitant administration of tramadol and carbamazepine is not recommended. |
| Tramadol | CYP2D6 inhibitors | Concomitant administration may lead the inhibition of the metabolism of tramadol. |

## Dosage and Administration

**Table 10. Dosing and Administration[3-12]**

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| **Single-Entity Products** | | | |
| Tapentadol | Management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, management of neuropathic pain | Safety and efficacy in pediatric patients ≤18 years of age have not been established. | Extended release tablet:<br>50 mg<br>100 mg<br>150 mg<br>200 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time:<br>Extended-release tablet: initial, 50 mg twice daily; maintenance, titrate to adequate analgesia; maximum, 500 mg daily<br><br>Relief of moderate to severe acute pain in patients 18 years of age or older:<br>Tablets: initial, 50 mg, 75 mg, or 100 mg every four to six hours; maximum, 700 mg on the first day of therapy and 600 mg on subsequent days | | 250 mg<br><br>Tablet:<br>50 mg<br>75 mg<br>100 mg |
| Tramadol | Management of moderate to moderately severe pain in adults:<br>Tablet: initial, 25 to 50 mg in the morning titrated to QID; maintenance, 50 to 100 mg every four to six hours as needed; maximum, 400 mg daily<br><br>Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time:<br>Extended-release capsules, extended-release tablets (patients not currently on tramadol immediate-release products): initial, 100 mg QD and titrated to pain relief; maximum 300 mg QD<br><br>Extended-release capsules, extended-release tablets (patients currently on tramadol immediate-release products): initial, calculate the 24-hour tramadol immediate-release dose and round down to nearest 100 mg increment and administer QD | Safety and efficacy in patients under 16 years of age have not been established. | Extended-release capsule:<br>100 mg<br>150 mg<br>200 mg<br>300 mg<br><br>Extended-release tablet:<br>100 mg<br>200 mg<br>300 mg<br><br>Orally disintegrating tablet:<br>50 mg<br><br>Tablet:<br>50 mg |
| **Combination Products** | | | |
| Tramadol/ acetaminophen | Short-term (five days or less) management of acute pain:<br>Tablet: initial, two tablets every four to six hours as needed for five days or less; maximum, eight tablets daily | Safety and efficacy has not been established in pediatric patients. | Tablet:<br>37.5 mg/325 mg |

QD=once-daily, QID=four times daily

## Clinical Guidelines

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendation(s) |
|---|---|
| National Comprehensive Cancer Network: **Adult Cancer Pain (2012)**[48] | · Pain is one of the most common symptoms associated with cancer.<br>· 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.<br>· This guideline is unique it that it contains the following components:<br>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.<br>o A formal comprehensive pain assessment must be performed.<br>o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect.<br>o Psychosocial support must be available.<br>o Specific educational material must be provided to the patient.<br>· The pain management algorithm distinguishes three levels of pain intensity, based on a 0 to 10 numerical rating scale: severe pain (7 to 10), moderate pain (4 to 6) and mild pain (1 to 3).<br>· Pain associated with oncology emergency should be addressed while treating the underlying condition.<br>· 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.<br>· Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids.<br>· For 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.<br>· Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids.<br>· 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 are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.<br>· Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es).<br>· Fentanyl, hydromorphone, morphine, and oxycodone are the opioids commonly used in the United States. An individual approach should be used to determine opioid starting dose, frequency and titration in order to achieve a balance between pain relief and medication adverse effects. |


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|---|---|
| | · In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.”<br>· “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”.<br>· 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.<br>· 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 |


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|---|---|
| | 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.<br>· 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.<br>· 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 effects, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing.<br>· 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%.<br>· 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.<br>· 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.<br>· 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.<br>· If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patient should be converted to an extended-release oral medication (if feasible) or another extended-release 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 extended-release opioids.<br>· Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety.<br>· 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.<br>· 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.<br>· The term adjuvant refers to medication that is coadministered to manage an adverse event of an opioid or to adjuvant analgesics that is 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). |


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| | |
|---|---|
| | · 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.<br>· Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain.<br>· Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attention should also be focused on psychosocial support and providing education to patients and families. |
| American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[49] | · 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.<br>· 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.<br>· 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.<br>· 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.<br>· Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education.<br>· Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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 |


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| | |
|---|---|
| | frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultations with a mental health or addiction specialist.<br>· 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 discontinuation of chronic opioid therapy.<br>· When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and reassess benefits relative to harms.<br>· 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.<br>· Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse events or inadequate benefit despite dose increases.<br>· 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.<br>· Clinicians should anticipate, identify, and treat common opioid-associated adverse events.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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.<br>· 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. |

<table>
<tr>
<td>Treatment Guidelines from The Medical Letter:<br>Drugs for Pain (2010)[50]</td>
<td>· The nonopioid analgesics acetaminophen, aspirin and NSAIDs are preferred for initial management of mild to moderate pain.<br>· For moderate pain, NSAIDs have been shown to be more effective than acetaminophen and aspirin, and may be equal to or greater than acetaminophen/opioid combination products or opioids administered via injection, at recommended doses.<br>· Moderate pain that does not respond to nonopioids can be treated with weak opioids combined with nonopioid analgesics.<br>· Strong, full opioid agonists are the drugs of choice for the treatment of most types of severe pain (some sever neuropathic pain may respond to nonopioids).<br>· Full opioid agonists generally have no ceiling effect for their analgesia and the dose may be increased as tolerated based on adverse effects.<br>· Patients who do not respond to one opioid may respond to another.<br>· When frequent “as needed” dosing becomes impractical, long-acting opioids may be helpful.<br>· Combination regimens, including opioids, non-opioids and adjuvant analgesics, are useful for severe chronic pain, such as pain in cancer patients.</td>
</tr>
<tr>
<td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society:<br>Diagnosis and Treatment of Low Back Pain (2007)[14]</td>
<td>· Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.<br>· The potential interventions for low back pain are outlined below:
<table>
<tr><td colspan="4">Interventions for the Management of Low Back Pain</td></tr>
<tr><td colspan="2">Intervention Type</td><td>Acute pain (duration <4 weeks)</td><td>Subacute or chronic pain (duration >4 weeks)</td></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="8">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.<br><br>· Physicians should conduct a focused history and physical examination to</td>
</tr>
</table>


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| | 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.<br>· 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.<br>· 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.<br>· Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation). These agents should be used with caution.<br>· Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.<br>· Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another.<br>· 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)**[15] | Nonpharmacologic recommendations for the management of hand osteoarthritis<br>· It is recommended that health professionals should:<br>o Evaluate the ability to perform activities of daily living.<br>o Instruct in joint protection techniques.<br>o Provide assistive devices, as needed, to help patients perform activities of daily living.<br>o Instruct in use of thermal modalities.<br>o Provide splints for patients with trapeziometacarpal joint osteoarthritis.<br><br>Pharmacologic recommendations for the initial management of hand osteoarthritis<br>· It is recommended that health professionals should use one or more of the following:<br>o Topical capsaicin.<br>o Topical NSAIDs, including trolamine salicylate.<br>o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors.<br>o Tramadol.<br>· It is conditionally recommend that health professionals should not use the following:<br>o Intraarticular therapies.<br>o Opioid analgesics.<br>· It is conditionally recommend that:<br>o In persons ≥75 years of age should use topical rather than oral NSAIDs.<br>o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. |

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| | Nonpharmacologic recommendations for the management of knee osteoarthritis<br>· It is strongly recommend that patients with knee osteoarthritis do the following:<br>o Participate in cardiovascular (aerobic) and/or resistance land-based exercise.<br>o Participate in aquatic exercise.<br>o Lose weight (for persons who are overweight).<br>· It is conditionally recommend that patients with knee osteoarthritis do the following:<br>o Participate in self-management programs.<br>o Receive manual therapy in combination with supervised exercise.<br>o Receive psychosocial interventions.<br>o Use medially directed patellar taping.<br>o Wear medially wedged insoles if they have lateral compartment osteoarthritis.<br>o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis.<br>o Be instructed in the use of thermal agents.<br>o Receive walking aids, as needed.<br>o Participate in tai chi programs.<br>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).<br>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).<br>· No recommendation is made regarding the following:<br>o Participation in balance exercises, either alone or in combination with strengthening exercises.<br>o Wearing laterally wedged insoles.<br>o Receiving manual therapy alone.<br>o Wearing knee braces.<br>o Using laterally directed patellar taping.<br><br>Pharmacologic recommendations for the initial management of knee osteoarthritis<br>· It is conditionally recommend that patients with knee osteoarthritis use one of the following:<br>o Acetaminophen.<br>o Oral NSAIDs.<br>o Topical NSAIDs.<br>o Tramadol.<br>o Intraarticular corticosteroid injections.<br>· It is conditionally recommend that patients with knee osteoarthritis not use |


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| | the following:<br>o Chondroitin sulfate.<br>o Glucosamine.<br>o Topical capsaicin.<br>· No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics.<br><br>Nonpharmacologic recommendations for the management of hip osteoarthritis<br>· It is strongly recommend that patients with hip osteoarthritis do the following:<br>o Participate in cardiovascular and/or resistance land based exercise.<br>o Participate in aquatic exercise.<br>o Lose weight (for persons who are overweight).<br>· It is conditionally recommend that patients with hip osteoarthritis do the following:<br>o Participate in self-management programs.<br>o Receive manual therapy in combination with supervised exercise.<br>o Receive psychosocial interventions.<br>o Be instructed in the use of thermal agents.<br>o Receive walking aids, as needed.<br>· No recommendation is made regarding the following:<br>o Participation in balance exercises, either alone or in combination with strengthening exercises.<br>o Participation in tai chi.<br>o Receiving manual therapy alone.<br><br>Pharmacologic recommendations for the initial management of hip osteoarthritis<br>· It is conditionally recommend that patients with hip osteoarthritis use one of the following:<br>o Acetaminophen.<br>o Oral NSAIDs.<br>o Tramadol.<br>o Intraarticular corticosteroid injections.<br>· It is conditionally recommend that patients with hip osteoarthritis not use the following:<br>o Chondroitin sulfate.<br>o Glucosamine.<br>· No recommendation is made regarding the use of the following:<br>o Topical NSAIDs.<br>o Intraarticular hyaluronate injections.<br>o Duloxetine.<br>o Opioid analgesics. |
| American Academy of Orthopedic Surgeons: **Clinical Practice Guideline on Osteoarthritis of the Knee (2008)**[51] | Nonpharmacological/surgical therapy<br>· Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening.<br>· Patients with symptomatic osteoarthritis of the knee should use patellar taping for short term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. |

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| | · Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus and/or a loose body.<br><br>Pharmacological therapy<br>· Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee.<br>· Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment:<br>o Acetaminophen (not to exceed 4 g per day).<br>o NSAIDs.<br>· Patients with symptomatic osteoarthritis of the knee and increased gastrointestinal risk (age ≥60 years, comorbid medical conditions, history of peptic ulcer disease, history of gastrointestinal bleeding, concurrent corticosteroids and/or concomitant use of anticoagulants) should receive one of the following analgesics for pain:<br>o Acetaminophen (not to exceed 4 g per day).<br>o Topical NSAIDs.<br>o Nonselective oral NSAIDs plus gastro-protective agent.<br>o Cyclooxygenase-2 inhibitors.<br>· Intraarticular corticosteroids can be used for short-term pain relief for patients with symptomatic osteoarthritis of the knee. |
| British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)**[52] | Management of acute gout<br>· After an acute gout episode, affected joints should be rested and analgesic and antiinflammatory drug therapy should be commenced immediately and continued for one to two weeks.<br>· Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications.<br>· Physicians should follow standard guidelines for the use of NSAIDs and cyclooxygenase-2 inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations.<br>· Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy.<br>· Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally.<br>· Opiate analgesics can be used as adjunct therapy.<br>· Intraarticular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments.<br><br>Diet, lifestyle modification and non-pharmacological therapy<br>· In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack.<br>· Affected joints should be elevated and exposed in a cool environment.<br>· Moderate physical exercise should be encouraged.<br><br>Management of recurrent, intercritical and chronic gout |

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| | · The plasma urate should be maintained below 300 µmol/L.<br>· Uric acid lowering drug therapy should be started if further attacks occur within one year and should also be offered to patients with tophi, renal insufficiency, and uric acid stones and to patients who need to continue treatment with diuretics.<br>· Uric acid-lowering drug therapy should be delayed until one to two weeks after inflammation has settled.<br>· Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increasing by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma urate <300 µmol/L) or maximum dose (900 mg daily) is reached.<br>· Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulphinpyrazone in patients with normal renal function or benzbromarone in patients with mild to moderate renal insufficiency.<br>· Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to six months. An NSAID or cyclooxygenase-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the duration of therapy should be limited to six weeks.<br>· Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided. |
| The European League Against Rheumatism: **European League Against Rheumatism Evidence Based Recommendations for Gout. Part II: Management. Report of a Task Force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT) (2006)**[53] | · Urate lowering therapy is recommended in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.<br>· The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation. The goal is to achieve and maintain serum uric acids ≤6 mg/dL.<br>· Oral colchicine and/or NSAIDs are first line agents for the systemic treatment of acute gouty attacks. In the absence of contraindications, an NSAID is a convenient and well accepted option.<br>· Low doses of colchicine (0.5 mg three times daily) may be sufficient for some patient with acute gout. Higher doses may lead to side effects such as diarrhea and gastrointestinal discomfort.<br>· Intraarticular aspirations and injection of long acting steroid is an effective and safe treatment for an acute gouty attack.<br>· Allopurinol is an appropriate long-term urate-lowering agent. It is recommended that allopurinol be started at a 100 mg daily dose and increased by 100 mg every two to four weeks if required. The dose must be adjusted in patients with renal impairment. If toxicity occurs, alternatives to allopurinol include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitization, in cases of mild rash only.<br>· Uricosuric agents such as probenecid and sulphinpyrazone (not available in the United States) can be used as an alternative to allopurinol in patients with normal renal function. The agents are contraindicated in patients with urolithiasis.<br>· Prophylaxis against acute attacks during the first months of urate lowering therapy can be achieved by colchicine (0.5 to 1.0 mg daily) and/or an NSAID (with gastro-protection if indicated).<br>· When gout is associated with diuretic therapy, stop the diuretic if possible. |


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| | For the treatment of hypertension and hyperlipidemia consider the use of losartan and fenofibrate, respectively (both have modest uricosuric effects). |
| European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[16] | Painful polyneuropathy<br>· 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.<br>· Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine).<br>· Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain.<br>· Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse.<br>· In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful.<br><br>PHN<br>· Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin.<br>· 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.<br>· Strong opioids and capsaicin cream are recommended as second-line therapies.<br><br>Trigeminal neuralgia<br>· Recommended first-line treatments include carbamazepine and oxcarbazepine.<br>· Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable side effects may be prescribed lamotrigine but should also be considered for a surgical intervention.<br><br>Central pain<br>· Recommended first-line treatments include amitriptyline, gabapentin or pregabalin.<br>· Tramadol may be considered second-line.<br>· Strong opioids are recommended as second- or third-line if chronic treatment is not an issue.<br>· 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. |
| American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful** | Anticonvulsants<br>· If clinically appropriate, pregabalin should be offered for treatment.<br>· Gabapentin and sodium valproate should be considered for treatment.<br>· There is insufficient evidence to support or refute the use of topiramate for treatment.<br>· Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment.<br><br>Antidepressants<br>· Amitriptyline, venlafaxine, and duloxetine should be considered for the |


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| **Diabetic Neuropathy (2011)[17]** | treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another.<br>· Venlafaxine may be added to gabapentin for a better response.<br>· 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.<br><br>Opioids<br>· Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other.<br><br>Other pharmacologic options<br>· Capsaicin and isosorbide dinitrate spray should be considered for treatment.<br>· Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment.<br>· Lidocaine patch may be considered for treatment.<br>· There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment.<br><br>Nonpharmacologic options<br>· Percutaneous electrical nerve stimulation should be considered for treatment.<br>· Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment.<br>· 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)[54]** | Neuropathy<br>· 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.<br>· Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene.<br>· 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.<br>· Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes.<br>· Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy.<br>· When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized.<br>· 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.<br>· Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms.<br>· Maintain a referral network for podiatric and peripheral vascular studies and care. |


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| American Diabetes **Association: Diabetic Neuropathies (2005)**[55] | Algorithm for the management of symptoms diabetic polyneuropathy<br>· 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)**[56] | · Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN.<br>· There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another.<br>· Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine.<br>· 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.<br>· In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN.<br>· Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit.<br>· 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.<br>· 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)**[57] | · Tramadol is recommended for the management of pain in fibromyalgia.<br>· Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia.<br>· Corticosteroids and strong opioids are not recommended.<br>· 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.<br>· Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia. |

## Conclusions

Tramadol (Ultram®) and tapentadol (Nucynta®) are both centrally-acting opioid analgesics that produce analgesia through their binding to μ opioid receptors and weak inhibition of norepinephrine reuptake.[3,4] Tramadol also has an inhibitory effect on serotonin reuptake. Tapentadol is approved by the Food and Drug Administration for the relief of moderate-to-severe acute pain and tramadol is approved for the management of moderate-to-moderately severe pain. Extended-release (ER) formulations are available for both tramadol (ConZip®, Ryzolt® and Ultram ER®) and tapentadol (Nucynta ER®) and are indicated for moderate-to-moderately severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[5-8] In addition, tapentadol ER is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[8] Tramadol is available in an orally disintegrating tablet (Rybix ODT®) and in combination with acetaminophen (Ultracet®).[9,10] The


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tramadol/acetaminophen combination is indicated for the short-term (less than five days) management of acute pain.[10] Tramadol is available generically in immediate-release (IR) and extended-release formulations as well as in combination with acetaminophen. Currently there is no generic available for tapentadol.[12]

Clinical studies have generally demonstrated that tramadol and tapentadol are effective in the management of moderate-to-moderately severe chronic pain and for the relief of moderate-to-severe conditions of acute pain including low back pain, osteoarthritis and diabetic peripheral neuropathy.[18-46] Clinical studies evaluating tapentadol (both IR and ER) have generally demonstrated a significant pain relief compared to placebo with a similar analgesic profile compared to oxycodone (both IR and ER). Furthermore, both formulations of tapentadol may be associated with a more favorable adverse event profile compared to oxycodone.[23,24,26,27,30,35-37] There is a risk of seizures with both tramadol and tapentadol products; however, the risk is believed to be higher with tramadol.[1,3-10] Both tapentadol products are classified as Schedule II controlled substances and the extended-release formulation carries a Black Box Warning regarding the risk of abuse associated with its use.[8] Tramadol and tramadol-containing products are not currently scheduled.

Current guidelines for the treatment of low back pain recommend opioids or tramadol in patients with severe pain that has not responded to treatment with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs).[14] Tramadol may be considered an initial treatment option along with topical capsaicin and topical or oral NSAIDs for osteoarthritis of the hand, knee or hips.[15] Guidelines established by the European Federation of Neurological Societies and the American Academy of Neurology generally recommend tramadol as a second-line therapy for the treatment of polyneuropathies.[16,17] The role of immediate- or extended-release tapentadol are not specifically incorporated into currently available treatment guidelines; however, in most cases no preference is given to one single opioid over another.

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