OPTUMRx

Therapeutic Class Overview
Dopamine Agents

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other non-motor manifestations. Nearly 1 million people in the United States (US) have PD and an estimated 60,000 new cases are diagnosed annually *(Chou 2020, Jankovic 2020, Parkinson's Foundation 2018).*
  - Current treatment options for PD include levodopa, dopamine agonists (DAs) (eg, bromocriptine, pramipexole, ropinirole), monoamine oxidase (MAO)-B inhibitors, anticholinergic agents, amantadine, and catechol-O-methyl transferase (COMT) inhibitors. The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and is the first choice if symptoms, especially bradykinesia, become troublesome; however, levodopa-induced motor fluctuations develop within several years of starting therapy in a substantial number of patients *(Spindler et al 2021).*
  - DAs are commonly used as monotherapy in early PD, or in combination with other therapies in more advanced disease. DAs are ineffective in patients who show no response to levodopa, and while the DAs possibly delay the need to initiate levodopa therapy, their use is associated with adverse effects such as impulse control disorders. While PD symptoms can initially be controlled with DAs, few patients can be adequately maintained on monotherapy for more than a few years *(Spindler et al 2021).*
  - Amantadine is an N-methyl-D-aspartate (NMDA) receptor antagonist used for short-term monotherapy in mild PD. This drug has a low incidence of side effects compared to other therapies for early PD, but the treatment benefit may be transient. In advanced PD, it may be used to manage dyskinesia and motor fluctuations related to levodopa (*Spindler et al 2021*).
- Restless legs syndrome (RLS) is a neurological movement disorder characterized by an urge to move the legs, commonly in response to uncomfortable dysesthesia. Clinically important RLS affects around 2.5% of adults in the US and Northern Europe. There is higher prevalence in women and with increasing age *(Winkelman et al 2016).*
  - RLS is classified as primary or secondary in origin; secondary RLS may be attributed to comorbid iron deficiency, end-stage renal disease (ESRD), or pregnancy.
  - Consequences of RLS include impairment in sleep quantity and quality, mood and anxiety disorders, worsening of quality of life, and loss of work productivity.
  - Current guideline-recommended treatment options for RLS include DAs and gabapentin enacarbil.
- Tardive dyskinesia is an extrapyramidal side effect of long-term therapy with dopamine antagonists, particularly antipsychotics. The annual incidence of tardive dyskinesia is estimated to be 5 to 25% with first-generation antipsychotics; rates of tardive dyskinesia are thought to be lower with second-generation antipsychotics, but tardive dyskinesia has still been reported with these agents (*Deik 2020*).
  - Symptoms of tardive dyskinesia may include chorea, dystonia, akathisia, athetosis, and stereotyped behaviors (*Deik 2020*).
  - When tardive dyskinesia develops, common interventions include discontinuing the offending agent and switching from a first-generation antipsychotic to a second-generation antipsychotic, if applicable. Several agents have been studied for tardive dyskinesia treatment, but most produce only a slight to moderate benefit. Medications that have been studied include clonazepam, botulinum toxin, tetrabenazine, trihexyphenidyl, ginkgo biloba, and amantadine (*Liang et al 2021*).
- Pramipexole, ropinirole, and rotigotine are classified as non-ergot DAs; they have largely replaced ergot DAs (cabergoline, bromocriptine) in clinical use due to better safety and tolerability. Mirapex (pramipexole) tablets, Requip (ropinirole) tablets, and Neupro (rotigotine) transdermal patch are Food and Drug Administration (FDA)-approved for the treatment of PD and RLS. The pramipexole and ropinirole extended-release (ER) products are FDA-approved for PD.

- Rotigotine was originally approved in 2007 but was withdrawn from the US market in 2008 over concerns related to inconsistent absorption from the patch. Drug absorption issues were resolved by the manufacturer and a new formulation of rotigotine patch received FDA approval in 2012 *(Aurora et al 2012, Drugs@FDA 2021).*
- Apokyn (apomorphine) subcutaneous (SC) injection and Kynmobi (apomorphine) sublingual film are additional non-ergot DA approved for acute, intermittent hypomobility associated with PD.
- Horizant (gabapentin enacarbil) is indicated for moderate-to-severe primary RLS and for the management of postherpetic neuralgia in adults. Horizant will not be addressed in this class review but is included in the Neuropathic Pain and Fibromyalgia Therapeutic Class Overview.

- Amantadine is the only available anti-Parkinsonian NMDA antagonist. Amantadine immediate-release tablets, capsules, and oral solutions are FDA approved for PD, drug-induced extrapyramidal reactions, and influenza A prophylaxis and treatment. Gocovri (amantadine extended release [ER] capsule) is FDA approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy, with or without concomitant dopaminergic medications. Osmolex ER (amantadine ER tablet) is FDA approved for PD and drug-induced extrapyramidal reactions.
- Levodopa and levodopa combinations are excluded from this review.
- Medispan class: Antiparkinson Dopaminergics - Nonergoline Dopamine Receptor Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine capsules	✔
amantadine tablets	✔
amantadine oral solution	✔
Apokyn (apomorphine) injection	-
Kynmobi (apomorphine) sublingual film	-
Cycloset (bromocriptine) tablets	-
Gocovri (amantadine) ER capsules	-
Mirapex (pramipexole) tablets	✔
Mirapex ER (pramipexole) extended-release tablets	✔
Neupro (rotigotine) transdermal patch	-
Osmolex ER (amantadine) ER tablets	-
Parlodel (bromocriptine) capsules	✔
Parlodel (bromocriptine) tablets	✔
Requip (ropinirole) tablets	✔
Requip XL (ropinirole) extended-release tablets	✔

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	amantadine	Gocovri (amantadine ER capsule)	Osmolex (amantadine ER tablet)	apomorphine	bromocriptine	Cycloset (bromocriptine tablet)	Kynmobi	pramipexole	pramipexole ER	ropinirole	Ropinirole ER	rotigotine
Acromegaly					✔							
Acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced PD				✔								

Indication	amantadine	Gocovri (amantadine ER capsule)	Osmolex (amantadine ER tablet)	apomorphine	bromocriptine	Cycloset (bromocriptine tablet)	Kynmobi	pramipexole	pramipexole ER	ropinirole	Ropinirole ER	rotigotine
Acute, intermittent treatment of "off" episodes in patients with PD.							✔					
Drug-induced extrapyramidal reactions	✔		✔									
Dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications		✔										
Adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes		✔										
Hyperprolactinemia-associated dysfunctions					✔							
Moderate-to-severe primary RLS								✔		✔		✔
PD	✔		✔		✔			✔	✔	✔	✔	✔
Prophylaxis and treatment of uncomplicated influenza A virus illness	✔											
T2DM, as an adjunct to diet and exercise						✔						

Abbreviations: ER = extended release, PD = Parkinson's disease, RLS = restless leg syndrome, T2DM = type 2 diabetes mellitus

(*Prescribing information: Amantadine 2020, Apokyn 2020, Cycloset 2020, Gocovri 2021, Kynmobi 2020, Mirapex 2020, Mirapex ER 2020, Neupro 2020, Osmolex ER 2018, Parlodel 2019, Requip 2020, Requip XL 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

PD

- The efficacy of DAs for the symptomatic treatment of PD has been confirmed in meta-analyses of randomized controlled trials (RCTs) *(Baker et al 2009, Stowe et al 2008, Zhou et al 2014).*
  - A meta-analysis of 25 RCTs (N = 5185) in patients with early PD found that DAs were effective as monotherapy in PD symptom reduction based on the United Parkinson's Disease Rating Scale (UPDRS). When directly compared to levodopa as the initial therapy choice, DAs provided less symptom improvement than levodopa, but levodopa-treated patients were more likely to experience dyskinesias and wearing-off. Non-ergot DAs, when analyzed separately from ergot DAs, provided similar results. Overall, DA-treated patients experienced increased treatment discontinuation due to non-motor adverse effects *(Baker et al 2009).*
  - A Cochrane Review meta-analysis of 29 RCTs (N = 5247) in patients with early PD found that patients randomized to a DA were less likely to develop dyskinesias or motor fluctuations vs levodopa-treated patients; however, non-motor adverse effects such as edema, constipation, dizziness, hallucinations, and nausea were all increased in DA-treated patients. Additionally, symptomatic control of PD appeared to be better with levodopa, but data were reported inconsistently *(Stowe et al 2008).*
  - A meta-analysis of 9 RCTs (N = 2857) evaluated the efficacy of the long-acting DAs (rotigotine transdermal patch, pramipexole ER, and ropinirole ER) vs placebo in patients with PD. Patients treated with the long-acting DAs achieved greater reduction in symptoms, but with a higher incidence of adverse effects, especially in early PD patients *(Zhou et al 2014).*
- A Cochrane review meta-analysis of 3 RCTs (N = 482) in patients with PD who are receiving levodopa and suffering from motor complications compared bromocriptine and ropinirole as adjuvant therapies. Both agents demonstrated

similar outcomes for off-time reduction, dyskinesia as adverse event, motor impairment and disability, and dose reductions in levodopa (*Clarke et al 2001*).

- A Cochrane review including only 1 RCT (N = 163) concluded that the single trial lacked the necessary power to examine the comparative effectiveness between pramipexole and bromocriptine as adjuvant therapies in patients with PD who were receiving levodopa and suffering from motor complications. Compared with placebo, both agents improved off-time and reduced motor impairments and disability (*Clarke et al 2000*).
- In an evidence-based comparison of large, double-blind, RCTs of cabergoline, pramipexole, and ropinirole used as monotherapy in early PD, all agents were found similarly effective in reducing the risk of dyskinesia relative to levodopa. The risk reduction was slightly more evident for ropinirole and pramipexole. The mean change from baseline UPDRS score was comparable for pramipexole and ropinirole but was not evaluated for cabergoline. The proportion of withdrawals and AE profiles of the 3 agents were similar to each other, with the exception of edema, which was less in ropinirole-treated patients *(Inzelberg et al 2003)*.
- Transdermal rotigotine was compared to both pramipexole *(Poewe et al 2007)* and ropinirole *(Mizuno et al 2014)* in double-blind, RCTs in advanced stage PD. In the respective trials, rotigotine demonstrated noninferiority to pramipexole in the primary endpoint of change in absolute “off” time and noninferiority to ropinirole in the primary endpoint of change in UPDRS Part III (“on” state) from baseline. In both trials, rotigotine had a similar AE profile to the oral DAs, with the exception of higher rates of application site reactions.
- Several placebo-controlled RCTs have demonstrated the effectiveness of intermittent SC apomorphine for the treatment of “off” episodes in patients with advanced PD in whom conventional antiparkinson therapy had been optimized. Patients treated with apomorphine experienced improved mobility as measured by the UPDRS motor score 20 minutes after dosing. Patients previously unexposed to apomorphine were administered trimethobenzamide per labeled instructions to control nausea. Commonly reported adverse effects with apomorphine included yawning, nausea, dizziness, somnolence, and dyskinesias; most were considered mild to moderate in severity *(Apokyn prescribing information 2020, Dewey et al 2001, Pahwa et al 2007, Pfeiffer et al 2007).*
- A network meta-analysis of 21 studies evaluated the efficacy of ropinirole, rasagiline, rotigotine, entacapone, bromocriptine, apomorphine, pramipexole, sumanirole (not available in the US), and levodopa for PD treatment. In this study, apomorphine was found to be the most effective treatment for PD based on UPDRS III; it also had the highest efficacy for non-motor symptoms of PD (*Li et al 2018*).
- The efficacy of amantadine for treating dyskinesia in PD has been established in a meta-analysis of 11 RCTs (N = 356). Amantadine significantly improved UPDRS III, UPDRS IV, and Dyskinesia Rating Scale (DRS) scores compared to placebo (*Kong et al 2017*).
- The EASED and EASE LID studies support the efficacy of amantadine ER capsules (Gocovri) for the treatment of levodopa-induced dyskinesias in PD *(Pahwa et al 2017, Pahwa et al 2015)*. In the EASED study, amantadine ER capsules were superior to placebo in reduction of dyskinesia and increasing “on” time without troublesome dyskinesia (*Pahwa et al 2015)*. The EASE LID study found that amantadine ER capsules were superior to placebo for reducing Unified Dyskinesia Rating Scale (UDRS) scores and decreasing “off” time (*Pahwa et al 2017*).
- A pooled analysis of 2 identically designed Phase 3 studies (EASE LID and EASE LID 3) of amantadine ER capsules for dyskinesia in PD patients that were stable on 3 times a day levodopa therapy for at least 30 days (N=196) evaluated the change from baseline to 12 weeks in each patients UDRS scores. At 12 weeks the LS mean difference was -17.7 in the amantadine ER group (LS mean change in “off” time of 41.4%) vs -7.6 (LS mean change in “off” time of 13.9%) in the placebo group; demonstrating a percentage treatment difference of 27.3% (p < 0.0001) (*Elmer et al 2018).*
- A randomized, double-blind, placebo-controlled study evaluated apomorphine sublingual film (Kynmobi) in 109 patients with PD experiencing ≥ 2hours of “off” time per day, with predictable morning off periods, responsive to levodopa and on stable doses of PD medications. The primary endpoint was the in-clinic change from pre-dose to 30 min post-dose in the UPDRS motor score at 12 weeks. The change from pre-dose to 30 min post-dose in UPDRS motor score at week 12 was -11·1 (least mean square [SE], 1·46; 95% confidence interval [CI], -14·0 to -8·2) with apomorphine sublingual film and -3·5 (SE, 1·29; 95% CI, -6·1 to -0·9) with placebo (difference, -7·6; SE, 1·96; 95% CI, -11·5 to -3·7; p=0·0002). The most common side effects were oropharyngeal events (*Olanow et al 2020*).

RLS

- The efficacy of DAs for the treatment of RLS symptoms has been confirmed in meta-analyses and systematic reviews of RCTs *(Quilici et al 2008, Scholz et al 2011, Zintzaras et al 2010).*

- In a Cochrane Review of 38 RCTs (N = 7365) enrolling patients with moderate-to-severe RLS, the non-ergot DAs (lisuride [not currently approved in the US], pramipexole, rotigotine, and ropinirole) demonstrated superior efficacy vs placebo in improvement of the International RLS Severity Rating Scale (IRLS), decrease in periodic limb movements in sleep, and improved sleep efficiency. Compared to placebo, patients taking DAs experienced more adverse effects and were more likely to discontinue treatment *(Scholz et al 2011)*.
- A meta-analysis of 18 RCTs (N = 2848) in patients with RLS showed significant improvement in the IRLS with DAs (pramipexole, ropinirole, rotigotine, and cabergoline) vs placebo. The difference in IRLS score was statistically significantly better with pramipexole vs ropinirole; the difference between pramipexole and rotigotine was nonsignificant *(Zintzaras et al 2010)*.
- In a meta-analysis of 14 placebo controlled RCTs of pramipexole or ropinirole for RLS, superior efficacy was confirmed for both treatments' vs placebo based on improvement in the IRLS. An indirect comparison showed, with a probability of ≥ 95%, a superior reduction in the mean IRLS score and significantly lower rate of nausea, vomiting, and dizziness with pramipexole vs ropinirole. Head-to-head trials are needed to confirm these results *(Quilici et al 2008)*.

- A network meta-analysis of 35 studies examined the efficacy of DAs (pramipexole, ropinirole, and rotigotine), gabapentin enacarbil, and pregabalin in the treatment of RLS. All treatments were superior to placebo, but no difference in IRLS score reduction was seen between active treatments. Gabapentin enacarbil and rotigotine had the highest Clinical Global Impressions-Improvement (CGI-I) response rates among the studied treatments (*Iftikhar et al 2017*).

Drug-induced extrapyramidal reactions

- A Cochrane meta-analysis concluded that more studies are needed before amantadine, bromocriptine, or other therapies can be recommended for the treatment of antipsychotic-induced tardive dyskinesia (*El-Sayeh et al 2018*).
- One small crossover RCT (n=22) found that amantadine reduced Abnormal Involuntary Movements Scale (AIMS) scores in patients with drug-induced tardive dyskinesia, while placebo did not (*Pappa et al 2010)*.

CLINICAL GUIDELINES

PD

- The American Academy of Neurology (AAN) practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* recommends that in patients who require the initiation of dopaminergic treatment, levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs).
  - Treatment of PD patients with cabergoline, ropinirole, and pramipexole results in fewer motor complications (wearing off, dyskinesias, "on/off" motor fluctuations) than levodopa, but is also associated with more frequent adverse events, including hallucinations, somnolence, and edema.
  - Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile.

- **European Federation of Neurological Societies (EFNS) and Movement Disorders Society (MDS) - European Section (ES)** *(Oertel et al 2011a)*
  - This joint guideline outlines recommendations for treatment of late (complicated) PD, including treatment of motor complications and the nonmotor symptoms of PD. A summary of the treatment of motor complications is provided.
  - *Motor fluctuations: Wearing-"off" (end of dose akinesia, predictable "on"-"off")*
    - In the early phase, when motor fluctuations are just becoming apparent, adjustments in frequency of levodopa dosing during the day (4 to 6 daily doses) may attenuate wearing-"off".
    - COMT inhibitors or MAO-B inhibitors may be added: No recommendations can be made on which treatment should be chosen first. On average, all reduce "off" time by about 1 to 1.5 hours per day.
      - No difference has been demonstrated between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic, and is only recommended in patients who have failed all other available medications.
      - Rasagiline should not be added to selegiline due to cardiovascular (CV) safety issues.
    - DAs may be added: efficacious in reducing "off" time in patients experiencing wearing-"off". Currently, no DA has proven better than another; switching from 1 DA to another can be helpful in some patients.
      - First line: Non-ergot DAs.
      - Second Line: Ergot DAs (association with lung, retroperitoneal, and heart valve fibrosis).
    - Standard levodopa can be switched to a CR formulation:
      - CR formulation of levodopa can improve wearing-"off".

- CR formulation of levodopa is useful for the treatment of night-time akinesia (nocturnal end-of-dose akinesia).
- Amantadine or an anticholinergic may be added: In patients with disabling recurrent "off" symptoms that fail to improve further with the aforementioned strategies, the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms in some cases.

- **The 2019 International Parkinson and Movement Disorder Society released an evidence-based review on treating the nonmotor symptoms of PD** (*Seppi et al 2019*). Pramipexole is clinically useful for treating depressive symptoms in PD, and rotigotine is possibly useful for treating sleep and wakefulness disorders in PD.

- **The 2018 International Parkinson and Movement Disorder Society released an evidence-based review on treating the motor symptoms of PD** (*Fox et al 2018*). Pramipexole, ropinirole, and rotigotine are DAs rated as clinically useful in patients requiring symptomatic therapy in early PD or requiring adjunct therapy to levodopa in early or stable PD. Bromocriptine and amantadine are listed as possibly useful in patients with early or stable PD requiring adjunct therapy to levodopa. Ropinirole ER is possibly useful in patients with early PD requiring symptomatic therapy. In patients with treated PD on optimized oral levodopa, pramipexole, ropinirole, rotigotine, apomorphine are clinically useful and bromocriptine and apomorphine are possibly useful for treating motor fluctuations. Amantadine is clinically useful for treating dyskinesia in patients with PD on optimized oral levodopa.

RLS

- In 2017, the International Parkinson and Movement Disorder Society updated the evidence-based review of treatment of RLS (*Winkelmann et al 2018*). The review considers ropinirole, rotigotine, pramipexole, and cabergoline to be efficacious for treating idiopathic RLS.
- In moderate-to-severe primary RLS, the AAN treatment guideline *(Winkelman et al 2016)* recommends clinicians consider prescribing medication to reduce RLS symptoms. Strong evidence supports pramipexole, rotigotine, cabergoline (rarely used due to cardiac valvulopathy risk), and gabapentin enacarbil use; moderate evidence supports ropinirole, pregabalin, and intravenous ferric carboxymaltose use. Few head-to-head comparisons exist to suggest agents preferentially.
- The American Academy of Sleep Medicine RLS practice parameter *(Aurora et al 2012)* recommends treatment of RLS with pramipexole or ropinirole, as the benefits clearly outweigh the harms. Gabapentin enacarbil or rotigotine can be utilized, but there is uncertainty in the balance between benefits and harms. Given the potential of side effects, including heart valve damage, cabergoline should only be used if other recommended agents have been tried first and failed. Other treatment options with low levels of evidence and unclear benefit/harm balance include gabapentin, pregabalin, carbamazepine, clonidine, and supplemental iron.

Drug-induced extrapyramidal reactions

- The AAN practice guideline on the treatment of tardive syndromes (*Bhidayasiri 2013*) recommends that amantadine may be considered for use with neuroleptics to treat tardive syndromes in the short term; however, the level of evidence for this recommendation is low. Other treatments that may be considered for treatment of tardive syndromes include tetrabenazine, clonazepam, and ginkgo biloba. Data are insufficient to support or refute the use of bromocriptine for the treatment of tardive syndromes.

SAFETY SUMMARY

Contraindications

- Concomitant use of apomorphine with 5HT3 antagonists, including antiemetics (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron).
- Hypersensitivity to sodium metabisulfite (in Kynmobi).
- Extended-release amantadine products (Gocovri and Osmolex ER) are contraindicated in patients with ESRD.
- Bromocriptine formulations (including Parlodel) are contraindicated in patients with uncontrolled hypertension.
- The bromocriptine brand formulation, Cycloset, is additionally contraindicated in patients with syncopal migraine, postpartum patients, and lactating patients.

Warnings and precautions

- All the non-ergot DAs have warnings for sudden onset of sleep and somnolence; syncope; hypotension, including orthostatic hypotension; hallucinations and psychotic-like behaviors; dyskinesia; and impulse control or compulsive behaviors.
- The rotigotine patch and apomorphine injection contain sodium metabisulfite that may cause allergic-type reactions in those with sulfite sensitivity.
- Application site reactions can occur with the rotigotine patch and may be severe.
- Apomorphine may cause coronary events, prolong QTc and cause torsades de pointes and sudden death. The injection is for SC use only; thrombus formation and pulmonary embolism have been observed following intravenous administration.
- Apomorphine sublingual film may cause nausea and vomiting, oral mucosal irritation, increase risk of falls, withdrawal emergent hyperpyrexia, or confusion.
- Based on animal data, the DAs may cause fetal harm and should only be used in pregnancy if the benefit justifies the potential risk to the fetus.
- Amantadine products have warnings for suicidal ideation; hallucinations and psychotic behavior; possible increased seizure activity in patients with a history of epilepsy; sudden onset of sleep and somnolence; withdrawal-emergent hyperpyrexia and confusion; and impulse control or compulsive behaviors.
- Extended-release amantadine products have additional warnings for dizziness and orthostatic hypotension. Concomitant use of alcohol is not recommended.
- Bromocriptine products have warnings for somnolence and sudden sleep onset; symptomatic hypotension, including orthostatic hypotension; impulse control or compulsive behaviors; and hallucinations and psychotic-like behaviors.
- When bromocriptine mesylate is being used to treat PD in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine mesylate is considered to be medically contraindicated.
- Bromocriptine should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the postpartum period, the patient should be observed with caution.
- Safety during long-term use of bromocriptine for more than 2 years at the doses required for PD has not been established.

Key adverse fffects

- All the non-ergot DAs may cause nausea, vomiting, drowsiness/somnolence, dizziness/hypotension, hallucinations, dyskinesia, and peripheral edema.
  - Apomorphine causes severe nausea and vomiting when administered at recommended doses; treatment with the concomitant antiemetic trimethobenzamide is recommended.
  - Apomorphine sublingual film may cause oral/pharyngeal soft tissue swelling or pain, and paresthesia.
  - Patients have reported postural deformities, including antecollis, camptocormia (Bent Spine Syndrome), and pleurothotonus (Pisa syndrome), after starting or increasing the dose of pramipexole. Postural deformity may occur several months after starting treatment or increasing the dose. Reducing the dose or discontinuation has been reported to improve postural deformity in some patients and should be considered if postural deformity occurs.
- Rotigotine may cause application site reactions and disturbances in initiating and maintaining sleep.
- Augmentation is an adverse effect related to long-term treatment of RLS with a dopaminergic medication and consists of iatrogenic worsening of RLS symptoms.
- Adverse reactions associated with amantadine include nausea, dizziness, insomnia, hallucination, depression, anxiety, dry mouth, peripheral edema, constipation, ataxia/falls, and orthostatic hypotension.
- Adverse reactions associated with bromocriptine use in PD include nausea, dyskinesia, hallucinations, confusion, “on-off” phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, vertigo, dry mouth, peripheral edema, urinary frequency, incontinence, and retention, anxiety, blepharospasm, and dysphagia.

DOSING AND ADMINISTRATION

- Gradual dose titration during initiation and withdrawal of therapy is required with DAs. Titration schedules vary among products and indications.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Tablet, capsule, oral solution	Oral	PD and influenza A prophylaxis and treatment: Once or twice daily Drug-induced extrapyramidal reactions: Twice daily	Dose adjustment required for renal impairment (CrCl <50 mL/min) and patients 65 years of age or older. Dose may need to be reduced for patients with heart failure, peripheral edema, or orthostatic hypotension. Use for influenza treatment/prophylaxis is not recommended due to high resistance rates (*CDC 2020*)
Apokyn (apomorphine)	Injection	SC	As needed	The first dose of apomorphine should be given under medical supervision; doses should be titrated to effect and tolerance and separated by at least 2 hours. Treatment with a concomitant antiemetic (eg, trimethobenzamide) is recommended, starting 3 days prior to the first dose of apomorphine. Treatment with trimethobenzamide should only be continued if necessary to control nausea and vomiting, and generally no longer than 2 months. The starting apomorphine dose should be reduced in patients with mild or moderate renal impairment; studies in patients with severe renal impairment have not been conducted.
Cycloset (bromocriptine)	Tablet	Oral	T2DM: Once daily within 2 hours after waking in the morning	Cycloset should be taken with food. The initial dose can be increased weekly by 1 tablet until maximal tolerated daily dose is achieved. Dose adjustments required during concomitant use of moderate CYP3A4 inhibitors. Avoid concomitant use with strong CYP3A4 inhibitors.
Gocovri (amantadine)	ER capsule	Oral	1 capsule once daily at bedtime for 1 week, then increase to 2 capsules daily at bedtime.	Do not crush or chew; capsules may be opened and sprinkled onto a teaspoonful of soft food (ie, applesauce). Avoid concomitant alcohol use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Dose adjustment required for patients with moderate to severe renal impairment; contraindicated in patients with ESRD. Not interchangeable with other amantadine products
Kynmobi (apomorphine)	Sublingual film	Oral	As needed	10 to 30 mg per dose, separated by at least 2 hours. Treatment with a concomitant antiemetic (eg, trimethobenzamide) is recommended, beginning 3 days prior to initial dose.
Mirapex (pramipexole)	Tablet	Oral	PD: 3 times daily RLS: Once daily 2 to 3 hours before bedtime	Dosage reduction required in PD patients with renal impairment. In RLS patients with moderate and severe renal impairment, the duration between titration steps should be increased to 14 days.
Mirapex ER (pramipexole)	ER tablet	Oral	PD: Once daily	In patients with moderate renal impairment, pramipexole ER tablets should initially be taken every other day; pramipexole ER has not been studied in patients with severe renal impairment or patients on hemodialysis. Tablets must be swallowed whole and must not be chewed, crushed, or divided. Patients may be switched overnight from pramipexole IR tablets to ER tablets at the same daily dose.
Neupro (rotigotine)	Patch	TD	PD, RLS: Once daily	The patch should be applied once daily to a new site on the skin; the same site should not be used more than once every 14 days. Multiple patches may be used to achieve the prescribed dose.
Osmolex ER (amantadine)	ER tablet	Oral	PD, drug-induced extrapyramidal reactions: Once daily in the morning	Dose may be titrated in weekly intervals. When discontinuing the drug, reduce dose gradually for 1 to 2 weeks before discontinuation. Do not crush, chew, or divide tablets. Frequency of administration requires adjustment in patients with moderate to severe renal impairment; contraindicated in ESRD.
Parlodel (bromocriptine)	Tablets, capsules	Oral	Hyperprolactinemia-Associated Dysfunctions: Once daily Acromegaly: Once daily at bedtime	It is recommended that bromocriptine be taken with food. Patients should be evaluated frequently during dose escalation to determine the lowest dosage that produces a therapeutic response.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			PD: Twice daily	When being treated for acromegaly, patients should be reevaluated monthly and dosage adjusted based on reductions of growth hormone or clinical response.
Requip (ropinirole)	Tablet	Oral	PD: 3 times daily RLS: Once daily, 1 to 3 hours before bedtime	No dose adjustment is necessary in patients with moderate renal impairment; dosage adjustment required in patients with ESRD.
Requip XL (ropinirole)	ER tablet	Oral	PD: Once daily	In patients with ESRD on hemodialysis, dosage reduction is recommended. No dose adjustment necessary in patients with moderate renal impairment. Tablets must be swallowed whole and not be chewed, crushed, or divided. Patients may be switched directly from ropinirole IR to ropinirole ER with the initial switching dose approximately matching the total daily dose of ropinirole IR.

Abbreviations: CrCl = creatinine clearance; CYP3A4 = Cytochrome P450 3A4; ER = extended-release; ESRD = end-stage renal disease; IR = immediate release; PD = Parkinson's disease; RLS = Restless Legs Syndrome; SC = subcutaneous; TD = transdermal
See the current prescribing information for full details

CONCLUSION

- PD is a neurodegenerative disorder caused by progressive dopamine depletion in the brain and characterized by tremor, bradykinesia, and rigidity. Non-motor and neuropsychiatric symptoms also commonly occur. Current treatment options include levodopa, DAs, MAO-B inhibitors, anticholinergic agents, amantadine, and COMT inhibitors. DAs are commonly used as monotherapy in early PD, or in combination with other therapies in more advanced disease. While PD symptoms can initially be controlled with DAs, few patients can be adequately maintained on monotherapy for more than a few years before levodopa is needed. Amantadine is an NMDA receptor antagonist used for short-term monotherapy in mild PD. In advanced PD, it may be used to manage dyskinesia and motor fluctuations related to levodopa *(Chou 2020, Jankovic 2020, Spindler 2021).*
- RLS is a neurological movement disorder characterized by an urge to move the legs, commonly in response to uncomfortable dysesthesia. Consequences of RLS include impairment in sleep quantity and quality, mood and anxiety disorders, worsening of quality of life, and loss of work productivity. *(Winkelman et al 2016).*
- Tardive dyskinesia is an extrapyramidal side effect of long-term therapy with dopamine antagonists, particularly antipsychotics. Symptoms of tardive dyskinesia include chorea, dystonia, akathisia, athetosis, and stereotyped behaviors (*Deik 2020*). A number of agents have been studied for tardive dyskinesia treatment, but most produce only a slight to moderate benefit (*Liang 2021*). Treatments that may be considered according to current guidelines include clonazepam, tetrabenazine, amantadine, and gingko biloba (*Bhidayasiri 2013*).
- The non-ergot DAs Mirapex (pramipexole) tablets, Requip (ropinirole) tablets, and Neupro (rotigotine) transdermal patch are FDA-approved for the treatment of PD and RLS. The pramipexole and ropinirole ER products are FDA-approved for PD. Apokyn (apomorphine) is available as a SC injection for acute, intermittent hypomobility associated with advanced PD. Ergot DAs bromocriptine capsules and tablets (including brand name Parlodel) are FDA-approved for the treatment of PD, but are generally less preferred than non-ergot DAs due to adverse event profiles.
- Amantadine immediate-release tablets, capsules, and oral solutions are FDA approved for PD, drug-induced extrapyramidal reactions, and influenza A prophylaxis and treatment. Gocovri (amantadine ER capsule) is FDA approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy, with or without concomitant

dopaminergic medications. Osmolex ER (amantadine ER tablet) is FDA approved for PD and drug-induced extrapyramidal reactions.

- The efficacy of DAs for the symptomatic treatment of PD has been confirmed in meta-analyses of RCTs. The DAs improved UPDRS motor scores vs placebo, but with increased incidence of adverse effects *(Baker et al 2009, Stowe et al 2008, Zhou et al 2014).*
- The efficacy of amantadine for treating dyskinesia in PD has been established in a meta-analysis of 11 RCTs (N = 356). Amantadine significantly improved UPDRS III, UPDRS IV, and Dyskinesia Rating Scale (DRS) scores compared to placebo (*Kong et al 2017*). The EASED and EASE LID studies support the efficacy of amantadine ER capsules (Gocovri) for the treatment of levodopa-induced dyskinesias in PD, showing reduction of dyskinesia and decreased "off" time vs placebo (*Pahwa et al 2017, Pahwa et al 2015)*.
- The efficacy of DAs for the treatment of moderate-to-severe RLS has been demonstrated in meta-analyses and systematic reviews of RCTs. DA-treated patients showed improvement in IRLS scores vs placebo *(Quilici et al 2008, Scholz et al 2011, Zintzaras et al 2010).*
  - Two meta-analyses suggest better efficacy with pramipexole vs ropinirole in RLS, although head-to-head trials are lacking *(Quilici et al 2008, Zintzaras et al 2010).*
- A Cochrane meta-analysis concluded that more studies are needed before amantadine or other therapies can be recommended for the treatment of antipsychotic-induced tardive dyskinesia (*El-Sayeh et al 2018*). One small crossover RCT (n=22) found that amantadine reduced Abnormal Involuntary Movements Scale (AIMS) scores in patients with drug-induced tardive dyskinesia, while placebo did not (*Pappa et al 2010)*.
- The AAN practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* suggests that levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs). Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile. The guidelines focused on PD from the International Parkinson and Movement Disorder Society (*Fox et al 2018, Seppi et al 2019)* consider pramipexole, ropinirole immediate-release, and rotigotine as clinically useful DAs in patients requiring symptomatic therapy in early PD or requiring adjunct therapy to levodopa in early or stable PD. Bromocriptine and amantadine are listed as possibly useful in patients with early or stable PD requiring adjunct therapy to levodopa. Ropinirole extended release is possibly useful in patients with early PD requiring symptomatic therapy. In patients with treated PD on optimized oral levodopa, pramipexole, ropinirole, rotigotine, apomorphine are clinically useful and bromocriptine and apomorphine are possibly useful for treating motor fluctuations. Amantadine is clinically useful for treating dyskinesia in patients with PD on optimized oral levodopa. Pramipexole is clinically useful for treating depressive symptoms in PD, and rotigotine is possible useful for treating sleep and wakefulness disorders in PD.
- Current RLS guidelines suggest that the DAs, specifically ropinirole, rotigotine, and pramipexole, be used for the treatment of primary moderate-to-severe RLS. Few head-to-head comparisons exist to suggest agents preferentially *(Aurora et al 2012, Winkelman et al 2016, Winkelmann et al 2018)*.
- The AAN practice guideline on the treatment of tardive syndromes (*Bhidayasiri 2013*) states that amantadine may be considered for use with neuroleptics to treat tardive syndromes in the short term.
- All of the DAs have warnings for sudden onset of sleep and somnolence; syncope; hypotension, including orthostatic hypotension; hallucinations and psychotic-like behaviors; dyskinesia; and impulse control or compulsive behaviors. The rotigotine patch may cause application site reactions.
- Amantadine products have warnings for suicidal ideation; hallucinations and psychotic behavior; sudden onset of sleep and somnolence; withdrawal-emergent hyperpyrexia and confusion; and impulse control or compulsive behaviors. Extended-release amantadine products have additional warnings for dizziness and orthostatic hypotension.
- Common adverse effects of the DAs include nausea, vomiting, drowsiness/somnolence, dizziness/hypotension, hallucinations, dyskinesia, and peripheral edema. Apomorphine causes severe nausea and vomiting when administered at recommended doses; concomitant treatment with the antiemetic trimethobenzamide is recommended.
- Additional adverse reactions associated with bromocriptine use in PD include confusion, "on-off" phenomenon, faintness/fainting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, shortness of breath, constipation, vertigo, dry mouth, urinary frequency, incontinence, and retention, anxiety, blepharospasm, and dysphagia.
  - Bromocriptine should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the postpartum period, the patient should be observed with caution.

- Safety during long-term use of bromocriptine for more than 2 years at the doses required for PD has not been established.

- Adverse reactions associated with amantadine include nausea, dizziness, insomnia, hallucination, depression, anxiety, dry mouth, peripheral edema, constipation, ataxia/falls, and orthostatic hypotension.

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