Antiparkinson's Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Therapeutic Class	Drug	Manufacturer	Parkinson's Disease	Drug-induced EPS	RLS
Anticholinergics	benztropine[1]	generic	X	X (except TD)	
	trihexyphenidyl[2]	generic	X	X	
Dopa decarboxylase Inhibitor	carbidopa (Lodosyn®)[3]	generic, Valeant/Bausch	X (only as adjunct to levodopa/carbidopa)		
Dopamine precursor	levodopa* (Inbrija®)[4]	Acorda	X (only as an adjunct levodopa/carbidopa)		
Dopamine precursor/dopa decarboxylase inhibitor	levodopa/carbidopa* (Dhivy™) [5]	Riverside	X		
	levodopa/carbidopa (Sinemet®)[6]	generic, Organon	X		
	levodopa/carbidopa sustained-release[7]	generic	X		
	levodopa/carbidopa ER* (Rytary®)[8]	Amneal	X		
	levodopa/carbidopa-oral disintegrating tablet (ODT)[9]	generic	X		
	levodopa/carbidopa enteral suspension* (Duopa™)[10]	Abbvie	X (advanced PD)		
MAO-B inhibitors	rasagiline (Azilect®)[11]	generic, Teva Neuroscience	X		
	safinamide (Xadago®)[12]	US Worldmeds/Supernus	X (only as adjunct to levodopa/carbidopa)		
	selegiline[13]	generic	X (only as adjunct to levodopa/carbidopa)		
	selegiline, oral disintegrating (ODT)* (Zelapar®)[14]	Valeant/Bausch	X (only as adjunct to levodopa/carbidopa)		
Dopamine agonists	apomorphine (Kynmobi™)[15]	Sunovion	X§		
	bromocriptine (Parlodel®)[16]	generic, Validus	X (only as adjunct to levodopa/carbidopa)		
	pramipexole (Mirapex®)[17]	generic, Boehringer Ingelheim	X		X
	pramipexole ER (Mirapex® ER)[18]	generic, Boehringer Ingelheim	X		
	ropinirole[19]	generic	X		X
	ropinirole ER[20]	generic	X		
	rotigotine (Neupro®)[21]	UCB	X		X

ER = extended-release; EPS = extrapyramidal symptoms; RLS = restless legs syndrome; TD = tardive dyskinesia

FDA-Approved Indications (continued)

Therapeutic Class	Drug	Manufacturer	Parkinson's Disease	Drug-induced EPS	RLS
COMT inhibitors	entacapone (Comtan®)[22]	generic, Novartis/Almatica	X (only as adjunct to levodopa/carbidopa)		
	opicapone (Ongentys®)[23]	Neurocrine Biosciences	X (only as adjunct to levodopa/carbidopa)		
	tolcapone (Tasmar®)[24]	generic, Valeant/Bausch	X (only as adjunct to levodopa/carbidopa)		
Dopamine precursor/dopa decarboxylase inhibitor/ COMT inhibitor	levodopa/carbidopa/ entacapone* (Stalevo®)[25]	generic, Novartis/Almatica	X		
Gabapentinoid	gabapentin enacarbil*,† (Horizant®)[26]	Arbor			X
N-Methyl-D-aspartate (NMDA) receptor type	amantadine‡[27]	generic	X	X	
	amantadine ER* (Gocovri®)[28]	Adamas	X‖		
	amantadine ER* (Osmolex® ER)[29]	Vertical/Adamas	X	X	
Adenosine receptor antagonist	istradefylline (Nourianz®)[30]	Kyowa Kirin	X (only as adjunct to levodopa/carbidopa)		

ER = extended-release; EPS = extrapyramidal symptoms; RLS = restless legs syndrome; TD = tardive dyskinesia

Rivastigmine (Exelon) will not be reviewed here due to a concurrent indication for Alzheimer's disease.

* Approved under the FDA's 505(b)(2) pathway, which allows for at least some of the information submitted for approval to be from studies not conducted by or for the applicant.

† Gabapentin enacarbil is also FDA-approved for postherpetic neuralgia (PHN). The PHN indication will not be included in this review.

‡ Amantadine is also approved for the treatment and prophylaxis of seasonal influenza A virus infection, which will not be included in this review.

§ For the acute, intermittent treatment of "off" episodes

‖ As an adjunct to levodopa, for the treatment of dyskinesia, with or without concurrent dopaminergic medications; as adjunctive treatment to levodopa/carbidopa in patients experiencing "off" episodes

OVERVIEW

Parkinsonism

Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity.[31] This disease affects approximately 1% of individuals older than 60 years and the incidence increases significantly with age.[32,33] The term "parkinsonism" describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait disturbances.[34] Secondary

parkinsonism, which has a different etiology and pathology than PD, is the predominant clinical manifestation of a number of disorders, including brain tumors near the basal ganglia, cerebral atherosclerosis, head trauma, and progressive supranuclear palsy.[35] Secondary parkinsonism can also be caused by toxins and drugs, especially antipsychotic agents.

Parkinson's disease and secondary parkinsonism are characterized by striatal dopamine deficiency. In PD, the degeneration of dopamine-containing neurons in the substantia nigra leads to the formation of Lewy bodies (intracellular neuronal inclusion bodies). While Lewy bodies are not present in secondary parkinsonism, the nigral striatal pathway may be impaired and nigral cell loss or loss of striatal cellular elements may occur.[36]

Despite advances in treatments over the years, there is no cure for PD. Symptomatic therapy can provide benefit for quite some time, but the continued, however slow, progression of PD eventually results in significant disability. Patients may not require treatment in the early stages of PD if symptoms do not cause functional impairment.[37] As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments.[38] It is generally recommended that medication regimens be kept as simple as possible since the risk of adverse effects is generally lower when fewer agents are used at higher doses than when multiple drugs are used at lower doses.[39,40]

Anticholinergics were the first medications indicated for the treatment of PD. Anticholinergics, such as benztropine and trihexyphenidyl, improve motor symptoms in some patients with PD, especially younger patients with resting tremor as a predominant symptom. Today, they are used primarily as adjuncts to levodopa treatment and as treatments for tremor symptoms. These drugs often cause side effects in the elderly and are contraindicated in patients with glaucoma, benign prostatic hypertrophy, and dementia.[41,42,43]

A major breakthrough in the treatment of PD was the replacement of dopamine in the brain by using levodopa (exogenous dopamine does not cross the blood-brain barrier). Combination of levodopa with carbidopa, a peripheral dopa decarboxylase inhibitor that does not cross the blood-brain barrier, led to an increase in the amount of levodopa available to the brain for conversion to dopamine and a reduction in the incidence of nausea and vomiting.[44] Although levodopa provides benefit to nearly all PD patients, long-term treatment with levodopa is complicated by the development of motor fluctuations, dyskinesias, and neuropsychiatric complications.[45,46,47,48] Patients may experience a "wearing-off" effect characterized by a shorter duration of benefit from each levodopa dose, causing parkinsonian symptoms to re-emerge. Patients can also experience an "on-off" effect characterized by unpredictable, abrupt fluctuations in motor state from when the medication is effective and symptoms are controlled ("on") to when parkinsonian symptoms worsen ("off"). Inhaled levodopa is designed to bypass the gastrointestinal (GI) tract and quickly address the wearing-off effect observed in patients already treated with carbidopa/levodopa and may be administered on an as needed basis.[49] Additionally, as PD progresses, patients develop symptoms that do not respond well to levodopa therapy, including freezing episodes, autonomic dysfunction, falling, and dementia.

Monoamine oxidase B (MAO-B) is an enzyme predominantly located in the brain that breaks down several chemicals, but primarily dopamine. Since MAO-B is abundant in the striatum and involved in dopamine metabolism, the theory is that MAO-B inhibition will increase the quantity of dopamine available and result in the reduction of some of the motor symptoms seen with PD.[50] Rasagiline (generic, Azilect) and selegiline (generic, Zelapar), highly selective inhibitors of MAO-B, have been shown to cause a slight improvement in motor performance upon initiation of therapy and to delay the development of

disability that requires the addition of levodopa. Rasagiline is 3 times more potent than selegiline. Although their effectiveness as neuroprotective agents has yet to be demonstrated by clinical trials, the MAO-B inhibitors are effective as adjuncts to allow lower doses of levodopa while lengthening dosage intervals. Rasagiline, safinamide (Xadago), and selegiline are all approved for use as adjunct to levodopa in later stage disease because they can increase the percent of "on" time in patients with advanced PD. Rasagiline is also approved for use as monotherapy in early PD, as well as an adjunct to other PD agents.

Dopamine agonists are used in early PD. These agents have a levodopa-sparing effect and can reduce the frequency of "off" time. While monotherapy with dopamine agonists has been shown to reduce the subsequent dyskinesias and other motor complications in comparison to levodopa, monotherapy has the potential to cause orthostatic hypotension and neuropsychiatric adverse effects, such as confusion and hallucinations.[51] Because of this, these agents should be avoided in patients with confusion or memory or cognitive impairment, as well as in those at risk of hypotension.[52,53] An injectable formulation of apomorphine (Apokyn®), a non-ergot dopamine agonist, has been approved for the treatment of hypomobility in advanced PD; as an injectable product, it will not be discussed in this review.[54]

The addition of catechol-O-methyltransferase (COMT) inhibitors reduces the end-of-dose failure ("wearing off") of levodopa therapy that causes motor complications. By reducing the peripheral metabolism of levodopa, COMT inhibitors allow for the use of lower doses of levodopa and both agents are approved as adjuncts to levodopa therapy.[55] Some experts recommend the initiation of a COMT inhibitor at the onset of levodopa therapy to reduce the risk of developing motor complications.

Unlike most drugs to treat PD, adenosine A2a antagonists are not dopaminergic.[56] While the exact mechanism of adenosine A2a antagonists in PD is not known, early research indicates they may be neuroprotective and prevent dyskinesia when used with levodopa.[57] Istradefylline (Nourianz) is approved as adjunctive therapy to levodopa/carbidopa to decrease "off" episodes and is a once-daily oral option.

The 2021 guidelines from the American Academy of Neurology (AAN) state that treatment with levodopa provides superior benefit at reducing motor symptoms when compared to treatment with either dopamine agonists or MAO-B inhibitors. While incidence is low, levodopa is more likely than other agents to cause dyskinesia in the first 5 years of therapy. Discontinuation rates are lower with levodopa than dopamine agonists and MAO-B inhibitors. Immediate-release levodopa is preferred over controlled-release levodopa or levodopa/carbidopa/entacapone for early PD.[58] Guidelines for the treatment initiation for Parkinson disease is under development.[59]

An evidence-based review updated in 2018 by the Movement Disorder Society ranked the efficacy of the various treatments based on placebo-controlled trials of patients with PD that were performed between 2004 and 2016.[60] In the review, oral levodopa/carbidopa, the MAO-B inhibitors, and the dopamine agonists are all rated as efficacious for symptomatic monotherapy in patients with PD; exceptions to this are bromocriptine and ropinirole ER which are considered likely efficacious. The anticholinergics, as well as amantadine, are rated as likely efficacious as monotherapy. As symptomatic adjunct therapy to levodopa, the nonergot dopamine agonists, rotigotine, tolcapone, and rasagiline are considered efficacious; anticholinergics, amantadine, and bromocriptine are likely efficacious. There is insufficient evidence to rate selegiline. Entacapone and safinamide are noted to be nonefficacious as an adjunct therapy to levodopa. For the prevention/delay of motor fluctuations, pramipexole is efficacious. For the prevention/delay of dyskinesia, pramipexole and ropinirole are efficacious; bromocriptine is likely efficacious. Efficacious treatments for motor fluctuations include COMT inhibitors, levodopa/carbidopa (standard and extended-release formulations), rasagiline, and dopamine agonists; exception to this is

bromocriptine, which is likely efficacious. Amantadine is rated efficacious for the treatment of dyskinesia. Duodenal administration of levodopa/carbidopa was also likely efficacious for treatment of motor fluctuations and dyskinesia.

Restless Leg Syndrome

Restless legs syndrome (RLS) is a neurological sensory disorder in which patients experience irrepressible sensations in the legs or arms while sitting or lying still to cause them to move their arm or legs. Providers will need to rule out other movement disorders with similar symptoms to RLS, such as periodic limb movement disorder (PLMD), antipsychotic drug adverse effects, and dyskinesis, to correctly diagnose and treat these symptoms. Studies suggest that RLS is associated with the dopamine system and depletion of iron stores.[61] Historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants (including the immediate-release formulation of gabapentin), iron replacement (in patients with low serum ferritin levels), and dopaminergic agents (e.g., carbidopa/levodopa). Prior to 2000, levodopa was the dopaminergic agent most studied for RLS. Pramipexole (Mirapex), ropinirole, and rotigotine (Neupro) are approved for an indication of RLS and there has been increased focus on the use of dopamine agonists in the treatment of this disorder. Gabapentin enacarbil (Horizant) is also FDA-approved for RLS.

When nonpharmacologic modifications like sleep hygiene, avoiding medications that provoke RLS, and lifestyle adjustments are ineffective, pharmacologic therapies should be added.[62] The American Journal of Medicine 2007 review of guidelines and standards of practice for RLS reported that dopaminergic therapy appeared to be the most effective and relieved symptoms rapidly. For chronic RLS, an algorithm by an expert panel recommended the non-ergot dopamine agonists pramipexole, ropinirole or rotigotine (Neupro), as drugs of choice, but state that treatment should be initiated with gabapentin or pregabalin if appropriate.[63] Levodopa or levodopa/carbidopa is recommended for intermittent RLS.

The 2012 American Academy of Sleep Medicine (AASM) RLS practice parameters recommend pramipexole and ropinirole for RLS.[64] Gabapentin enacarbil is also recommended, but conservatively since it was relatively new at the time the guidelines were published. Levodopa with dopa decarboxylase inhibitor is recommended but for patients with intermittent RLS who do not require daily therapy for RLS. Carbamazepine, gabapentin, pregabalin, clonidine, and, for patients with low ferritin levels, iron supplementation, are listed as options; however, evidence to support their use in RLS is limited. The guidelines note that rotigotine is effective in the treatment of moderate to severe RLS, but the patch was off the market at the time of guideline update; a reformulated version was reintroduced in 2012.

The 2016 American Academy of Neurology (AAN) RLS practice guideline recommends pramipexole, rotigotine, and gabapentin enacarbil for patients with moderate to severe primary RLS to reduce RLS symptoms (all Level A).[65] In patients with periodic limb movements of sleep (PLMS) who require improvement in sleep parameters, ropinirole (Level A), pramipexole, rotigotine, and gabapentin enacarbil (Level B) are recommended. Gabapentin enacarbil (Level A), ropinirole, pramipexole, rotigotine, or pregabalin (Level B) are recommended to improve objective sleep measures.

Early trials indicated that gabapentin may provide effective treatment for RLS.[66,67] Gabapentin absorption occurs through active transport by low-capacity nutrient transporters expressed in a narrow region of the upper small intestine. As a result, gabapentin bioavailability decreases with increasing dose and plasma exposure to gabapentin is variable among patients.[68] Additionally, the short half-life of gabapentin requires frequent dosing. Gabapentin enacarbil (Horizant) is an actively transported prodrug of gabapentin with absorption by high-capacity nutrient transporters located throughout the large and

small intestine. After absorption, gabapentin enacarbil is converted to gabapentin by carboxylesterases. Gabapentin enacarbil is an extended-release tablet and dosed once daily. Gabapentin is not interchangeable with gabapentin enacarbil.

PHARMACOLOGY[69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99]

Therapeutic Class	Drug	Mechanism of Action
Anticholinergics	benztropine trihexyphenidyl	▪ Suppress central cholinergic activity ▪ Inhibit the reuptake and storage of dopamine at central dopamine receptors, thereby prolonging dopamine action
Dopa decarboxylase inhibitor	carbidopa (Lodosyn)	▪ Inhibits L-amino-acid-decarboxylase (L-AAD) and prevents the decarboxylation of levodopa
Dopamine precursor	levodopa (Inbrija)	▪ Immediate precursor to dopamine
Dopamine precursor / dopa decarboxylase inhibitor	levodopa / carbidopa (Dhivy, Duopa, Rytary, Sinemet)	▪ Levodopa is the immediate precursor to dopamine ▪ Carbidopa inhibits L-amino-acid-decarboxylase (L-AAD) and prevents the decarboxylation of levodopa
MAO-B inhibitors	rasagiline (Azilect) safinamide (Xadago) selegiline selegiline (Zelapar)	▪ Select irreversible inhibitors of MAO-B activity ▪ Block dopamine breakdown ▪ Increase dopaminergic activity ▪ Interfere with dopamine reuptake at the synapse
Dopamine agonists	apomorphine (Kynmobi)	▪ Non-ergoline dopamine agonist that binds to the D2 dopamine receptor within the caudate-putamen
	bromocriptine (Parlodel) pramipexole (Mirapex, Mirapex ER) ropinirole	▪ Directly stimulate the dopamine receptors in the corpus striatum
	rotigotine (Neupro)	▪ Non-ergoline dopamine agonist that binds to the D2 dopamine receptor within the caudate-putamen
COMT inhibitors	entacapone (Comtan) opicapone (Ongentys) tolcapone (Tasmar)	▪ Inhibit COMT (catechol-O-methyltransferase) ▪ Prevent peripheral conversion of levodopa to 3-O-methyldopa (3OMD) ▪ Increase plasma levodopa levels
Dopamine precursor / dopa decarboxylase inhibitor / COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo)	▪ Levodopa is the immediate precursor to dopamine ▪ Carbidopa inhibits L-AAD and prevents the decarboxylation of levodopa ▪ Entacapone inhibits COMT and increases plasma levodopa levels
Gabapentinoid	gabapentin enacarbil (Horizant)	▪ Precise mechanism unknown in RLS ▪ In vitro studies show that gabapentin binds to voltage activated calcium channels
NMDA-type	amantadine amantadine ER (Gocovri, Osmolex ER)	▪ Increases dopamine and norepinephrine release ▪ Inhibits dopamine and norepinephrine reuptake ▪ Glutamate receptor antagonist
Adenosine receptor antagonist	istradefylline (Nourianz)	▪ Precise mechanism unknown in PD ▪ Adenosine A2A receptor antagonist through non-dopaminergic mechanism

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta, or kappa), or cannabinoid 1 receptor sites. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

PHARMACOKINETICS[100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Anticholinergics				
benztropine	--	--	CYP3A and hydroxylation	urine: 6
trihexyphenidyl	--	--	metabolites	urine
Dopamine precursor				
levodopa (Inbrija)	70*	2.3	decarboxylation by dopa decarboxylase and O-methylation by catechol-O-methyltransferase	--
Dopamine precursor / dopa decarboxylase inhibitor				
levodopa/carbidopa (generics, Sinemet, Rytary, Duopa, Dhivy)	--†	1.5-3.5	extensive	urine
MAO-B inhibitors				
rasagiline (Azilect)	36	3	CYP1A2	urine: 62 feces: 7
safinamide (Xadago)	95	20-26	metabolized by non-microsomal enzymes	urine: 5
selegiline	--	10	3 active metabolites	urine: 45
selegiline (Zelapar)	greater than conventional selegiline tablets	10	3 active metabolites – concentrations reduced 3- to 10-fold compared to conventional selegiline tablets	

The pharmacokinetics for levodopa/carbidopa/entacapone (Stalevo) is similar to the individual components of the drug.

* Relative bioavailability of levodopa inhalation powder is 70% relative to immediate-release levodopa tablets.

† Relative bioavailability of carbidopa and levodopa from Rytary relative to immediate-release tablets is 50% and 70% respectively and for levodopa from Duopa is 97%.

Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Dopamine agonists				
apomorphine (Kynmobi)	–	1.7	multiple metabolic process to include sulfation, glucuronidation, N-demethylation (CYP2B6, CYP2C8, CYP3A4/5), and conjugation	–
bromocriptine (Parlodel)	28	15	CYP3A	urine: 6
pramipexole (Mirapex)	> 90	8 (young) 12 (elderly)	unchanged	urine: 90
pramipexole ER (Mirapex ER)	> 90	8.5 (young) 12 (elderly)	unchanged	urine: 90
ropinirole	55	6	CYP1A2	urine: > 88
ropinirole ER	45-55	6	CYP1A2	urine: > 88
rotigotine (Neupro)	1-46 (varies based on patch location	5-7	multiple metabolic process to include conjugation, N-dealkylation and sulfate conjugation, and glucuronidation	urine: 71 feces: 23
COMT inhibitors				
entacapone (Comtan)	35	2.4	isomerization to CIS-isomer and direct glucuronidation of parent and CIS-isomer to inactive conjugate	urine: 10 feces: 90
opicapone (Ongentys)	**–**	**1-2**	**sulphation (primary), glucuronidation, methylation, conjugation**	**urine: 5** **feces: 70**
tolcapone (Tasmar)	65	2-3	glucuronidation to inactive conjugate	urine: 60 feces: 40
Gabapentinoid				
gabapentin enacarbil (Horizant)	75	5.1-6	extensive first pass hydrolysis	urine
NMDA-type				
amantadine	–	16-17	some metabolism	primarily urine
amantadine ER (Gocovri, Osmolex ER)	–	16	some metabolism	primarily urine
Adenosine receptor antagonist				
istradefylline (Nourianz)	–	83	extensive; primarily CYP1A1 and CYP3A4	urine: 39 feces: 48

CONTRAINDICATIONS/WARNINGS[131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161]

Hypersensitivity reactions have been reported with many agents in this class. No agent in this class should be used in patients with known hypersensitivity to any component of the medication.

A boxed warning appears in the tolcapone (Tasmar) prescribing information. Three fatal cases of acute, fulminant liver failure have been reported in the first 6 months of therapy. Patients must sign an informed consent to start therapy with tolcapone. The warning states that the actual incidence of hepatocellular injury appears to be 10- to 100-fold higher than the background incidence in the general population. Prior to therapy initiation, the patient should have no clinical evidence of liver disease or hepatic lab values greater than normal. If patients do not respond to tolcapone in 3 weeks, therapy should be stopped.

Concomitant use of non-selective MAO inhibitors with levodopa (Inbrija) and levodopa/carbidopa (generics, Dhivy, Duopa, Rytary, Sinemet) can result in hypertension; simultaneous use of these agents is contraindicated. The MAOI must be discontinued 2 weeks prior to starting levodopa and levodopa/carbidopa. Levodopa/carbidopa is also contraindicated in patients with narrow-angle glaucoma. COMT inhibitors should not be used with nonselective MAO inhibitors as well.

Amantadine is contraindicated in patients with a known hypersensitivity to amantadine or rimantadine. The renal clearance of amantadine is lower in patients with renal impairment. Amantadine ER (Gocovri, Osmolex ER) is contraindicated in patients with end-stage renal disease (creatinine clearance < 15 mL/min). Additional warnings for amantadine ER include falling asleep during activities of daily living, suicidality and depression, hallucinations/psychotic behavior, dizziness and orthostatic hypertension, impulsive control/compulsive behaviors, and withdrawal-emergent hyperpyrexia and confusion.

The anticholinergics, benztropine and trihexyphenidyl, should not be given to patients with narrow angle glaucoma. Benztropine should be used cautiously in patients with benign prostatic hypertrophy because it can exacerbate urinary retention. In addition, the manufacturer considers prostatism, dementia, and tardive dyskinesia contraindicated to the use of this drug. These agents were added to the Beers Criteria list for potentially inappropriate medication use in older adults in 2012 and have remained on this list in the 2015 and 2019 updates.[162,163,164]

Due to potentially fatal reactions that have occurred in patients receiving MAO inhibitors concomitantly with meperidine, the use of rasagiline (Azilect), safinamide (Xadago), and selegiline (Zelapar) with meperidine is contraindicated. For similar reasons, these 3 drugs should not be used concurrently with methadone, propoxyphene, or tramadol; and this contraindication is generally extended to all opioids. Rasagiline, selegiline, and safinamide are also contraindicated with the concurrent use of dextromethorphan, St. John's wort, or cyclobenzaprine. Rasagiline and selegiline are contraindicated for use with sympathomimetic amines due to the potential for severe hypertensive reactions. Other contraindications for the MAO-B inhibitors are general anesthesia, pheochromocytoma, and concurrent use with other MAO inhibitors. Concomitant use of serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), or tricyclic antidepressants (TCAs) is not recommended with the MAO-B inhibitors rasagiline or selegiline; while use of concomitant use of these agents with the MAO-B inhibitor safinamide is contraindicated. Safinamide warnings include hypertension, serotonin syndrome, falling asleep during activities of daily living, dyskinesia, impulse control/compulsive behavior, hallucinations/psychotic behavior, retinal pathology, withdrawal-emergent hyperpyrexia, and confusion.

COMT inhibitors also should not be used in patients with pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

Case reports of patients falling asleep during activities of daily living, including while operating a motor vehicle, have been reported with levodopa/carbidopa and dopamine agonists. Prescribers should monitor patients for somnolence and drowsiness; however, prescribers should be aware that some patients indicated they had no warning signs prior to the event. Class warning language has been added to all agents regarding these "sleep attacks" due to their central dopaminergic activity. Concomitant use with alcohol or other sedating medications may increase this risk.

Dopamine agonists appear to impair the systemic regulation of blood pressure resulting in orthostatic hypotension during dose escalation. Syncope has also been reported. Patients with PD appear to have a decreased response to orthostatic challenge and monitoring of orthostatic hypotension is recommended. Other precautions include a 9% increase in hallucinations, a 6% increase in risk of somnolence, and a potentiation of dopaminergic effects that may result in exacerbating dyskinesia. A human data study did not show statistical changes between treatment arms in retinal pathology but the animal data study in albino rats showed some retinal degeneration. Caution should be used to limit falls, which are also a higher risk due to the disease as well.

There is growing evidence that dopamine agonists are associated with disorders of impulse control, including pathologic shopping, gambling, and hypersexuality. In a retrospective analysis, the lifetime prevalence for these behaviors in patients with PD was 6.1%. This risk increased to 13.7% among those on dopamine agonists.[165] Risk factors for these disorders were younger age at PD onset ($p=0.006$), high novelty-seeking traits ($p<0.001$), medication-induced hypomania or mania ($p=0.001$), impaired planning ($p=0.002$), or personal or immediate family history of alcohol abuse ($p<0.05$).[166]

Cases of fibrotic complications (e.g., retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, cardiac valvulopathy) have been reported with ergot-derived dopaminergic agents, and caution should be used in patients with non-ergot derived dopaminergic agents as well.

Use of bromocriptine (Parlodel) is contraindicated if the patient has experienced hypersensitivity to bromocriptine, has uncontrolled hypertension, or has sensitivity to ergot alkaloids. Bromocriptine should be discontinued if the patient becomes pregnant; discontinuation should be considered if the patient has plans to become pregnant. Adverse effects during pregnancy, such as preeclampsia, eclampsia, or pregnancy-induced hypertension have been known to occur. Bromocriptine should be avoided in post-partum patients with a history of coronary cardiovascular disease or other severe cardiovascular condition unless withdrawal is considered medically contraindicated. Pramipexole (Mirapex, Mirapex ER), ropinirole, and rotigotine (Neupro) have a warning in the prescribing information regarding the potential for falling asleep during activities of daily living, and patients should be informed of this risk prior to starting treatment. Other factors, such as sedating medications, drug interactions increasing the exposure to these drugs, and sleep disorders, can increase the risk of excessive drowsiness or falling asleep. In addition, dopaminergic agonists tend to impair the regulation of blood pressure and can cause symptomatic hypotension and impaired capacity to respond to postural changes. Therefore, careful monitoring during dose escalation and informed risk is needed.

Reports of postural deformities have been reported up to several months after initiating treatment or increasing the dose of pramipexole (Mirapex, Mirapex ER). Dose reduction or discontinuation is recommended if this occurs.

Rotigotine (Neupro) contains sodium metabisulfate and contains a warning for those allergic to sulfites. Sulfites can result in allergic-type anaphylactic symptoms. Asthmatics may be more prone to sulfite sensitivities.

Hallucinations or psychotic-like behavior, and dyskinesia may occur with dopaminergic agents. Hallucinations generally present shortly after the starting therapy and may respond to a reduction in the levodopa dose. Post-marketing reports indicate that patients treated with rotigotine (Neupro) or ropinirole may experience new or worsening mental status changes during treatment, after initiation, or with dose increases. These changes may be severe, including psychotic-like behavior, leading to one or more manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, symptoms of mania, disorientation, aggressive behavior, agitation, and delirium. Istradefylline (Nourianz) may also increase the risk of exacerbating psychosis; therefore, it should not be used in patients with a major psychotic disorder. Istradefylline may also cause or exacerbate pre-existing dyskinesia when used in combination with levodopa.

Levodopa-containing agents may also cause patients to experience new or increased difficulty with impulse control and compulsive behaviors as with other drugs that increase central dopaminergic tone, such as bromocriptine (Parlodel), pramipexole (Mirapex), rotigotine (Neupro), and ropinirole. Istradefylline (Nourianz) may also cause patients to experience these behaviors when used in combination with other drugs to treat PD. Patients and caregivers should assess for the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while taking drugs that increase central dopaminergic tone or are used in combination with higher risk.

Additionally, due to the formulation, levodopa powder for inhalation (Inbrija) is not recommended for use in patients with underlying chronic lung disease. Treatment with levodopa may result in abnormal laboratory tests resulting in elevated liver function tests, abnormal blood urea nitrogen, hemolytic anemia, and positive direct antibody tests. Due to increases in catecholamines and their metabolites, treatment with levodopa and carbidopa/levodopa may result in an incorrect diagnosis for pheochromocytoma.

Levodopa-containing agent may increase the risk of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

In a meta-analysis, pramipexole and ropinirole were compared for the risk of somnolence.[167] The pooled, relative risk of somnolence was 4.98 compared to the placebo group based on 4 trials. In a comparison between patients taking levodopa and pramipexole or ropinirole, the pooled, relative risk was 2.06.

Reports have associated amantadine, levodopa, levodopa/carbidopa, and dopamine agonists with a symptom complex that resembles neuroleptic malignant syndrome with no other obvious etiology linked to rapid dose reduction and withdrawal, rapid titration, and any changes in dopaminergic therapy. Therefore, the dose should be titrated down slowly to prevent this withdrawal, this risk should be discussed with patients, and patients should be closely monitored during and following discontinuation.

Cardiovascular monitoring is recommended with all levodopa-containing products. Cardiovascular ischemic events have occurred in patients taking levodopa/carbidopa ER (Rytary) who had a history of ischemic heart disease or risk factors for ischemic heart disease. Patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias, should have their cardiac function monitored in an intensive cardiac care facility during initial dosage adjustments.

In August 2010, the FDA notified healthcare professionals about concerns that the use of levodopa/carbidopa/entacapone may be associated with an increased risk of cardiovascular events, including heart attack, stroke, and cardiovascular death, when compared to the use of carbidopa/levodopa. Based on findings from the Stalevo Reduction In Dyskinesia Evaluation – Parkinson's Disease (STRIDE-PD) trial, which reported an imbalance in the number of myocardial infarctions in patients treated with levodopa/carbidopa/entacapone compared to those receiving only carbidopa/levodopa, the FDA announced the intent to conduct a meta-analysis to validate these findings.[168] In October 2015, the FDA safety review did not find clear evidence of increased risk of CV events with use of entacapone or levodopa/carbidopa/entacapone; thus, no labeling changes were required.[169] Cardiovascular effects can occur with the concomitant use of drugs metabolized by COMT and a COMT inhibitor.

In March 2010, FDA alerted the public of a possible increased risk of prostate cancer with entacapone, used to treat Parkinson's disease.[170] In 2019, after review of additional data from required study and data from the Department of Veterans Affairs, the FDA determined that add-on entacapone was not associated with an increased risk of prostate cancer (hazard ratio [HR] 1.05; 95% CI, 0.76 to 1.44) or prostate cancer death (HR 0.93; 95% CI, 0.43 to 1.98) compared with treatment without add-on entacapone.[171]

Like several agents within this therapeutic class, other warnings with the COMT inhibitors include somnolence, hypotension or syncope, dyskinesia, hallucinations or psychosis, impulse control or compulsive disorders, and withdrawal-emergent hyperpyrexia or confusion.

Epidemiological studies have shown that patients with PD have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to PD or other factors, such as drugs used to treat PD, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using entacapone-containing products for any indication. Ideally, periodic skin examination should be performed by appropriately qualified individuals (e.g., dermatologists).

There are no specific contraindications to the use of gabapentin enacarbil (Horizant) listed in the product information. Gabapentin enacarbil may cause somnolence/sedation and dizziness; therefore, patients should become experienced with the way gabapentin enacarbil may affect them specifically before operating a motor vehicle or other heavy machinery. Gabapentin enacarbil is not recommended for patients who are required to sleep during the daytime and remain awake at night. Due to differing pharmacokinetic profiles, gabapentin enacarbil is not interchangeable with other gabapentin products. The safety and effectiveness of gabapentin enacarbil have not been studied in patients with epilepsy. Gabapentin enacarbil is a prodrug of the anticonvulsant gabapentin; therefore, patients taking gabapentin enacarbil should also be monitored for a potential increased risk of suicidal thoughts and behavior.

All patients treated with levodopa/carbidopa should be observed carefully for the development of depression and suicidal tendencies. Levodopa and levodopa/carbidopa may cause increased intraocular pressure in patients with glaucoma; this patient population should be monitored carefully.

Amantadine has warnings for death due to overdose, suicide and suicidality, CNS effects including increased seizure activity and CNS depression, congestive heart failure, and use in patients with untreated angle closure glaucoma due to its anticholinergic effects.

All patients taking levodopa/carbidopa should be observed for the development of depression and concomitant suicidal tendencies.

Delays in stomach emptying may delay the absorption of levodopa or levodopa/carbidopa, resulting in reduced efficacy of the drug. Administration of levodopa/carbidopa directly into the small intestine limits the impact of gastric emptying on its absorption and allows for relatively constant plasma concentrations of levodopa; potentially resulting in less motor fluctuations and dyskinesias. In addition, since levodopa/carbidopa (Duopa) can be administered via alternative routes (e.g., a feeding tube), complications from administration can arise (e.g., abscess, bezoar, ileus, intestinal perforation).

Selegiline (Zelapar) contains phenylalanine and may be harmful to patients with phenylketonuria (PKU).

Apomorphine (Kynmobi) use with 5-HT_3 antagonists is contraindicated. It also carries a warning for nausea and vomiting, for which an antiemetic (e.g., trimethobenzamide 300 mg 3 times a day) is recommended beginning 3 days before initiating apomorphine until as long as needed (generally 2 months). Cases of oral mucosal irritation/stomatitis have also been reported with apomorphine. Apomorphine also has a risk of QT prolongation and may cause priapism. Apomorphine contains sodium metabisulfite, which may cause allergic-type reactions. Animal studies have found retinal pathology from this agent as well. Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment.

DRUG INTERACTIONS[172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202]

Many different drug interactions occur with the antiparkinsonian agents. Drug interaction references should be reviewed when prescribing concomitant medications. Drugs that may antagonize dopamine agonists are phenothiazines, haloperidol, metoclopramide, and butyrophenones and diminish the effectiveness of the dopamine agonists. In addition, dopamine agonists should be used with caution with alcohol and other central nervous system (CNS) depressants. Use of levodopa/carbidopa in combination with dopamine-depleting agents, such as reserpine or tetrabenazine, is not recommended. Agents that are MAO or COMT inhibitors have significant interactions with agents metabolized via these pathways.

Patients taking apomorphine (Kynmobi) should not use 5-HT_3 antagonists and should use caution (e.g., lie down following nitroglycerin) when using antihypertensive agents and vasodilators. Apomorphine should also be used cautiously with other QT-prolongating agents.

Pramipexole (Mirapex, Mirapex ER) levels may be increased by renally-excreted basic drugs (e.g., cimetidine, verapamil, and quinidine).

Ropinirole may be potentiated by cytochrome P450 (CYP) 1A2 inhibitors, such as ciprofloxacin.

Because gabapentin enacarbil is not a substrate, inhibitor or inducer of any major cytochrome P450 enzymes or substrate or inhibitor of P-glycoprotein (P-gp) *in vitro*, no clinically relevant drug-to-drug interactions is expected.

Concurrent use with drugs containing hydrochlorothiazide or triamterene can reduce renal clearance of amantadine, possible possibly resulting in toxicity. Amantadine is a NMDA antagonist and may lead to additive adverse effects if combined with memantine. Amantadine may also interfere with the therapeutic effect of donepezil; concurrent use should be avoided.

The use of drugs with anticholinergic properties in combination with amantadine ER (Gocovri, Osmolex ER) may result in anticholinergic-like adverse effects requiring dose reduction. Urinary excretion of amantadine ER may be affected by the pH of the urine. Patients should be monitored for efficacy and adverse reactions when exposed to drugs that alter urine pH.

Live vaccines are not recommended during treatment with amantadine ER due to interference in efficacy of the vaccine.

High-protein diets and iron salts (such as in multivitamin tablets) may reduce clinical effectiveness of levodopa.

The recommended maximum daily dose of istradefylline (Nourianz) is 20 mg daily when used in combination with CYP3A4 inhibitors. Istradefylline should be avoided with strong CYP3A4 inducers. Additional monitoring for adverse reactions caused by concomitant CYP3A4 substrates and P-gp substrates is recommended when istradefylline is administered.

Isoniazid has some MAO inhibiting activity; therefore, monitor for hypertension and reaction to dietary tyramine in patients on concurrent isoniazid and safinamide.

For additional information on drug-drug interactions, see the *Contraindications/Warnings* section of this therapeutic class review.

ADVERSE EFFECTS[203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233]

Anticholinergics[234]

Adverse effects of anticholinergic drugs are common and often limit their use. The most common CNS effects include memory impairment, acute confusion, hallucinations, sedation, and dysphoria. Peripheral anticholinergic adverse effects include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia.

Levodopa (Inbrija)

The most common adverse reactions reported in ≥ 5% of patients and more often than placebo during clinical trial experience with inhaled levodopa were cough (15%), nausea (5%), upper respiratory infection (6%), and discolored sputum (5%).

Levodopa/carbidopa (generics, Dhivy, Duopa, Rytary, Sinemet)[235]

The most frequently reported adverse effects with levodopa are adventitious movements, such as choreiform or dystonic movements (10% to 90%), anorexia (50%), nausea/vomiting with or without abdominal pain and distress (80%), dry mouth, dysphagia, dysgeusia (4.5% to 22%), excessive drooling, ataxia, increased hand tremor, headache, dizziness, numbness, weakness/faintness, confusion, insomnia, hallucinations, delusions, agitation, and anxiety.

Nausea, dizziness, and headache are the most commonly reported adverse events for levodopa/carbidopa ER (Rytary). For levodopa/carbidopa enteral suspension (Duopa) the most common adverse reactions that occurred more frequently than with immediate-release formulations were complications of PEG-J device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, and incision site erythema.

Dopamine Agonists

Drug	Confusion	Constipation	Dizziness	Dyskinesia	Hallucinations	Nausea
apomorphine (Kynmobi)	reported	nr	9-11 (2)	nr	reported	21-28 (4)
bromocriptine (Parlodel)	reported	reported	reported	reported	reported	reported
pramipexole (Mirapex)	4-10 (1-7)	10-14 (6-9)	25-26 (24-25)	47 (31)	9-17 (3-4)	28 (18)
pramipexole ER (Mirapex ER)	nr	14 (2)	12 (7)	17 (8)	5 (1)	22 (9)
ropinirole	5-9 (1)	6 (nr)	40 (22)	> 1	> 5	60 (22)
ropinirole ER	nr	4 (2)	6-8 (3)	13 (3)	8 (2)	11-19 (4)
rotigotine (Neupro)	nr*	nr* 5-9† (19)	20-21 (11)* nr†	nr* 14-17† (7)	nr* 7-14† (3)	34-41 (13)* 22-28† (19)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.
*Early-stage PD in 6 mg/24 hour group.

†Advanced-stage PD at 8 mg/24 hour and 12 mg/24 hour

As rotigotine is a patch, application site reactions do occur. The adverse effect ranges from 15% in early stage PD to 23% in advanced-stage PD. Rotating the patch location may decrease the reaction. Dopamine agonists can cause peripheral edema and its associative weight gain. Patients more sensitive to fluid retention, such as congestive heart failure and renal insufficiency, should be monitored.

COMT Inhibitors

Drug	Anorexia	Diarrhea	Dyskinesia	Hallucinations	Orthostatic complaints	Nausea	Somnolence
entacapone (Comtan)	nr	8-20 (7)	13-25 (11)	4-9	13 (14)	10-20 (12)	4-8 (10)
opicapone (Ongentys)	nr	nr	20 (6)	3 (1)	5 (1)	nr	reported
tolcapone (Tasmar)	19-23 (13)	16-34 (8)	42-51 (20)	24	17-24 (14)	28-50 (18)	16-32

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Rare cases of fatal hepatotoxicity have been reported with tolcapone (Tasmar), leading to a recommendation of more stringent liver function monitoring.[236] In the 2006 Practice Parameters, the Quality Standards Subcommittee of the American Academy of Neurology recommends that tolcapone should only be used in PD patients taking levodopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapy.[237] The Practice Parameters recommend that liver function monitoring should be done per the product labeling:

baseline and then periodically (e.g., every 2 to 4 weeks) for the first 6 months and thereafter as clinically necessary. Tolcapone should be discontinued if alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase to more than twice the upper limit of normal.

MAO-B Inhibitors

Drug	Confusion	Dizziness	Dyskinesia	Orthostatic complaints	Nausea
rasagiline (Azilect)	> 1	1 (1)	18 (10)	6-9 (3)	10-12 (8)
safinamide (Xadago)	reported	nr	17-21 (9)	2 (1)	3-6 (4)
selegiline	3-6	6-12	34 (19)	reported	10-20
selegiline (Zelapar)	nr	11 (8)	6 (3)	< 2	11 (9)

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Selegiline's MAO-B specific selectivity is not absolute, even at the recommended daily dose of 10 mg. Rare cases of hypertensive reactions has been associated with the ingestion of tyramine-containing foods while on 10 mg dose. The precise dose at which selegiline becomes non-selective is unknown but is estimated to be in the range of 30 to 40 mg/day.

Rasagiline is approved without dietary restrictions except if high dose treatment is used resulting in the loss of selectivity above the recommended maximum dose. Rasagiline doses greater than 1 mg a day are not recommended due to the risk of hypertensive crisis and other adverse reactions.

Severe CNS toxicity (serotonin syndrome) has been reported with MAO-B inhibitors and antidepressant combinations. Rasagiline plasma concentration is increased when used in combination with ciprofloxacin or mild hepatic impairment. Patients with moderate or severe hepatic impairment should not use rasagiline.

Gabapentinoid

For both the 600 mg and 1,200 mg gabapentin enacarbil (Horizant) doses, somnolence/sedation and dizziness are the most common adverse effects. Balance disorder, edema, weight gain, blurred vision, disorientation, feeling drunk, lethargy, and vertigo also occurred. In simulated driving studies, a daily single 1,200 mg dose gabapentin enacarbil caused significant driving impairment between 2 and 14 hours after dosing. The impairment was similar to that caused by the active control, a single oral dose of diphenhydramine 50 mg. The 600 mg dose was not studied. However, since a 600 mg/day dose of gabapentin enacarbil can cause significant somnolence (similar to that of the 1,200 mg/day dose), the 600 and 1,200 mg/day doses may have similar effects on driving and a driving impairment warning was added to the package insert to warn patients not to drive until they have gained sufficient experience with the drug and to assess their personal level of driving impairment. Augmentation and rebound, which have occurred with dopamine agonists, have not been reported with gabapentin enacarbil.[238]

NMDA-Type

The most frequent adverse reactions with amantadine are nausea, dizziness (lightheadedness), and insomnia. Additional adverse reactions reported in > 10% of treated patients and more frequently than placebo during clinical trials with amantadine ER (Gocovri) are hallucination, dry mouth, peripheral edema, constipation, falls, and orthostatic hypotension.

Adenosine Receptor Antagonist

Dyskinesia was the most frequently reported adverse reaction and the most frequently reported adverse reaction causing study discontinuation in trials for istradefylline (Nourianz). Other common adverse reactions reported in ≥ 5% of patients treated with istradefylline and more frequently than placebo during clinical trials are dizziness, constipation, nausea, hallucination, and insomnia.

SPECIAL POPULATIONS[239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269]

Pediatrics

Benztropine should not be used in children 3 years of age or younger. The safety and effectiveness have not been established in pediatric patients for any of the other agents reviewed for treatment of PD. The safety and efficacy of gabapentin enacarbil (Horizant), used in RLS, have not been established in pediatric patients.

Pregnancy

Most agents in this class have been updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). New and updated PLLR compliant labels indicate the absence of adequate data on the developmental risk when used in pregnant women. The remaining agents, levodopa/carbidopa ODT, entacapone (Comtan), tolcapone (Tasmar), and amantadine, are Pregnancy Category C with the exception of bromocriptine (Parlodel). Bromocriptine (Parlodel) is Category B but should not be used during lactation in postpartum women.

Hepatic Impairment

Apomorphine use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C), but no dosage adjustment is recommended in patients with mild to moderate hepatic impairment.

A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. However, a boxed warning was added for patients with moderate cirrhotic liver disease (Child-Pugh Class B) because of the risk of potentially fatal, acute fulminant liver failure. The clearance and volume of distribution of unbound tolcapone was reduced by almost 50% thus increasing the unbound drug by 2-fold. If the patient exhibits clinical evidence of active liver disease or 2 SGPT/ALT or SGOT/AST values greater than the upper limit of normal, tolcapone therapy should not be initiated. Patients who developed hepatocellular injury on past tolcapone therapy may have an increased risk of liver injury if tolcapone therapy is re-introduced. Analysis of the post-marketing data indicates increases in SGPT/ALT or SGOT/AST, when present, generally occur within the first 6 months of treatment with tolcapone.

Due to increased opicapone exposure with hepatic impairment, a dosage adjustment (decreased by half) is required in patients with moderate (Child-Pugh B) hepatic impairment and use should be avoided in patients with severe (Child-Pugh C) hepatic impairment.

Use caution when using entacapone (Comtan, Stalevo) in patients with hepatic impairment.

Patients with mild hepatic impairment should have the dosage of rasagiline (Azilect) adjusted to 0.5 mg daily. Rasagiline should not be used in patients with moderate or severe hepatic impairment.

Safinamide (Xadago) concentrations are increased in patients with hepatic impairment. Safinamide is contraindicated in patients with severe hepatic impairment (Child-Pugh C). For patients with moderate hepatic impairment (Child-Pugh B), the maximum recommended dosage is 50 mg daily. If patients progress from moderate to severe hepatic impairment, treatment with safinamide should be discontinued. No dosage adjustments are required in those with mild hepatic impairment.

The recommended maximum daily dose for istradefylline (Nourianz) is reduced in patients with moderate hepatic impairment (Child-Pugh B) to 20 mg once daily. Istradefylline use should be avoided in patients with severe hepatic impairment. All of the other agents, except for benztropine and pramipexole, should be used with caution in patients with hepatic impairment.

The influence of hepatic function impairment on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic function impairment would not be expected to have a significant effect on pramipexole elimination.

The pharmacokinetics of ropinirole have not been studied in patients with hepatic function impairment. Because patients with hepatic function impairment may have higher plasma levels and lower clearance, ropinirole should be titrated with caution in these patients.

Renal Impairment

Apomorphine should be avoided in patients with severe and end-stage renal disease (ESRD), but no dosage adjustment is required in mild or moderate renal impairment.

Opicapone should be avoided in patients with ESRD.

Trihexyphenidyl and levodopa/carbidopa (generics, Rytary, Sinemet) should be used with caution in patients with renal impairment.

Pramipexole clearance correlates well with creatinine clearance; therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole dosage should be adjusted with renal impairment and creatinine clearance less than 60 mL/min. In dialysis patients, pramipexole is minimally removed by dialysis and caution should be exercised for these individuals.

Dosing adjustments for ropinirole are not needed in patients with moderate impairment. The recommended maximum total daily dose for ropinirole for Parkinson's disease is 18 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required. Use in patients with severe renal impairment without regular dialysis has not been studied.

All of the MAO-B inhibitors should be used with caution in patients with renal impairment.

The dosing frequency of gabapentin enacarbil (Horizant) should be altered in patients with renal impairment. For patients with an estimated creatinine clearance of 30 to 59 mL/min, 600 mg of gabapentin enacarbil should be administered on days 1 and 3, then daily thereafter. Gabapentin

enacarbil should not be used in patients with creatinine clearance < 30 mL/min or in patients on hemodialysis.

Amantadine is mainly excreted in urine; thus the dose should be reduced in patients with renal impairment. Amantadine ER (Gocovri, Osmolex ER) is contraindicated for use in patients with end-stage renal disease. The dose of amantadine ER capsules (Gocovri) should be reduced by 50% for patients with a creatinine clearance of 30 to 59 mL/min to a maximum dosage of 137 mg daily. If the creatinine clearance is 15 to 29 mL/min, the maximum dose should be 68.5 mg daily. The dosing interval for amantadine ER tablets should be extended to 48 hours for creatinine clearance 30 to 59 mL/min and every 96 hours for creatinine clearance 15 to 29 mL/min.

Geriatric

Pramipexole clearance decreases with age, as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (65 years of age and older) compared with young, healthy volunteers (younger than 40 years of age). This difference is most likely due to the decrease in renal function with age, since pramipexole clearance is correlated with renal function.

Pharmacokinetic studies demonstrated a reduced clearance of ropinirole in elderly patients. Dosage adjustment is not necessary because the dose is individually titrated to clinical response.

As amantadine is mainly renally eliminated the dose should be reduced in patients 65 years of age or older. Clinical trial experience demonstrated an increase in hallucinations and falls in patients 65 years of age or older using amantadine ER (Gocovri).

Patients 65 years of age and older experienced adverse reactions with greater frequency in the levodopa (Inbrija) clinical trials. The reported adverse reaction differences for older versus younger patients, respectively, were cough (25% versus 5%), upper respiratory tract infection (11% versus 2%), nausea (7% versus 3%), vomiting (4% versus 2%), extremity pain (4% versus 0%), and discoloration of nasal discharge (4% versus 0).

Tobacco Smokers

Tobacco smoking can decrease the efficacy of istradefylline (Nourianz). The recommended dose of istradefylline in patients who smoke ≥ 20 cigarettes daily (or the equivalent of another tobacco product) is 40 mg once daily.

DOSAGES[270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300]

Parkinson's Disease

Therapeutic Class	Drug	Initial Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Anticholinergics	benztropine	0.5 mg	6 mg	1 to 2 times daily	0.5 mg, 1 mg, 2 mg tablets
	trihexyphenidyl	1 mg	15 mg	3 to 4 times daily	2 mg, 5 mg tablets; 2 mg/5 mL elixir
Dopa decarboxylase inhibitor	carbidopa (Lodosyn)	25 mg	200 mg	3 to 4 times daily	25 mg tablets

Parkinson's Disease Dosages (continued)

Dopamine precursor	levodopa (Inbrija)	Two 42 mg capsules	420 mg	up to 5 times daily	42 mg per capsule; 60 capsules/ package; breath activated device
Dopamine precursor/dopa decarboxylase inhibitor	levodopa/carbidopa (Dhivy)	25/100 mg	200 mg carbidopa	3 to 4 times daily	25/100 mg functionally scored tablet (into fourths)
	levodopa/carbidopa (Sinemet)	25/100 mg	200 mg carbidopa	3 to 4 times daily	10/100 mg, 25/100 mg, 25/250 mg (generic only) tablets
	levodopa/carbidopa sustained release	50/200 mg	200 mg carbidopa	twice daily	25/100 mg, 50/200 mg sustained-release tablets
	levodopa/carbidopa ER (Rytary)	23.75/95 mg	612.5 mg carbidopa	3 times daily	23.75/95 mg, 36.25/145 mg, 48.75/195 mg, 61.25/245 mg extended-release capsules
	levodopa/carbidopa ODT	25/100 mg	200 mg carbidopa	3 to 4 times daily	10/100 mg, 25/100 mg, 25/250 mg orally disintegrating tablets
	levodopa/carbidopa enteral suspension (Duopa)	Based on current levodopa dose (see label package insert for details)	2000 mg levodopa (500 mg carbidopa)	Infuse over 16 hours using the CADD®-Legacy 1400 portable infusion pump	20 mg/4.63 mg/mL enteral suspension in a 100 mL cassette
MAO-B Inhibitors	rasagiline (Azilect)	0.5 to 1 mg	1 mg	once daily	0.5 mg, 1 mg tablets
	safinamide (Xadago)	50 mg	100 mg	once daily	50 mg, 100 mg tablets
	selegiline	5 mg	10 mg	twice daily with breakfast and lunch	5 mg capsules; 5 mg tablets
	selegiline ODT (Zelapar)	1.25 mg	2.5 mg	once daily before breakfast and without liquid	1.25 mg orally disintegrating tablets
	rotigotine (Neupro)	Early stage: 2 mg Advanced stage: 4 mg	Early stage: 6 mg Advanced stage: 8 mg	once daily	1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patches

Parkinson's Disease Dosages (continued)

Therapeutic Class	Drug	Initial Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Dopamine agonists*	apomorphine (Kynmobi)	10 mg/dose (under medical supervision)	150 mg	given every 2 hours up to a maximum of 5 doses/day	10 mg, 15 mg, 20 mg, 25 mg, 30 mg sublingual (SL) film; titration kit
	bromocriptine (Parlodel)	1.25 mg	100 mg	twice daily with meals	2.5 mg tablets (SnapTabs®); 5 mg capsules
	pramipexole (Mirapex)	0.125 mg	4.5 mg	3 times daily	0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg tablets
	pramipexole ER (Mirapex ER)	0.375 mg	4.5 mg	once daily; swallow tablet whole and must not be chewed, crushed, or divided	0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, 4.5 mg tablets
	ropinirole	0.25 mg	24 mg	3 times daily	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablets
	ropinirole ER	2 mg	24 mg	once daily as a whole tablet and must not be chewed, crushed, or divided	2 mg, 4 mg, 6 mg, 8 mg, 12 mg tablets
COMT inhibitors	entacapone (Comtan)	200 mg	1,600 mg	200 mg with each dose of levodopa/carbidopa	200 mg tablets
	opicapone (Ongentys)	50 mg		once daily at bedtime; do not eat for 1 hour before or after opicapone dose	25 mg, 50 mg tablets
	tolcapone (Tasmar)	100 mg	600 mg	3 times daily	100 mg tablets
Dopamine precursor/dopa decarboxylase inhibitor/COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo)	one tablet	Based on maximum dose of entacapone: 50,75,100, 125 and 150 mg: 8 tablets/day; Based maximum dose of carbidopa: 200 mg: 6 tablets/day	every 3 to 5 hours	50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg, 125/31.25/200 mg, 150/37.5/200 mg, 200/50/200 mg tablets

*Dosing conversion between the extended-release dopamine agonists and their immediate-release counterparts can be found in the package insert of the extended-release products.

Parkinson's Disease Dosages (continued)

Therapeutic Class	Drug	Initial Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
NMDA-Type	amantadine	100 mg	400 mg	100 mg twice daily	100 mg capsules; 100 mg tablets; 50 mg/5 mL syrup
	amantadine ER (Gocovri‡)	137 mg	274 mg	once daily at bedtime	68.5 mg, 137 mg extended-release capsules
	amantadine ER (Osmolex ER)	129 mg	322 mg	once daily in the morning	129 mg, 193 mg, 258 mg, 322 mg extended-release tablets
Adenosine receptor antagonist	istradefylline (Nourianz)	20 mg	40 mg	once daily	20 mg, 40 mg tablets

‡ Amantadine ER (Gocovri) is not interchangeable with amantadine or amantadine ER (Osmolex ER).

Restless Leg Syndrome

Therapeutic Class	Drug	Initial Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Dopamine agonists	pramipexole (Mirapex)	0.125 mg	0.75 mg	once daily 2 to 3 hours prior to bedtime	0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg tablets
	ropinirole	0.25 mg	4 mg	once daily 1 to 3 hours prior to bedtime	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablets
	rotigotine (Neupro)	1 mg	3 mg	once daily	1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patches
Gabapentinoid	gabapentin enacarbil (Horizant)	600 mg*	1,200 mg†	once daily	300 mg, 600 mg tablets

* Gabapentin enacarbil is given as a single 600 mg dose once daily with food at approximately 5:00 PM.

† Clinical trials included a 1,200 mg dose; however, this dose resulted in increased adverse effects with no additional benefit.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this review. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class

review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

The clinical efficacy of antiparkinson's agents is determined in the literature primarily through the use of the total or partial Unified Parkinson Disease Rating Scale (UPDRS). Part I of the UPDRS is an evaluation of mentation, behavior, and mood. Part II is a self-reported evaluation of the Activities of Daily Living (ADL) and includes speech, swallowing, handwriting, ability to cut food, dressing, hygiene, falling, sialorrhea (salivation), turning in bed, and walking. Part III is a clinician-scored motor examination that is extensive and includes speech, resting tremor, facial expression and mobility, rigidity, hand and leg movements, gait, posture, and bradykinesia. Each item is rated on a scale of zero (normal) to 4 (can barely perform). Part IV is the Hoehn and Yahr staging scale and Part V is the Schwab and England ADL scale.[301]

Scales used to estimate health outcomes are the European Quality of Life Scale (EQ-5D) and Parkinson's disease quality of life scale (PDQUALIF). EQ-5D is a generic measure of health status, which provides a simplified descriptive profile and a single index value.[302] With this profile and index value, a clinical and economic evaluation of health care in population health surveys can be determined. PDQUALIF is a 33-item instrument evaluating 7 domains: social/role function, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function, plus 1 item of Global Health-Related Quality of Life (HRQOL).[303]

The efficacy of Osmolex ER is based on bioavailability studies comparing it to immediate-release amantadine.[304] The efficacy of Dhivy is based on bioavailability studies comparing it to a carbidopa 25 mg/levodopa 100 mg immediate-release tablet.[305]

Parkinson's Disease

anticholinergics

There is a paucity of high-quality evidence supporting the use of anticholinergics in the treatment of PD. The benefits of these agents in the treatment of PD are well recognized throughout the medical community.

In one study of benztropine, 29 patients with mild to moderate PD and stabilized on levodopa/carbidopa were randomized in double-blind crossover fashion to receive benztropine or placebo.[306] Benztropine conferred significantly greater improvement than placebo as measured by the clinician and patient global assessment. Statistically significant improvements were noted in rigidity, finger tapping speed, and activities of daily living during the benztropine phase. There were no significant adverse events noted.

Dopamine precursor

levodopa (oral)

Levodopa revolutionized the treatment of PD when it was introduced over 40 years ago. Although there is little evidence from high quality clinical trials to support its use, it is considered the gold standard for the treatment of PD.[307] The response to levodopa therapy in PD is seen as a dramatic improvement in function and, often times, quality of life. Symptoms that usually respond to levodopa treatment include rigidity, tremor, bradykinesia, gait, and micrographia. Other symptoms of PD, such as imbalance,

dysarthria, sexual dysfunction, excessive sweating, sensory problems, and constipation, do not always respond well to levodopa therapy. Oral levodopa, as a single-agent, is no longer available in the US.

levodopa (Inbrija)

Patients who had experienced ≥ 2 hours of daily "off" time per day despite carbidopa/levodopa treatment were randomized to receive up to 5 daily doses of levodopa of 84 mg of inhaled levodopa (n=114) or placebo (n=112).[308] The mean UPDRS Part III scores at the time of screening in the "on" state were 14.9 for the treatment group and 16.1 for the placebo group. The primary efficacy endpoint of this trial was the change in UPDRS Part III score from pre-dose "off" state to 30 minutes post-dose at week 12. At the conclusion of the trial, the change in UPDRS Part III score was -9.8 and -5.9 assessed 30 minutes following treatment and placebo, respectively. For patients treated with inhaled levodopa, 58% of patients returned to an "on" state which was sustained through 60 minutes following the dose compared to 36% of patients in the placebo group (p=0.003).

Dopamine precursor/dopa decarboxylase inhibitor

levodopa/carbidopa IR (Sinemet) versus levodopa/carbidopa CR

A total of 618 patients were studied in 36 centers worldwide in a blinded, randomized, parallel study.[309] Measures of efficacy and adverse effects were recorded at 3-month intervals for 5 years. A patient diary and a physician-recorded questionnaire evaluated motor fluctuations and dyskinesias and the Nottingham Health Profile (NHP) evaluated quality of life. After 5 years, the mean dose of levodopa/carbidopa IR was 426 mg per day, and the bioavailable dose of levodopa/carbidopa CR was 510 mg per day (mean 736 mg per day). After 5 years, 20.6% of the levodopa/carbidopa IR group and 21.8% of the levodopa/carbidopa CR group had motor fluctuations or dyskinesia. Sixteen percent of both groups had changes in motor response by the questionnaire's definition. There was no significant difference between the 2 treatment groups.

levodopa/carbidopa IR versus levodopa/carbidopa ER (Rytary)

A randomized, double-blind, multicenter, double-dummy, 22-week trial of levodopa/carbidopa ER to levodopa/carbidopa IR in patients with advanced Parkinson's (n=393) found use of the extended-release product resulted in 3.9 hours of off-time during waking hours compared to 4.9 hours of off-time with immediate-release levodopa/carbidopa after dosage adjustments ($p<0.05$).[310] Levodopa/carbidopa ER also increased on-time without troublesome dyskinesia during waking hours versus baseline by 1.8 hours ($p<0.05$). The final daily dose of levodopa from the extended-release product was approximately double the final daily dosage from the immediate-release formulation.

levodopa/carbidopa (Sinemet) versus levodopa/carbidopa/entacapone (Stalevo)

The STRIDE-PD study evaluated 747 patients with PD over a period of 134 weeks.[311] In this double-blind trial, patients were randomized to levodopa/carbidopa or levodopa/carbidopa/ entacapone. The primary endpoint was time to onset of dyskinesia. The study found that patients taking levodopa/carbidopa/entacapone had a shorter time to onset and increased frequency of dyskinesia. While not significantly different, time to wearing off and motor scores did trend in favor of the levodopa/carbidopa/ entacapone group.

levodopa/carbidopa enteral suspension (Duopa) versus immediate-release levodopa/carbidopa capsules

Duopa efficacy was shown in 71 patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations with 3 hours or more of "off" time while on treatment with oral immediate-release carbidopa-levodopa and other Parkinson's disease medications in a randomized, double-blind, double-dummy, active-controlled, parallel group study.[312] Subjects were randomized to levodopa/carbidopa enteral suspension and placebo capsules, or placebo suspension and immediate-release carbidopa-levodopa capsules. Subjects in both groups had a PEG-J device inserted and suspension was infused daily over 16 hours. Efficacy was assessed by the mean change from baseline to week 12 total daily mean "Off" time normalized to a 16-hour wake period. The mean change in "Off" time from baseline was -4 hours for Duopa and -2.1 hours for immediate-release levodopa/carbidopa capsules (p=0.0015).

levodopa/carbidopa IR early-start versus delayed-start

In a double-blind, placebo-controlled, multicenter trial, 445 patients with early Parkinson's disease were randomized to receive carbidopa/levodopa 25/100 mg three times daily for 80 weeks (n=222; early-start) or placebo for 40 weeks, followed by carbidopa/levodopa 25/100 mg three times daily for 40 weeks (n=223; delayed-start).[313] The primary outcome was the difference in the mean change in UPDRS score from baseline to week 80. At week 80, the early-start difference in UPDRS score was -1 ± 13.1 points compared to the delayed-start difference of -2 ± 13 points. The difference in UPDRS scores over time between these groups, 1 point (95% CI, -1.5 to 3.5; p=0.44), was not significant. The authors determined that early-start carbidopa/levodopa did not have a disease-modifying effect on the progression of Parkinson's disease in early Parkinson's patients.

MAO-B Inhibitors

rasagiline (Azilect) versus entacapone (Comtan)

In an 18-week, double-blind, multicenter, randomized trial, the efficacy of rasagiline was compared to entacapone and placebo.[314] A total of 687 patients were randomly assigned to receive rasagiline (n=231; 1 mg once daily), entacapone (n=227; 200 mg with every levodopa dose), or placebo (n=229). The primary outcome measured was to determine the change in total daily off time, based on the intention-to-treat population. Other measures included the clinical global improvement (CGI) score and unified Parkinson's disease rating scale (UPDRS) scores, which was also based on the intention-to-treat population. Results demonstrated that both rasagiline and entacapone reduced mean daily off time (-1.18 hours for rasagiline and -1.2 hours for entacapone versus -0.4 hours for placebo; p=0.0001 and p<0.0001, respectively), and increased daily on time without troublesome dyskinesia (0.85 hours versus 0.03 hours for placebo; p=0.0005 for both). Significant mean improvements in CGI scores were recorded (-0.86 for rasagiline and -0.72 for entacapone versus -0.37 for placebo; p<0.0001 and p=0.0002, respectively). Changes in UPDRS scores also significantly improved for activities of daily living during off time (-1.71 for rasagiline and -1.38 for entacapone versus placebo; p<0.0001 and p=0.0006, respectively) and motor function during on time (-2.94 and -2.73 versus placebo; both p<0.0001). Frequency of adverse events was similar for all treatments. Eighty-eight patients (13%) who were assigned treatment did not complete the study (n=23 rasagiline, n=30 entacapone, n=35 placebo), mainly due to withdrawal of consent (n=34) and adverse events (n=34). This study demonstrated that once-daily rasagiline reduces mean daily off time and improves symptoms of PD in levodopa-treated patients with motor fluctuations but did not demonstrate superiority over entacapone.

In the Attenuation of Disease Progression with Azilect Given Once-Daily (ADAGIO) study, a placebo-controlled, double-blind, multicenter, randomized study in which 1,176 patients with untreated early Parkinson's disease were randomly assigned to receive rasagiline 1 mg (n=288) or 2 mg (n=293) per day for 72 weeks or placebo (n=593) for 36 weeks followed by rasagiline 1 mg or 2 mg for 36 weeks.[315] Of 1,176 individuals, 266 (22.6%) did not complete the full study. The primary outcome measure was the need for additional antiparkinsonian therapy and changes in non-motor experience of daily living and fatigue scales, and changes in unified Parkinson's disease rating sale (UPDRS) scores between early versus delayed treatment. UPDRS scores were evaluated at 12, 26, 48, and 72 weeks. Results indicate rasagiline 1 mg had a smaller mean increase in UPDRS from weeks 12-36, less worsening of score from baseline to week 72 in the early start group and noninferiority between the delayed start group and the early-start group from weeks 48 to 72. Rasagiline 2 mg did not meet these endpoints. In nonmotor symptoms and rates of disease progression, rasagiline 1 mg and rasagiline 2 mg, reduced the need for additional antiparkinsonian therapy. At 36 weeks, when comparing the early start group versus the delayed-start group, the UPDRS motor subscores was improved with rasagiline 1 mg (mean difference, -1.88; p<0.0001) and rasagiline 2 mg (mean difference, -0.18; p<0.0001) relative to placebo At 72 weeks, the only improvement in UPDRS subscore between the early start group and the delayed-start groups was for the activities of daily living in the rasagiline 1 mg group. (-0.62; p=0.35). Rasagiline 1 mg, a selective MAO-B inhibitor, delayed the need for symptomatic antiparkinson drugs and improved UPDRS scores to a greater extent for 72 weeks (p=0.2).

safinamide (Xadago) versus placebo

Two double-blind, placebo-controlled, multi-national, 24-week trials evaluated PD patients experiencing "off" time during treatment with carbidopa/levodopa and other PD agents.[316,317] In both studies, the primary measure of effectiveness was the change from baseline in total daily "on" time without troublesome dyskinesia. Secondary endpoints included "off" time and reduction in UPDRS Part III (motor examination). In Study 1**,** patients (n=645) were randomized to safinamide 50 mg/day (n=217), safinamide 100 mg/day (n=216), or placebo (n=212), and had at least 1 post-baseline assessment of "on" time. The breakdown of patients taking stable doses of other PD classes of medications, in addition to levodopa/decarboxylase inhibitor, were as follows: dopamine agonists (61%), COMT inhibitors (24%), anticholinergics (37%), and amantadine (14%). Use of MAO inhibitors was not allowed. The average daily dosage of levodopa was 630 mg and the mean duration of PD was about 8 years. Daily safinamide at both doses significantly increased "on" time compared to placebo (50 mg/day, p=0.0356; 100 mg, p=0.0238). The effect of safinamide 100 mg on "on" time was only slightly numerically greater than the effect of safinamide 50 mg. The time course of improvement in total daily "on" time was similar between both doses. In Study 2, patients (n=549) were randomized to safinamide 100 mg daily (n=274) or placebo (n=275) for up to 24 weeks. Patients were taking levodopa/decarboxylase inhibitor and dopamine agonists (74%), COMT inhibitors (18%), anticholinergics (17%), and amantadine (30%). Use of MAO inhibitors was prohibited. The average daily dosage of levodopa was 777 mg. The mean duration of PD was about 9 years. Daily safinamide at both doses significantly increased "on" time compared to placebo (100 mg, p<0.001).

selegiline with levodopa/decarboxylase inhibitor (DDCI) versus levodopa/DDCI versus bromocriptine

Between 1985 and 1990, 782 patients were recruited into an open pragmatic multicenter trial and were randomized to receive levodopa/decarboxylase inhibitor (DDCI), levodopa/DDCI plus selegiline, or bromocriptine.[318] The patients were followed for 10 years and results were reported from the Parkinson's Disease Research Group of the United Kingdom trial. The main endpoints evaluated were

mortality, disability, and motor complications. Other endpoints assessed health-related quality of life and mental function. The median duration of follow-up at final assessment was 14 years in the 166 (21%) surviving participants, who could be contacted. After adjustment for baseline characteristics, disability scores were better in the levodopa than in the bromocriptine arm (Webster: 16.6 versus 19.8; p=0.03; Northwestern University Disability: 34.3 versus 30, p=0.05). Physical functioning (difference 20.8; 95% confidence interval (CI), 10 to 31.6; p<0.001) and physical summary scores (difference 5.2; 95% CI, 0.7 to 9.7; p=0.03) on the 36-item Short-Form health survey were also superior on levodopa. Differences in mortality rates and prevalence of dyskinesias, motor fluctuations, and dementia were not significantly different. Results demonstrate that there were no long-term advantages in terms of reducing mortality or motor disability to initiating treatment with bromocriptine compared with levodopa in early PD. Also, bromocriptine did not sustain the initial improvement in reduced frequency of motor complications. Selegiline combined with levodopa arm was prematurely terminated after six years due to increased mortality in patients. No evidence was demonstrated of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment.

Dopamine Agonists

apomorphine (Kynmobi) versus placebo

The efficacy of apomorphine SL film was established in a randomized, double-blind, placebo-controlled, parallel-group, multicenter study (NCT02469090) in 141 patients with PD experiencing at least 2 hours of "off" time per day and predictable morning "off" episodes.[319,320] The mean duration of PD was 9 years (range, 2 to 22 years). Patients were on a stable dose of concomitant levodopa for ≥ 4 weeks prior to screening; the mean levodopa dose was 1,033 mg. Adjunct therapy included dopaminergic agonists (oral, 51%; other, 8%), monoamine oxidase B inhibitors (41%), and amantadine derivatives (21%). The baseline mean number of daily "off" episodes was 3.9 and mean duration was about 1 hour. Oral antiemetic therapy was started 3 days prior to starting apomorphine SL therapy, which could be stopped during the maintenance phase at the discretion of the investigator. Patients arrived at the study site in an "off" state; the last dose of carbidopa/levodopa and any other adjunctive PD medications was no later than midnight the night before. Apomorphine SL film was started at the study site with a dose of 10 mg and titrated to a dose that achieved a full "on" response (within 45 minutes of the dose) and was tolerated during the titration phase. If the patient tolerated the dose but did not adequately respond, the patient returned to the study site within 3 days and the dose was increased by 5 mg. The dose was titrated in this manner until a full "on" response was achieved or a maximum apomorphine dose of 35 mg was reached. A total of 32 patients (22%) discontinued therapy during the titration phase, including 12 (8.5%) due to adverse events and 11 (7.8%) due to limited or no benefit. A total of 109 patients were randomized 1:1 to receive apomorphine SL film or placebo during the maintenance phase. Patients self-administered up to 5 doses per day during maintenance. The Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part III (MDS-UPDRS III) was measured pre-dose, and at 15, 30, 45, 60, and 90 minutes post-dose. The MDS-UPDRS III is a 20-point scale to monitor signs of PD, with higher scores indicating more severe symptoms. The mean score at baseline was 43.1. The primary endpoint was the mean change from pre-dose to 30 minutes post-dose in the MDS-UPDRS III score at week 12 of the maintenance phase. Treatment with apomorphine SL film led to a least-square mean improvement in the MDS-UPDR III score of -11.1 points (95% CI, -14 to -8.2) compared to -3.5 points (95% CI, -6.1 to -0.9) with placebo (least-square mean treatment difference, -7.6 [95% CI, -11.5 to -3.7]; p=0.0002). In addition, the response rate for full response within 30 minutes at week 12, a key secondary endpoint, was significantly greater with apomorphine SL film than placebo

(35% versus 16%; p=0.043). Significant improvements in clinical global impression of improvement (CGI-I) and Patient Global Impression (PGI) of Improvement (PGI-I) at week 12 were also reported with apomorphine SL film over placebo. During the maintenance phase, adverse effects led to treatment discontinuation in 15 (28%; primarily oropharyngeal events) and 5 (9%) of patients in the apomorphine and placebo groups, respectively. One death due to myocardial infarction was reported in the apomorphine group in a patient with known cardiac risk factors.

pramipexole (Mirapex) versus levodopa

A multicenter, parallel-group, double-blind, randomized, controlled trial compared initial treatment with pramipexole and levodopa in early Parkinson disease, followed by levodopa supplementation, with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality-of-life outcomes.[321] The trial enrolled 301 patients with early Parkinson disease who required dopaminergic therapy to treat emerging disability. Subjects received 0.5 mg of pramipexole 3 times per day with levodopa placebo or 25/100 mg of carbidopa/levodopa 3 times per day with pramipexole placebo. The dosage was escalated during the first 10 weeks for patients with ongoing disability. Thereafter, investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability. Patients initially on pramipexole had a significant reduction in the risk of developing dyskinesias (25% versus 54%; p<0.001) and wearing-off (47% versus 63%; p=0.02). Patients initially receiving levodopa had a significant risk reduction for freezing (25 versus 37%; p=0.01). At the end of 2 years, disabling dyskinesias and quality of life scores were similar in both groups. The mean improvement in the total Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to 2 years was greater in the levodopa group than in the pramipexole group (p=0.003). Compared with levodopa, pramipexole was associated with more somnolence (36% versus 21%; p=0.005) and edema (42% versus 15%; p<0.001). The study concluded that initial treatment with pramipexole resulted in lower incidences of dyskinesias and wearing off compared with initial treatment with levodopa. Initial treatment with levodopa resulted in lower incidences of freezing, somnolence, and edema and provided for better symptomatic control, as measured by the UPDRS, compared with initial treatment with pramipexole. Both options resulted in similar quality of life. Levodopa and pramipexole both appear to be reasonable options as initial dopaminergic therapy for Parkinson disease, but they are associated with different efficacy and adverse effect profiles.

The CALM-PD trial evaluated the development of motor complications in subjects with early PD randomized to initial treatment with either pramipexole or levodopa.[322] A secondary finding of the trial was a higher than anticipated development or worsening of somnolence and edema and development of hallucinations. In a secondary analysis of data from the CALM-PD trial, baseline patient characteristics were evaluated for their associations with the development or worsening of somnolence and edema and the development of hallucinations using Cox proportional hazards regression models. Kaplan-Meier estimates of the 4-year incidence of the development or worsening of somnolence and edema and the development of hallucinations were 35%, 45%, and 17% of all patients, respectively. Somnolence was associated with initial pramipexole treatment, male gender, and greater than 5 systems with a comorbid illness. Edema was associated with initial pramipexole treatment, female gender, and comorbid cardiac disease. Hallucinations were associated with Mini-Mental State Examination score > 28 and greater than 5 systems with comorbid illness. Comorbid illnesses are important and overlooked risk factors for the development of somnolence, edema, and hallucinations. When initiating pramipexole therapy, patients must be monitored for somnolence and edema, and it should be realized that slight decrements in cognitive function and older age are associated with increased risk of hallucinations.

A 2-year, open-label extension of the CALM-PD trial was added to the original 4 year trial.[323] Of the 301 patients that originally participated in the 4-year study, 222 were enrolled in the open-label 2-year extension. The primary outcome was the time-weighted average of self-reported disability scores in the "on" and "off" states on the Schwab and England Activities of Daily Living (ADL) Scale at the final visit. The reported mean scores on this scale in the initial pramipexole and initial levodopa groups did not differ at 6 years (79.9 versus 82.5, respectively; p=0.19). Initial treatment with levodopa more commonly led to adverse effects, such as dopaminergic motor complications (68.4% for levodopa versus 50% for pramipexole; p=0.002), including wearing off, on-off effects, or dyskinesias, but disabling dyskinesias were uncommon in both groups. Scores on the Epworth Sleepiness Scale were significantly higher with initial pramipexole than initial levodopa (11.3 versus 8.6, respectively; p<0.001), indicating more sleepiness in the pramipexole group. Mean changes from baseline on the UPDRS were not statistically significant but did favor levodopa (0.5 for levodopa versus 2.4 for pramipexole; p=0.11). This benefit was less than had been seen in the 4-year trial.

A multicenter, parallel-group, double-blind, randomized, placebo-controlled trial evaluated the safety, tolerability, and efficacy of adjunctive pramipexole therapy in PD patients of African, Asian, or Hispanic heritage treated with levodopa.[324] One hundred forty-four PD patients of African, Asian, or Hispanic heritage enrolled from January 1997 to August 1998 and were observed until October 1998 at 17 Parkinson Study Group sites in the United States and Puerto Rico. Subjects received pramipexole 0.375 mg per day to a maximum tolerated dose ≤ 4.5 mg per day over a 6-week period or placebo, achieving optimum levels in the 4-week maintenance period. The main outcome measure was the change in the sum of the UPDRS activities of daily living and motor skills from baseline to the tenth week. Parkinsonism improved with pramipexole, UPDRS score 10.27 at 10 weeks, versus placebo, UPDRS score 6.54 at 10 weeks (p=0.012) and was similar in each group. Adverse events occurred in 85% of patients on pramipexole and 69% on placebo. Hallucinations and insomnia were more common on pramipexole than placebo (p=0.023 and p=0.045, respectively). Pramipexole is an effective adjunctive PD therapy in patients of African, Asian, or Hispanic heritage and tolerability and safety overall were similar among groups; however, differences in profiles of adverse effects and tolerability were suggested.

A randomized trial investigated the effect of therapy on HRQOL and explored factors that influenced the HRQOL profiles and subdomains.[325] A total of 301 subjects with early Parkinson's disease were randomized to either initial pramipexole or initial levodopa, and then followed every 3 months over a 4-year period. Health outcomes were estimated by using the EQ-5D and PDQUALIF, and the incremental effectiveness as the accumulated difference in the total HRQOL was calculated over time between treatments. The subgroup analyses (by sex, race, age, baseline patient characteristics, and occurrence of adverse events) were conducted using the same approach. Sensitivity analysis was performed to test the how missing data effected the results. The results indicated that all 3 HRQOL measures reported similar profiles over time characterized by initial improvement over the first 3 to 6 months, followed by a gradual decline in years 2, 3, and 4. The difference in HRQOL between the treatment arms widened in favor of pramipexole in years 3 and 4 for all HRQOL measures used (EQ-5D: Year 3 0.048, p=0.03; Year 4 0.071, p=0.04). The analyses suggested that the effect of pramipexole on HRQOL was mediated through nonmotor functions, whereas the effect of levodopa on HRQOL was mediated primarily through motor domains. These results indicate that pramipexole has an improved nonmotor effect and levodopa has an improved mobility effect, and these drugs affect the different domains to improve the patient's HRQOL differently.

ropinirole versus levodopa

A 5-year trial of ropinirole and levodopa in early PD showed that ropinirole is associated with reduced incidence of dyskinesias.[326] The *post hoc* analysis investigated whether the dyskinesia-sparing benefit of ropinirole is lost when levodopa is added to the regimen and evaluated other risk factors for developing dyskinesias. Patients receiving levodopa had a significantly higher risk of dyskinesias than those receiving ropinirole monotherapy (hazard ratio [HR], 6.67; 95% CI, 3.23 to 14.29; p<0.001). When patients randomized to ropinirole were treated with supplementary levodopa, the development of dyskinesias was not significantly different from that in those receiving levodopa from the start (HR, 0.80; 95% CI, 0.48 to 1.33; p=0.39). However, the onset of dyskinesias was delayed by approximately 3 years compared with levodopa monotherapy. The risk of developing dyskinesias during maintained initial ropinirole monotherapy is very low. Only once levodopa is added does the risk substantially change. Early use of ropinirole postpones the onset of dyskinesias, but these benefits decline when levodopa therapy is started, with no evidence of a subsequent rapid "catch-up" or a lasting preventive effect.

pramipexole (Mirapex) versus ropinirole

Sixty patients with "*de novo*" idiopathic PD were randomized into 1 of 2 dopamine agonist monotherapy groups to receive oral ropinirole at 15 mg per day or pramipexole at 2.1 mg per day.[327] Dose of the dopamine agonist could be increased in the following 2 years but levodopa could not be added until the study, designed to investigate the possible occurrence of wearing-off during dopamine agonist monotherapy, ended. Wearing-off was assessed by self-evaluation charts confirmed by a blinded observation of a 30% or greater deterioration in the UPDRS motor score. Proc Mixed and Kaplan-Meier curves evaluated treatment variables as a function of time. T-tests were used to compare *post hoc* variables reclassified according to wearing-off occurrence. Thirty patients received ropinirole and 30 patients received pramipexole therapy. Eighteen patients (30%) experienced wearing-off 15 to 21 months after beginning monotherapy with no differences observed between the treatments. Statistical evaluation gave evidence of differences between patients who experienced wearing-off and those who did not; however, UPDRS scores deteriorated similarly. Study findings provide evidence of wearing-off phenomena in patients with early PD treated with non-ergot dopamine agonist monotherapy.

ropinirole immediate-release versus ropinirole ER

Efficacy and Safety Evaluation in Parkinson's Disease (EASE-PD) monotherapy studied ropinirole ER and ropinirole immediate-release.[328] The primary outcomes measured in the study were the relationship between ropinirole systemic exposure in terms of steady-state area under the curve between time zero and 24 hours after dose ($AUC_{[0\text{-}24,ss]}$), change from baseline in UPDRS total motor score, and awake time spent "off." In EASE-PD Monotherapy, the data demonstrated that the relationship between the decrease in UPDRS motor score and $AUC_{(0\text{-}24,ss)}$ was similar for both formulations, with a 60% to 80% probability of response for the exposure range studied. In patients with early PD, similar clinical benefit was achieved at $AUC_{(0\text{-}24,ss)}$ values associated with doses of 8 to 12 mg and higher doses (up to 24 mg). The results demonstrated that the exposure-response relationship was optimized with the dose range of 8 to 12 mg, providing the most clinical benefit for the improvement in UPDRS total motor score in patients with early PD. This study, however, did not demonstrate superiority of either the immediate-release or extended-release form of ropinirole.

pramipexole (Mirapex) versus pramipexole ER (Mirapex ER)

A randomized, double-blind, placebo-controlled, multicenter trial compared extended-release pramipexole, immediate-release pramipexole, and placebo in patients diagnosed with early PD.[329] Patients were initiated at 0.375 mg daily, followed by a flexible titration up to 4.5 mg daily, based on efficacy and tolerability. Patients on levodopa therapy at the outset of the trial were excluded, but levodopa was allowed as a rescue medication. Stable doses of MAO-B inhibitors, anticholinergics, or amantadine were allowed. The primary efficacy endpoint was the change from baseline in Parts II + III of the UPDRS after 18 weeks of treatment. Patients receiving extended-release pramipexole experienced a change of -8.1 points versus -5.1 points with placebo ($p<0.03$).

rotigotine (Neupro) versus ropinirole and placebo

A multicenter, double-blind, multinational, randomized, double-dummy, placebo- and ropinirole-controlled study in patients with early stages of PD with 561 patients randomized in a 2:2:1 ratio to receive either rotigotine, ropinirole, or placebo.[330] Under the double-dummy design, each patient took capsules (either placebo or active) and applied a patch (placebo or active) each day. Patients with ropinirole were titrated in a 13-week period to reach maximum dose of 24 mg/24 hours while patients with rotigotine used a 4-week titration schedule to reach a maximum dose of 8 mg/24 hours. Once a patient and investigator agreed about the optimal dose reached, the patient was then maintained on that dose throughout the 24-week maintenance period. The primary efficacy variable was the proportion of patients who responded to treatment. A "responder" was defined as a patient with a 20% or greater decrease in UPDRS Parts II + Parts III (motor) scores from the original baseline visit to the end of the double-blind maintenance period. A secondary efficacy variable includes absolute change in UPDRS II + III scores from the baseline visit to the end of the double-blind maintenance period, changes in UPDRS Part II and Part III subscale scores, and demonstration of noninferiority to ropinirole. Safety and tolerability were assessed by adverse events as reported by the patient or observed by the investigator. Dose-to-dose comparison was made from those receiving ropinirole less than 12 mg/day compared to rotigotine less than 8 mg/day. A total of 215 patients were assigned to rotigotine patch, 228 to oral ropinirole, and 118 to placebo. A total of 409 patients completed the study with 53 withdrawing from the ropinirole group, 62 withdrawing from the rotigotine group, and 33 withdrawing from the placebo group. The primary endpoint indicated treatment with rotigotine resulted in a higher proportion of responders (52%) compared with placebo (30%); $p<0.0001$. The ropinirole group proportion of responders (68%) when compared to placebo. In addition, other efficacy endpoints show significant improvement in absolute UPDRS Parts II + III subtotal score observed for patients in both the rotigotine and ropinirole mean decrease from baseline. For rotigotine, the mean decrease was -7.2 standard deviation (SD) (± 9.9) versus placebo -2.2 (SD ± 10.2) while ropinirole means decrease was -11 (SD ± 10.5) ($p<0.0001$). Common adverse events in the rotigotine group were application site reactions (17%), nausea (13%), dizziness (7%), and vomiting (6%). Adverse events in the ropinirole group were nausea (16%), somnolence (12%), dizziness (8%), and vomiting (5%). Placebo group adverse events include nausea (14%), somnolence (17%), and dizziness (9%). Serious adverse events (SAE) were reported in 8%, 10%, and 13% receiving placebo, rotigotine-treated, and ropinirole-treated patients, respectively. Approximately 5% of patients receiving placebo, 17% of rotigotine-treated patients, and 13% of ropinirole-treated patients reported adverse events leading to discontinuation. As a result, the trial demonstrated that transdermal rotigotine is safe and effective. The study reported 92% of rotigotine users were at the maximal doses whereas 26% of ropinirole users were at maximum dose.

rotigotine (Neupro) and placebo

A multicenter, double-blind, randomized study was performed with 277 patients with early-stage idiopathic PD for 6 months.[331] Patients were randomized to either rotigotine or placebo in a 2:1 ratio. Starting dose was 2 mg/24hours and titrated weekly to effective dose or 6 mg/24hours patch and maintained for 6 months. Primary efficacy measures were the change in the UPDRS scores (part II and III) from baseline to end of treatment and responder rates (patients with ≥ 20% improvement). The mean decrease in UPDRS subtotal scores was 3.98 (± 0.707) points lower those receiving placebo (p<0.0001). UPDRS part III was -3.50 (± 7.26) which contributed the most to the UPDRS improvement. The rotigotine group also had more responders than placebo group (48% versus 19%; p<0.0001). A total of 78% of the rotigotine group (n=142) completed the trial versus 84% of the placebo group (n=81). Adverse events were noted to be generally mild to moderate. The most commonly reported treatment emergent adverse event included application site reaction, nausea, somnolence, dizziness, and headache. The study observed significant differences between the rotigotine group and placebo with relative well tolerance to the medication. At the conclusion of the study, study participants were offered the opportunity to enroll in a prospective, open-label study for up to 6 years at optimal dose (up to 16 mg/24 h).[332] Adjunctive levodopa was allowed. Results from the 6-year longitudinal study indicate the medication was well tolerated for up to 6-years and that adverse effects reported were similar to those observed in shorter studies.

The PREFER study looked at advanced PD with its major treatment challenge to reduce "off" time. The "off" time is defined as a period in the day where the medication the patient is on no longer controls their symptoms. PREFER was a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 2 transdermal doses of rotigotine in subjects with advanced PD with ≥ 2.5 hours of daily "off" time.[333] Patients (n=351) were randomized to placebo patches (n=120), rotigotine 8 mg/24hours patches (n=120), or rotigotine 12 mg/24hours patches (n=111). The primary efficacy endpoint was the absolute number of daily hours in the "off" state. A secondary endpoint was the percentage of subjects achieving ≥ 30% response in absolute time spent "off" from baseline. In the rotigotine 8 mg/24hours group, the absolute change in daily "off" between baseline and the end of the maintenance phase averaged -2.7 hours (95% CI, -2.1 to -3.4; p<0.0001). The 12 mg/24hours group averaged -2.1 hours (95% CI, -1.5to -2.8; p=0.0031) versus the placebo group averaging -0.9 hours (95% CI, -0.32 to -1.51). *Post hoc* analysis concluded the difference in decrease between the 8 mg/24hours group and the 12 mg/24 hours group was not significant. The reviewers' note the secondary endpoints show that the 8 mg/24 hours and the 12mg/24 hours group had a higher proportion of subjects with a ≥ 30% decrease in absolute "off" time at 56.6% and 55.1%, respectively.

The RECOVER study is a double-blind, placebo-controlled trial, where 287 subjects with unsatisfactorily early morning motor symptom control were randomized in a 2:1 ratio to receive rotigotine or placebo.[334] Efficacy end points was improvement from baseline to end of maintenance in UPDRS Part III as -3.55 (95% CI, -5.37 to -1.73; p-0.00002) and -4.26 (95% CI, -6.08 to -2.45; p<0.0001). The reviewers' note the study results show clinically significant improvement with the use of rotigotine for early morning motor impairment and nocturnal sleep disturbance.

rotigotine versus pramipexole

In another double-blind, double-dummy randomized study to evaluate the wearing off type motor fluctuations seen in advanced PD, a controlled trial study (CLEOPATRA-PD) with 506 patients was randomized into rotigotine (up to 16 mg/24 h), pramipexole (4.5 mg/day), or placebo for 6 months.[335]

Mean absolute change in off time from baseline compared with placebo was -1.58 hours (95% CI, -2.27 to -0.9; p<0.0001) for rotigotine and -1.94 hours (95% CI, -2.63 to -1.25; p<0.0001) for pramipexole. The reviewers' note these results show rotigotine and pramipexole were equally efficacious for change in absolute off time from baseline. Responder rates for pramipexole were slightly improved over rotigotine at 67% versus 59.7% while placebo was at 35%. Both drugs were well tolerated and had similar adverse effect profiles.

COMT Inhibitors

entacapone (Comtan) versus tolcapone (Tasmar)

A multicenter, double-blind, randomized, active-control trial involving 150 patients with advanced, fluctuating PD examined the efficacy and safety of replacing entacapone with tolcapone.[336] Patients receiving entacapone at least 15 or more days were randomly assigned to continue entacapone (n=75) or switch to tolcapone (n=75) and were followed for 3 weeks. Efficacy measures included changes in on time (without disabling dyskinesia) and an investigator's global assessment (IGA). The on time increased by greater than or equal to 1 hour per day (primary efficacy measure) in 43% of entacapone-treated patients and 53% of tolcapone-treated patients, and by greater than or equal to 3 hours per day in 13% and 25%, respectively. The IGA indicated moderate to marked improvements in 25% of entacapone patients and 39% receiving tolcapone. Response rates (the proportion of patients with greater than or equal to 1 hour per day increase in on time and improvements on IGA) were 17% with entacapone and 32% with tolcapone. Dyskinesia was the most common adverse event affecting 29% of entacapone and 31% of tolcapone recipients. One patient in each group had elevated liver enzymes, resulting in treatment withdrawal (levels returned to normal thereafter in both cases). Tolcapone did offer increased on time in more patients than the entacapone and also demonstrated moderate to marked improvements in more patients than the entacapone per the IGA. Statistical analysis was not reported to substantiate the statistical significance of the data, but tolcapone was clinically more efficacious in this patient population.

opicapone (Ongentys) versus placebo (with and without an active comparator)

The efficacy of opicapone as adjunctive treatment to levodopa/carbidopa in PD patients experiencing "off" episodes was evaluated in 2 randomized, double-blind, parallel-group, placebo- and active-controlled (BIPARK-1), or placebo-controlled (BIPARK-2) trials.[337,338] Eligible patients must have experienced symptoms of "off" episodes for a minimum of 4 weeks, with average total daily "off" time while awake of at least 1.5 hours. In BIPARK-1, patients aged 30 to 83 years (n=600) were randomized 1:1:1:1:1 to receive opicapone (5 mg, 25 mg, or 50 mg once daily), placebo, or entacapone (200 mg with each levodopa dose). The primary endpoint was change from baseline in absolute time in the "off" state, based on 24-hour patient diaries. Treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline versus placebo, -60.8 min; 95% CI, -97.2 to -24.4; p=0.0015) and non-inferior to entacapone (mean difference in change from baseline, -26.2 min; 95% CI, -63.8 to 11.4; p=0.0051). Treatment with opicapone 5 mg (p=0.056) or 25 mg (p=0.08) did not significantly differ from placebo. In BIPARK-2, patients aged 30 to 83 years (n=427) were randomized 1:1:1 to receive opicapone 25 mg or 50 mg once daily or placebo for 14 to 15 weeks followed by a 1-year open-label phase when all patients received treatment with opicapone. The primary endpoint was change from baseline in absolute time in the "off" state, based on 24-hour patient diaries. Treatment with opicapone 50 mg was superior to placebo (adjusted treatment difference from baseline versus placebo, -54.3 min; 95% CI, -96.2 to -12.4; p=0.008). Treatment with opicapone 25 mg did not significantly differ from placebo (adjusted

treatment difference from baseline versus placebo, -37.2 min; 95% CI, -80.8 to 6.4; p=0.11). The off-time reduction was sustained throughout the open-label phase (−126.3 minutes at 1 year open-label endpoint).

entacapone (Comtan) versus rasagiline (Azilect)

In the LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) trial, 687 patients were randomized in double-blind fashion to receive entacapone, rasagiline, or placebo for 18 weeks.[339] Between 85% and 90% of patients in each group completed the study. Total daily off time decreased by 21% (1.2 hours) with both active treatments compared to 7% (0.4 hours) with placebo (p<0.0001 for both comparisons to placebo). This was associated with a 0.9-hour increase in on time in the active treatment groups compared to a 0.03-hour increase with placebo (p=0.0005). Compared to placebo, entacapone and rasagiline significantly improved UPDRS ADL off time (p=0.0006 and p<0.0001, respectively), UPDRS motor function during on time (p<0.0001 for both agents), and CGI scores (p=0.0002 and p<0.0001, respectively). There was no between-group difference in the incidence of dyskinesia (approximately 5% in each group).

NMDA-Type

amantadine extended-release capsules (Gocovri) versus placebo

The safety and efficacy of amantadine ER capsules was evaluated in 2 randomized, double-blind, placebo-controlled trials in the treatment of dyskinesia in patients with Parkinson's disease with at least one hour of dyskinesia during the day and mild functional impairment due to dyskinesia.[340,341] The primary endpoint in both studies was the change in Unified Dyskinesia Rating Scale (UDysRS) total score between baseline and week 12. The mean baseline UDysRS score was 40.1 (range: 8-76) and patients had a mean daily "on" time of 8.4 hours (range 0-15.3) and "off" time of 2.8 hours (range: 0-9.5). All patients were receiving a stable dose of levodopa as monotherapy (32%), or in combination with dopamine agonists (54%) and/or MAO-B inhibitors (44%). At week 12, the UDysRS score was significantly lower in the Gocovri 274 mg group (n= 63) compared to placebo (n=58) in Study 1 (treatment difference -7.9; p=0.0009). Study 2 also demonstrated a significant reduction from baseline of the UDysRS score in the Gocovri 274 mg group (n = 37) compared to placebo (n=38) at week 12 (treatment difference -14.4; p<0.0001). In both studies, there was a significant increase in "on" time for patients (study 1 treatment difference 2.7 hours (p<0.0001); study 2 treatment difference 1.9 hours (p=0.0168)) and a decrease in "off" time (study 1 treatment difference -0.9 hours (p=0.0171); study 2 treatment difference -1.1 hours (p=0.0199) between baseline and week 12 comparing placebo to the treatment group.

Adenosine Receptor Antagonist

istradefylline (Nourianz) versus placebo

Four multicenter, randomized, double-blind studies were conducted to evaluate the safety and efficacy of istradefylline compared to placebo for adjunctive treatment to carbidopa/levodopa in patients (n=1,143) with Parkinson's disease experiencing "off" episodes.[342] The primary efficacy endpoint was the change from baseline in daily awake "off" time during the 12 week studies based on 24-hour patient diaries. The secondary endpoint was the change from baseline in "on" time without dyskinesia. Patients enrolled in the studies had Parkinson's disease that was Hoehn and Yahr Stage II to IV and experienced at least 2 hours (mean, 6 hours) of "off" time daily on levodopa for at least a year with a stable dose for at least 4 weeks prior to screening (daily range, 416 mg to 785 mg). In studies 1 and 2, conducted in the US and Canada, patients treated with istradefylline 20 mg experienced 4.57% (p=0.025) fewer hours of

"off" time compared to baseline and patients treated with istradefylline 40 mg experienced 6.78% (p=0.007) fewer hours of "off" time compared to baseline. These were statistically significant changes from baseline compared with placebo. Also compared to placebo, patients experienced nominal additional "on" time without troublesome dyskinesia compared to baseline at 20 mg daily (0.55 hours [p=0.135]) and 40 mg (0.96 hours [p=0.026). Studies 3 and 4, completed in Japan, shared similar results with fewer hours of "off" time compared to placebo for 20 mg (-0.65 hours [p=0.028] and -0.76 hours [p=0.006], respectively) and 40 mg (-0.92 hours [p=0.002] and -0.74 hours [p=0.008], respectively).

Restless Leg Syndrome (RLS)

pramipexole (Mirapex) versus placebo

In a double-blind study, 339 patients (ages 18 to 80 years) with RLS were randomized to receive placebo or pramipexole 0.25, 0.5 or 0.75 mg daily for 12 weeks.[343] At the end of the study, the mean score on the International Restless Legs Scale (IRLS) change from baseline, the primary endpoint, was greater in patients receiving each dose of pramipexole than in those receiving placebo (all doses p<0.01); there was no significant difference between the 3 pramipexole dosages. Response, defined as a CGI-I score that was "much improved" or "very much improved," occurred in 72% of patients receiving pramipexole and 51.2% of patients receiving placebo.

A 6-week, randomized, placebo-controlled study evaluated the efficacy of pramipexole versus placebo in RLS.[344] Initially 345 patients were randomly assigned in a 1:2 ratio to receive either placebo (n=115) or pramipexole (n=230). The patient demographics and baseline characteristics were comparable between treatment groups. Initial dose of pramipexole was 0.125mg per day and was optimized using the PGI assessment to a maximum of 0.75 mg per day if necessary. The primary endpoints evaluated at week 6 were the change from baseline in the IRLS score and the proportion of patients reporting "much to very much improved" results with CGI-Improvement (CGI-I) assessments. Secondary endpoints assessed PGI and IRLS responder rates. At baseline, mean IRLS scores were 24.9 for placebo and 24.7 for pramipexole, indicating severely affected patients. After 6 weeks, adjusted mean reductions in IRLS score were 5.7 ± 0.9 for placebo (median dose 0.47 mg/day) and 12.3 ± 0.6 for pramipexole (median dose 0.35 mg/day) (p<0.0001). CGI-I responder rates were 32.5% for placebo and 62.9% for pramipexole (p<0.0001). For all secondary endpoints, pramipexole showed superior results. Pramipexole was well tolerated throughout the study.

A 12-week, randomized, placebo-controlled study evaluated the ability of pramipexole to improve sleep and decrease RLS symptoms.[345] Adults with moderate or severe RLS were randomized to receive placebo or pramipexole, which was flexibly titrated from 0.25 to 0.75 mg, 2 to 3 hours before bedtime. The primary outcome measures were changes in Medical Outcomes Study (MOS) sleep disturbance score and IRLS score at 12 weeks. The intent-to-treat population included 357 patients; 178 patients received pramipexole and 179 patients received placebo. At 12 weeks, the adjusted mean change from baseline was greater for pramipexole versus placebo for IRLS score (-13.4 ± 0.7 versus -9.6 ± 0.7, respectively) and MOS sleep disturbance score (-25.3 ± 1.5 versus -16.8 ± 1.5, respectively; p≤0.0001). Responder rates for CGI, PGI, and IRLS were also higher in the pramipexole group. RLS-QOL score was improved over placebo at week 12 (p<0.01) as were MOS sleep adequacy (p=0.0008) and quantity (p=0.08) scores. Nine percent of patients in each group withdrew because of adverse events.

A 3-week, randomized, double-blind, placebo-controlled, dose-finding study was performed in patients with moderate to severe RLS.[346] Patients (n=109) were randomized to receive between 0.125 to 0.75 mg per day of pramipexole or placebo. Polysomnographic (PSG) measures were taken along with patient

and clinician ratings to evaluate the effectiveness of various doses on RLS. Results demonstrated that the periodic limb movements during time in bed index (PLMI) decreased significantly in each pramipexole dose group (adjusted mean difference in log-transformed data: 0.125 mg, -1.54; 0.25 mg, -1.93; 0.5 mg, -1.89; and 0.75 mg, -1.52; p<0.0001). Also, the IRLS scores were significantly reduced in all doses, with the greatest adjusted mean reduction in the 0.5 mg group (-17.01). All doses, except the lowest pramipexole dose, demonstrated a higher percentage of responders (≥ 50% reduction of IRLS score) than for placebo (61.9% to 77.3%, versus 33.3%). In the pramipexole groups, 50% to 77.3% of patients rated their condition as "much better" or "very much better," compared with 38.1% of patients in the placebo group (p=0.0139 for the 0.5 mg dose). CGI scale ratings of "much improved" or "very much improved" were given to 61.9% to 86.4% of patients in the pramipexole groups, compared with 42.9% in the placebo group (p<0.05 for the 0.25 mg, 0.5 mg, and 0.75 mg groups). Pramipexole was well tolerated and did not produce somnolence at any dose.

ropinirole versus placebo

In a 12-week, double-blind, placebo-controlled, flexible-dose study, 381 patients were randomized to ropinirole (0.25 to 4 mg as needed and tolerated, once daily, 1 to 3 hours before bedtime) or placebo.[347] Significant treatment differences favoring ropinirole, compared with placebo, were observed for change in IRLS total score at week 12 (p<0.001), the primary endpoint, as well as for improvement in CGI-I at weeks 1 and 12. Ropinirole was associated with significantly greater improvements in subjective measures of sleep disturbance, quantity, and adequacy, as well as quality of life and anxiety. Although treatment differences favoring ropinirole in daytime somnolence were observed, they were not statistically significant (p=0.1). Ropinirole was generally well tolerated, with an adverse event profile consistent with other dopamine agonists.

In a double-blinded, placebo-controlled, parallel-group study, 65 patients with RLS and periodic leg movements in sleep (PLMS) were randomized to ropinirole (0.25 to 4 mg per day) or placebo for 12 weeks.[348] In the study, PLMS per hour decreased more with ropinirole (48.5 to 11.8), compared with placebo (35.7 to 34.2) (p<0.0001). Periodic limb movements with arousal per hour decreased from 7 to 2.5 with ropinirole but increased from 4.2 to 6 with placebo (p=0.0096). Periodic limb movements while awake per hour decreased from 56.5 to 23.6 with ropinirole but increased from 46.6 to 56.1 with placebo (p<0.0001). Ropinirole treatment significantly improved patients' ability to initiate sleep (p<0.05) and the amount of Stage 2 sleep (p<0.001) compared with placebo. There were no significant differences between groups in total sleep time and sleep efficiency. Sleep adequacy, measured subjectively, was significantly improved with ropinirole treatment (p=0.032). In contrast, the placebo group showed a greater increase in Stage 3/4 sleep (p<0.01). No serious adverse events occurred in either group. The study concluded that ropinirole is effective in the treatment of both the sleep and waking symptoms of RLS.

A 36-week study investigated the long-term efficacy of ropinirole in patients with RLS and evaluated the potential for relapse after discontinuation of active treatment.[349] Patients with primary RLS (n=202) received single-blind ropinirole for 24 weeks, and after meeting treatment continuation criteria were randomized for an additional 12 weeks to double-blind treatment with ropinirole or placebo. The primary efficacy measure was the proportion of patients relapsing during double-blind treatment. Additional efficacy measures included time to relapse, withdrawals due to lack of efficacy, improvement on the CGI-I scale, change in IRLS score during double-blind treatment, and changes in sleep and QOL parameters. Significantly fewer patients relapsed on ropinirole (32.6%) versus placebo (57.8%) (p=0.0156). Time to relapse was longer with ropinirole, and more patients on placebo withdrew from

the study due to lack of efficacy. Patients showed improvements in IRLS and CGI-I scores, sleep, and QOL parameters with single-blind ropinirole. These efficacy measures were better maintained during the double-blind phase with ropinirole but reduced with placebo. Ropinirole was well tolerated, and adverse events were typical for dopamine agonists.

In a double-blind, randomized, 12-week study, 267 patients with moderate to severe RLS were randomly assigned to ropinirole (0.25 to 4 mg/day) or placebo, 1 to 3 hours before bedtime.[350] Improvements were significantly greater for ropinirole than placebo for the primary endpoint; the change in IRLS score at week 12 (p=0.02). Ropinirole was also superior to placebo in showing improvement of CGI-I, as well as sleep and quality of life parameters.

rotigotine (Neupro) versus placebo

In a randomized, double-blind, placebo-controlled weekly dose efficacy trial, 458 patients with moderate to severe idiopathic RLS were randomly assigned to transdermal rotigotine 1 mg/24 h, rotigotine 2 mg/24 h, rotigotine 3 mg/24hours or placebo for 6 months.[351] Primary outcomes were absolute change from baseline to end of maintenance in IRLS sum score and the CGI item 1 score which is defined as a 50% improvement in the respective score at the end of the maintenance versus baseline. A total of 68% of patients completed the study. The IRLS sum score and the CGI score improved during the titration phase and remained stable during the maintenance phase. All 3 strengths indicate treatment differences against placebo for RLS when measured with IRLS or CGI item 1 score (1mg/24 hr, -5.1; 2 mg/24 hr, -7.7; 3 mg/24 h, -8.2 [p<0.0001]). Rotigotine efficacy increases with increasing dose from 1 mg to 3 mg.[352] The long-term efficacy of rotigotine up to 4 mg/24hours in the treatment of RLS (n=295) was assessed in a 5-year study (OLE trial). The study found that efficacy was maintained for up to 5 years at a level consistent with the initial 6-week double-blind trial.[353]

A randomized, double-blinded, placebo-controlled trial assessed efficacy and safety of rotigotine in the treatment of idiopathic RLS over a 6-month maintenance period.[354] Patients (n=505) were randomly assigned to 5 groups to receive either placebo or rotigotine (0.5, 1, 2, or 3 mg/24 h) delivered by once-daily transdermal patch. The 2 co-primary efficacy parameters decreased from baseline to end of maintenance in IRLS sum score and in CGI-1 score. On both primary measures, 2 and 3 mg/24 hours rotigotine was superior to placebo (p<0.001). Adjusted treatment differences to placebo for the IRLS sum score were -4.5 (95% CI, -6.9 to -2.2) for 2 mg/24 hours rotigotine, -5.2 (95% CI, -7.5 to -2.9) for 3 mg/24 hours rotigotine, and for CGI item 1 -0.65 (95% CI, -1 to -0.3) and -0.9 (95% CI, -1.3 to -0.5) for the 2 and 3 mg/24 hours doses, respectively. Skin reactions (27%) and dopaminergic side effects, such as nausea (18.1%) and headache (11.6%), were mostly mild or moderate in rotigotine. Rotigotine transdermal patches releasing 2 to 3 mg/24 hours significantly reduced the severity of RLS symptoms. Treatment efficacy was maintained throughout the 6-month double-blind period.

gabapentin enacarbil (Horizant) versus placebo

A 12-week double-blind, placebo-controlled study randomized subjects (n=325) (1:1:1) to gabapentin enacarbil 1,200 mg (n=113), gabapentin enacarbil 600 mg (n=115), or placebo (n=97).[355] The mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders rated “very much” or “much” improved on the CGI-I at week 12 were the co-primary endpoints. A total of 42 patients withdrew from the study prior to completion with 79% in placebo (n=77); 87% in gabapentin enacarbil 1,200 mg (n=98); and 90% in gabapentin enacarbil 600 mg (n= 104) completing the study. Gabapentin enacarbil 1,200 mg mean had a IRLS total score at week 12 compared with placebo with the adjusted mean treatment difference for change from baseline of -3.5 (95% CI, -5.6 to -1.3;

p=0.0015). Gabapentin enacarbil 600 mg group had a mean IRLS total score at week 12 compared to placebo with the adjusted mean treatment difference for change from baseline of -4.3 (95% CI, 6.4 to -2.3; p<0.0001). On the CGI-I ratings where responders rated "much" or "very much" at week 12, the adjusted odds ratio for gabapentin enacarbil 1,200 mg is 4.3 (95% CI, 2.34 to 7.86; p<0.0001) and gabapentin enacarbil 600 mg 3.3 (95% CI, 1.84 to 5.99; p<0.0001. The most commonly reported treatment-emergent adverse events overall with gabapentin enacarbil 1,200 mg and 600 mg were dizziness and somnolence. Statistically significant differences (p<0.05) were also observed in another 12-week randomized, double-blind, placebo-controlled study (n=220) between gabapentin enacarbil 1,200 mg and placebo at 12 weeks for both the mean change from baseline in the IRLS Scale total score and the proportion of responders ("much improved" or "very much improved") on the CGI-I Scale.[356,357]

SUMMARY

Parkinson's Disease (PD)

Although dopamine agonists are effective adjuncts to levodopa in patients who begin to experience motor complications with levodopa, evidence suggests preferably using these agents as initial symptomatic therapy to reduce the risk for development of these motor complications. When used in early PD, dopamine agonists indicated for monotherapy, such as pramipexole (Mirapex, Mirapex ER), ropinirole, and rotigotine (Neupro), delay the need for levodopa treatment and its adverse effects. In general, monotherapy with these dopamine agonists is effective in a majority of patients for 1 year or less. A minority of patients may obtain benefits for periods as long as 3 years or more. In advanced disease, dopamine agonists increase "on" time and allow decreases in levodopa dose. Pramipexole and rotigotine may reduce the risk of development of dyskinesias compared to levodopa. Ropinirole ER, ropinirole, and rotigotine demonstrated similar efficacy and safety in Unified Parkinson Disease Rating Scale (UPDRS) motor scores in clinical trials. All the dopamine agonists reported mild to moderate adverse effects. Amantadine is likely efficacious as monotherapy and adjunctive therapy to levodopa and may be useful for the treatment of dyskinesia. Additional studies of amantadine ER capsules (Gocovri) have supported the addition to levodopa to decrease dyskinesia and improve daily "on" and "off" times; Gocovri is also FDA-approved as adjunctive treatment to levodopa/carbidopa in patients experiencing "off" episodes. Apomorphine sublingual film (Kynmobi) is also approved for the treatment of "off" episodes of PD.

Dopamine agonists do not treat all features of PD, such as freezing, postural instability, autonomic dysfunction, and dementia, nor have they been shown to stop disease progression. Dopamine agonists are associated with neuropsychiatric, sedative, and other agonist-specific side effects, such as hallucination, symptomatic hypotension, and psychosis. The non-ergot dopamine agonists, pramipexole, ropinirole, and rotigotine, might be better tolerated and cause fewer serious side effects than the older ergot agents, such as bromocriptine (Parlodel). The risk of hypotension and somnolence appears to be higher with ropinirole than with pramipexole, while pramipexole appears to have a higher risk of hallucinations than ropinirole. Pramipexole and ropinirole carry bolded type warnings as patients report falling asleep while engaged in the activities of daily living, although all antiparkinson's agents now carry a class warning regarding the risk of "sleep attacks." Rotigotine is a dopamine agonist in a topical patch formulation which provides drug in a continuous delivery.

Levodopa/carbidopa (Dhivy, Duopa, Sinemet, Rytary), with or without a COMT inhibitor, should be added when dopamine agonist monotherapy no longer provides adequate control of the patient's symptoms. Treatment with levodopa/carbidopa benefits virtually all patients with PD. Although effective

for the treatment of PD, levodopa/carbidopa is associated with motor fluctuations (wearing off, on-off phenomenon, dose failures, freezing episodes) and dyskinesia (peak-dose, diphasic, dystonic), especially problematic in patients with young-onset PD. Administration of levodopa/carbidopa directly into the small intestine limits the impact of gastric emptying on its absorption and allows for relatively constant plasma concentrations of levodopa; potentially resulting in less motor fluctuations and dyskinesias. In patients with significant on-off phenomenon levodopa/carbidopa enteral formulation (Duopa) may be a consideration but it requires insertion of a PEG-J device and infusion over 16 hours thus limiting use. In addition, efficacy has only been compared to immediate-release suspension and not controlled/extended-release formulations which might have less problems with on-off phenomenon. Levodopa in combination with carbidopa is available in both immediate-release and controlled/extended-release formulations and an enteral suspension. Levodopa/carbidopa should be titrated up slowly to avoid side effects such as nausea, vomiting, and hypotension. Inhaled levodopa (Inbrija) is another option for the intermittent treatment of "off" episodes in patients who are being treated with carbidopa/levodopa. Patients may inhale the contents of 2 capsules up to 5 times daily based on the individual need for additional "off" episode control.

Istradefylline (Nourianz), an adenosine receptor antagonist, is an additional adjunctive treatment option to levodopa/carbidopa to decrease "off" episodes. Clinical trial experience with istradefylline use in combination with levodopa/carbidopa allowed patients to continue use of additional adjunctive medications targeting different symptoms and mechanisms of action. Metabolic drug interactions and smoking history should be considered when istradefylline is added to other medications.

Selegiline (Zelapar) has been used historically as a neuroprotective agent. After a review of the literature, the American Academy of Neurology reported that selegiline has a mild symptomatic benefit, but clinical evidence for neuroprotective benefit is nonexistent. Because orally disintegrating selegiline tablets avoid the first pass effect, clinical effectiveness can be achieved at lower doses than with conventional selegiline tablets, and results in lower concentrations of amphetamine metabolites. When used as an adjunct to levodopa, rasagiline (Azilect), safinamide (Xadago), and selegiline reduce motor fluctuations and increase "on" time; they also have levodopa-sparing effect. Rasagiline has an indication for monotherapy of PD. Based on the evidence, rasagiline would appear to be most effective in early PD. Unlike selegiline, rasagiline is an aminoindan derivative with no amphetamine metabolites. Safinamide has only been compared to placebo in clinical trials.

The COMT inhibitors, tolcapone (Tasmar), opicapone (Ongentys), and entacapone (Comtan), as adjunctive therapy to levodopa provide another therapeutic option for patients with advanced PD. These agents are easy to administer and require no dosage titration. The COMT inhibitors prolong the half-life and duration of action of levodopa and allow for a reduction in levodopa dose. They provide relief from the end-of-dose wearing-off phenomenon seen with levodopa. COMT inhibitors may reduce the risk for motor complications if used from the onset of levodopa therapy and have been shown to improve motor and ADL scores in stable levodopa responders. Side effects of COMT inhibitors include dyskinesia (due to increased dopamine), nausea, vomiting, diarrhea, hypotension, and neuropsychiatric problems. Tolcapone use is limited by its potential to cause liver injury.

Anticholinergics have some antiparkinsonian efficacy, particularly with respect to tremor, but they are relatively ineffective for the more disabling features of PD. They are also associated with muscarinic and cognitive side effects and may be associated with withdrawal effects.

Restless Leg Syndrome (RLS)

Pharmacologic treatments have been used to alleviate symptom severity and improve quality of life. Historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants, iron replacement, and dopaminergic agents but newer studies suggest that RLS is associated with the dopamine system and depletion of iron stores.

The 2012 American Academy of Sleep Medicine RLS practice guidelines recommend pramipexole, ropinirole and the extended-release gabapentin prodrug, gabapentin enacarbil for RLS. Gabapentin enacarbil is associated with significant sedation/dizziness. Rotigotine (Neupro) is a dopamine agonist formulated in patch form as once-daily dosing is effective for moderate to severe RLS.

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