Antiparkinson's Agents Review

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FDA-Approved Indications

Therapeutic Class	Drug	Manufacturer	Parkinson's Disease	Drug-induced EPS	RLS
Anticholinergics	benztropine (Cogentin®)[1]	generic	X	X except TD	
	procyclidine (Kemadrin®)[2]	Monarch	X	X	
	trihexyphenidyl (Artane®)[3]	generic	X	X	
Dopamine precursor / dopa decarboxylase inhibitor	levodopa/carbidopa (Sinemet®, Sinemet® CR)[4]	generic	X		
	levodopa/carbidopa (Parcopa™)	Schwarz	X		
MAO-B inhibitors	rasagiline (Azilect®)[5]	Teva Neuroscience	X		
	selegiline (Eldepryl®)[6]	generic	X (only as adjunct to levodopa/carbidopa)		
	selegiline (Zelapar™)[7]	Valeant	X (only as adjunct to levodopa/carbidopa)		
Dopamine agonists	bromocriptine (Parlodel®)[8]	Novartis	X (only as adjunct to levodopa/carbidopa)		
	pramipexole (Mirapex®)[9]	Boehringer Ingelheim	X		X
	ropinirole (Requip®)[10]	generic	X		X
	ropinirole (Requip® XL)[11]	GSK	X		
	rotigotine (Neupro®)[12]	Schwarz	X		
COMT inhibitors	entacapone (Comtan®)[13]	Novartis	X (only as adjunct to levodopa/carbidopa)		
	tolcapone (Tasmar®)[14]	Valeant	X (only as adjunct to levodopa/carbidopa)		
Dopamine precursor / dopa decarboxylase inhibitor / COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo®)[15]	Novartis	X		

EPS = extrapyramidal symptoms
RLS = restless legs syndrome
TD = tardive dyskinesia

Because of its effects on heart valves, the FDA withdrew pergolide from the market in March 2007. Monarch announced in June 2008 that they would discontinue the manufacturing of Kemadrin.

Overview

PARKINSONISM

Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity.[16] This disease affects more than 1.5 million Americans older than 50 years of age with the incidence increasing significantly with age.[17] The term "parkinsonism" describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait problems.[18] 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.[19] 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.[20]

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.[21] As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments.[22] It is generally recommended that medication regimens be kept as simple as possible since the risk of adverse effects is generally lower when one or two agents are used at higher doses than when multiple drugs are used at lower doses.[23]

Anticholinergics were the first and, for a time, most effective treatments for PD. Anticholinergics 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.[24,25]

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 [BBB]). Combination of levodopa with carbidopa, a peripheral dopa decarboxylase inhibitor that does not cross the BBB, 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.[26] 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.[27,28,29,30] Additionally, as PD progresses, patients develop symptoms that do not respond well to levodopa therapy, including freezing episodes, autonomic dysfunction, falling, and dementia.

Rasagiline (Azilect) and selegiline (Eldepryl, Zelapar), highly selective inhibitors of monoamine oxidase B (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 three 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. Both agents are approved for use as adjunct to levodopa in later stage disease because they can increase the percent of "on" time in advanced PD patients. Rasagiline is also approved for use as monotherapy in early PD.

Dopamine agonists [bromocriptine (Parlodel), pramipexole (Mirapex), ropinirole (Requip, Requip XL)] are often used as therapy in early PD. These agents have a levodopa-sparing effect and can reduce the frequency of "off" time. While monotherapy with pramipexole and ropinirole 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.[31] 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.[32,33] Rotigotine (Neupro), the first non-ergolinic dopamine receptor agonist to be approved by the FDA, is indicated for treatment of the signs and symptoms of early-stage idiopathic PD. The primary advantage of rotigotine is its delivery system for patients who may find challenges with oral therapy.[34] Apomorphine (Apokyn®), an injectable, non-ergot dopamine agonist has been approved for the treatment of hypomobility in advanced PD. However, it will not be considered in this review since it is an injectable product.

The addition of catechol-O-methyltransferase (COMT) inhibitors [entacapone (Comtan), tolcapone (Tasmar)] 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 are both approved as adjunct to levodopa therapy.[35] Some experts recommend the initiation of a COMT inhibitor at the onset of levodopa therapy to reduce the risk of developing motor complications.

RESTLESS LEGS SYNDROME

Restless Legs Syndrome (RLS) is a neurological disorder in which patients experience irrepressible sensations in the legs or arms while sitting or lying still. Studies suggest that RLS is associated with the dopamine system and depletion of iron stores.[36] Historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants, and dopaminergic agents. Prior to 2000, levodopa was the dopaminergic agent most studied for RLS. More recently, however, with the FDA approval of both pramipexole (Mirapex) and ropinirole (Requip) for an indication of RLS, there has been increased focus on the use of dopamine agonists in the treatment of this disorder.

Pharmacology

Therapeutic Class	Drug	Mechanism of Action
Anticholinergics	benztropine (Cogentin)	- Suppress central cholinergic activity - Inhibit the reuptake and storage of dopamine at central dopamine receptors, thereby prolonging the action of dopamine
	procyclidine (Kemadrin)	
	trihexyphenidyl (Artane)	
Dopamine precursor / dopa decarboxylase inhibitor	levodopa / carbidopa (Sinemet, Sinemet CR)	- Levodopa is the immediate precursor to dopamine - Carbidopa inhibits L-amino-acid-decarboxylase (L-AAD) and prevents the decarboxylation of levodopa
	levodopa / carbidopa (Parcopa)	
MAO-B inhibitors	rasagiline (Azilect)	- Irreversible inhibitors of monoamine oxidase (MAO) type B activity - Block dopamine breakdown - Increase dopaminergic activity - Interfere with dopamine reuptake at the synapse
	selegiline (Eldepryl)	
	selegiline (Zelapar)	
Dopamine agonists	bromocriptine (Parlodel)	- Directly stimulate the dopamine receptors in the corpus striatum
	pramipexole (Mirapex)	
	ropinirole (Requip, Requip XL)	
	rotigotine (Neupro)	- Stimulates dopamine receptors within the caudate-putamen in the brain
COMT inhibitors	entacapone (Comtan)	- Inhibit COMT (catechol-O-methyltransferase) - Prevent peripheral conversion of levodopa to 3-O-methyldopa (3OMD) - Increase plasma levodopa levels
	tolcapone (Tasmar)	
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

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
Anticholinergics				
benztropine (Cogentin)[37]	--	--	Metabolites	Mostly urine
procyclidine (Kemadrin)[38]	52-97	11.5-12.6	--	--
trihexyphenidyl (Artane)[39]	--	--	Metabolites	Urine
Dopamine precursor / dopa decarboxylase inhibitor				
levodopa/carbidopa (Sinemet, Parcopa)[40,41]	--	1.5 (levodopa)	Extensive	Urine
MAO-B inhibitors				
rasagiline (Azilect)	36	3	Two inactive metabolites	Urine: 62 Feces: 7
selegiline (Eldepryl)[42]	--	10	Three active metabolites	Urine: 45
selegiline (Zelapar)[43]	greater than conventional selegiline tablets	10	Three active metabolites – concentrations reduced three- to 10-fold compared to conventional selegiline tablets	
Dopamine agonists				
bromocriptine (Parlodel)[44]	28	15	Metabolites	Urine: 6
pramipexole (Mirapex)[45]	>90	8 (young) 12 (elderly)	--	Urine: 90
ropinirole (Requip)[46]	55	6	Inactive metabolites	Urine: >88
ropinirole (Requip XL)[47]	45-55	6	Inactive metabolites	Urine: >88
rotigotine (Neupro)[48]	--	3 (initial) 5-7 (terminal)	Inactive metabolites	Urine: 71 Feces: 11
COMT inhibitors				
entacapone (Comtan)[49]	35	2.4	Inactive metabolites	Urine: 10 Feces: 90
tolcapone (Tasmar)[50]	65	2-3	Inactive metabolites	Urine: 60 Feces: 40

The pharmacokinetics for levodopa/carbidopa/entacapone (Stalevo) are similar to the individual components of the drug.[51]

Contraindications/Warnings

A black box warning appears in the tolcapone (Tasmar) prescribing information. Three fatal cases of acute, fulminant liver failure have been reported. According to the warning, "the actual incidence of hepatocellular injury appears to be ten to 100-fold higher than the background incidence in the general population." If patients do not have a response to tolcapone in three weeks, therapy should be stopped. Patients must sign an informed consent to start therapy with tolcapone.[52]

Concomitant use of non-selective MAOI therapy with levodopa/carbidopa (Sinemet, CR) can result in hypertensive crisis; simultaneous use of these agents is contraindicated.[53]

Due to potentially fatal reactions that have occurred in patients receiving MAO inhibitors concomitantly with meperidine, the use of rasagiline (Azilect) and selegiline (Eldepryl, Zelapar) with meperidine is contraindicated. For similar reasons, these two drugs should not be used concurrently with methadone, propoxyphene, or tramadol. 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 MAO-B inhibitors with SSRIs and TCAs is not recommended.[54]

Use of bromocriptine (Parlodel) is contraindicated if the patient has experienced hypersensitivity to bromocriptine, has uncontrolled hypertension, or has sensitivity to ergot alkaloids. In patients being treated for hyperprolactinemia, bromocriptine should be discontinued if pregnancy is diagnosed. In patients being treated for acromegaly, prolactinoma, or Parkinson's disease, bromocriptine should be withdrawn in those who experience hypertensive disorders of pregnancy. Bromocriptine should not be used postpartum in women with a history of coronary artery disease or other severe cardiovascular disease.

In a meta-analysis, pramipexole (Mirapex) and ropinirole (Requip) were compared for the risk of somnolence.[55] The pooled, relative risk of somnolence was 4.98 compared to the placebo group based on four trials. In a comparison between patients taking levodopa and pramipexole or ropinirole, the pooled, relative risk was 2.06. Dopamine agonists have a warning in the prescribing information regarding the potential for falling asleep during activities of daily living.[56,57,58,59]

Rotigotine (Neupro) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. Also, in three double-blind, placebo-controlled studies in patients with early-stage PD, two percent (13 of 649) of rotigotine-treated patients reported hallucinations, some severe enough to cause discontinuation of therapy [0.2 percent (1 of 649)], compared to 0.7 percent (2 of 289) of placebo-treated patients.[60]

Drug Interactions

Many different drug interactions occur with the antiparkinsonian agents. Drug interaction references should be reviewed when prescribing concomitant medication.

Adverse Effects

Anticholinergics[61]

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 side effects include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia.

levodopa/carbidopa (Sinemet, Sinemet CR, Parcopa)[62]

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

Dopamine Agonists

Drug	Confusion	Constipation	Dizziness	Dyskinesia	Hallucinations	Nausea
bromocriptine (Parlodel)[63]	reported	reported	reported	reported	reported	reported
pramipexole (Mirapex)[64]	4 (1)	14 (6)	25 (24)	≥1	9 (3)	28 (18)
ropinirole (Requip)[65]	5	nr	40	≥1	5	60
ropinirole (Requip XL)[66]	nr	4 (2)	8 (3)	13 (3)	8 (2)	11 (4)
rotigotine (Neupro)[67]	nr	5 (4)	18 (11)	nr	2 (1)	38 (15)

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.

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 percent. This risk increased to 13.7 percent among those on dopamine agonists.[68] 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 ($p<0.05$).[69]

COMT Inhibitors

Drug	Anorexia	Diarrhea	Dyskinesia	Hallucinations	Orthostatic complaints	Nausea	Somnolence
entacapone (Comtan)[70,71]	nr	8-20 (7)	13-25 (11)	4-9	13 (14)	10-20 (12)	4-8 (10)
tolcapone (Tasmar)[72]	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.[73] In the 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." They go on to recommend that liver function monitoring should be done per the product labeling: baseline and then periodically (i.e., every two to four weeks) for the first six months and thereafter as clinically necessary. Tolcapone should be discontinued if ALT/AST increase to more than twice the upper limit of normal.

MAO-B Inhibitors

Drug	Confusion	Dizziness	Dyskinesia	Orthostatic complaints	Nausea
rasagiline (Azilect)[74]	>1	1 (1)	18 (10)	6-9 (3)	10-12 (8)
selegiline (Eldepryl)[75,76,77]	3-6	6-12	34 (19)	reported	10-20
selegiline (Zelapar)[78]	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.

Special Populations[79]

Pediatrics

Benztropine (Cogentin) should not be used in children three 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.

Pregnancy

All agents in this class are Pregnancy Category C except for bromocriptine (Parlodel). Bromocriptine is Category B, but should not be used during lactation in postpartum women.

Hepatic

Tolcapone (Tasmar) is contraindicated in patients with hepatic disease and should be used with caution in patients with any hepatic dysfunction.

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.

All of the other agents, except for benztropine, pramipexole (Mirapex), and rotigotine (Neupro), should be used with caution in patients with hepatic impairment.

Renal

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

Pramipexole (Mirapex) dosage should be adjusted with renal impairment and creatinine clearance less than 60 mL/minute.

Ropinirole (Requip, Requip XL) has not been studied in patients with severe renal impairment. Dosing adjustments are not needed in patients with moderate impairment.

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

Dosages

Parkinson's Disease

Therapeutic Class	Drug	Starting Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Anticholinergics	benztropine (Cogentin)	0.5 mg	6 mg	one to two times daily	0.5, 1, 2 mg tablets
	procyclidine (Kemadrin)	7.5 mg	20 mg	three to four times daily	5 mg tablets
	trihexyphenidyl (Artane)	1-2 mg	15 mg	three to four times daily	2, 5 mg tablets 2 mg/5 mL elixir
Dopamine precursor / dopa decarboxylase inhibitor	levodopa/carbidopa (Sinemet)	two tablets	eight tablets	every 2-5 hours	10/100, 25/100, 25/250 mg tablets
	levodopa/carbidopa (Parcopa)	two tablets	eight tablets	every 3-5 hours	10/100, 25/100, 25/250 mg disintegrating tablets
	levodopa/carbidopa (Sinemet CR)	two tablets	eight tablets	every 4-8 hours	25/100, 50/200 mg sustained release tablets
MAO-B Inhibitors	rasagiline (Azilect)	0.5-1 mg	1 mg	once daily	0.5, 1 mg tablets
	selegiline (Eldepryl)	10 mg	10 mg	twice daily	5 mg capsules; 5 mg tablets
	selegiline (Zelapar)	1.25 mg	2.5 mg	once daily	1.25 mg disintegrating tablets
Dopamine agonists	bromocriptine (Parlodel)	1.25 mg	100 mg	twice daily with food	2, 2.5 mg tablets; 5 mg capsules
	pramipexole (Mirapex)	0.375 mg	4.5 mg	three times daily	0.125, 0.25, 0.5, 1, 1.5 mg tablets
	ropinirole (Requip)	0.75 mg	24 mg	three times daily	0.25, 0.5, 1, 2, 3, 4, 5 mg tablets
	ropinirole (Requip XL)	2 mg	24 mg	once daily	2, 4, 8 mg tablets
	rotigotine (Neupro)	2 mg	6 mg	once daily	2 mg/24 hr, 4 mg/24 hr, 6 mg/24 hr transdermal patches
COMT inhibitors	entacapone (Comtan)	600 mg	1600 mg	200 mg with each dose of levodopa/carbidopa	200 mg tablets
	tolcapone (Tasmar)	300 mg	600 mg	three times daily	100, 200 mg tablets
Dopamine precursor/dopa decarboxylase inhibitor/COMT inhibitor	levodopa/carbidopa/ entacapone (Stalevo)	one tablet	six tablets	every three to five hours	50/12.5/200, 100/25/200, 150/37.5/200, 200/50/200 mg tablets

Restless Leg Syndrome

Therapeutic Class	Drug	Starting Daily Dose	Maximum Daily Dose	Recommended Dosing Schedule	Availability
Dopamine agonists	pramipexole (Mirapex)	0.125 mg	0.75 mg	once daily two to three hours prior to bedtime	0.125, 0.25, 0.5, 1, 1.5 mg tablets
	ropinirole (Requip)	0.25 mg	4 mg	once daily one to three hours prior to bedtime	0.25, 0.5, 1, 2, 3, 4, 5 mg tablets

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed, http://www.ifpma.org/clinicaltrials.html and review of information sent by manufacturers. Search strategy included the 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 percent 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/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 four (can barely perform). Part IV is the Hoehn and Yahr staging scale and Part V is the Schwab and England ADL scale.[80]

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 (Cogentin), 29 patients with mild to moderate PD and stabilized on levodopa/carbidopa were randomized in double-blind crossover fashion to receive benztropine or placebo.[81] 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.

LEVODOPA

Levodopa (Sinemet, Sinemet CR, Parcopa) 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.[82] The response to levodopa therapy in PD is seen as a dramatic improvement in function and, usually, 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.

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

A total of 618 patients were studied in 36 centers worldwide in a blinded, randomized, parallel study.[83] Measures of efficacy and adverse effects were recorded at three-month intervals for five 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 five 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 five years, 20.6 percent of the levodopa/carbidopa IR group and 21.8 percent 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 two treatment groups.

MAO-B INHIBITORS

rasagiline (Azilect) versus placebo

In a six-month, multicenter, double-blind study, 404 patients with early PD were randomized to fixed-dose rasagiline 1 or 2 mg/day or placebo.[84] Patients were not permitted to take other antiparkinson's agents with the exception of stable doses of anticholinergics, if necessary. At the conclusion of the study, the mean (±SE) change in UPDRS scores were 0.1 (±6.8), 0.7 (±5.8) and 3.9 (±7.5) in the rasagiline 1 mg, 2 mg, and placebo groups, respectively. When the prespecified adjustment for treatment and center was made, the changes were -4.2 (±1.5) and -3.6 (±1.5) in the rasagiline 1 and 2 mg groups, respectively, compared to placebo (p=0.0001 for comparisons of each dose to placebo). Response, defined as less than three unit change in UPDRS, occurred in 66 and 67 percent of patients on rasagiline 1 and 2 mg and 49 percent of patients on placebo (p=0.004 and 0.001, respectively for the 1 and 2 mg doses compared to placebo). There were no significant differences between groups in the percentage of patients needing levodopa (16.7 and 11.2 percent of patients receiving placebo and rasagiline, respectively) or in the time to need for additional therapy.

In a six-month, double-blind continuation of the previous study involving 371 of the original subjects, patients randomized to rasagiline were maintained on their original treatment while those randomized to placebo were switched to rasagiline 2 mg (delayed treatment).[85] At the conclusion of the study, the mean (±SE) change in UPDRS scores from baseline were 3.0 (±8.3), 2.0 (±7.5) and 4.2 (±8.8) in the rasagiline 1 mg, 2 mg and delayed treatment groups, respectively. Applying the same prespecified adjustment for treatment and center, the difference between the rasagiline 2 mg and delayed treatment group was 2.3 units in favor of the former

(p=0.01). There was no significant difference between the rasagiline 1 and 2 mg treatment groups.

In the PRESTO (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'Off') study, patients with PD experiencing motor fluctuations on levodopa therapy were randomized to receive rasagiline 0.5 or 1 mg or placebo daily in double-blind fashion.[86] Patients (n=472) were treated for 26 weeks. Mean total daily off time decreased significantly more in the rasagiline 0.5 mg (1.4 hours, 23 percent) and 1 mg (1.9 hours, 29 percent) groups than in the placebo group (0.9 hours, 15 percent; p<0.02 and 0.0001, respectively, for comparisons to placebo). Compared to placebo, patients receiving rasagiline had an additional 0.5 (0.5 mg) to 0.8 (1 mg) hours of daily on time without troublesome dyskinesias. The CGI was maintained to a greater extent in the active treatment groups than in the placebo group (p<0.003). Levodopa dosage reduction occurred in 16, 17, and eight percent of patients, respectively.

selegiline (Eldepryl) versus placebo

Two double-blind, placebo-controlled studies have shown that selegiline delays the emergence of disability and the progression of motor signs and symptoms in previously untreated PD patients.[87,88,89,90] Subsequent analyses, however, have shown that selegiline can induce symptomatic effects that may account for some or all of these benefits.[91] There are insufficient data to conclude that selegiline has a neuroprotective effect in PD. It does not halt disease progression and, in some studies, its initial benefits have not been maintained.[92,93,94]

selegiline (Zelapar) disintegrating tablets versus placebo

Ninety-four PD patients who were experiencing motor fluctuations with levodopa were randomized to receive adjunctive selegiline ODT (1.25 mg/day for six weeks, followed by 2.5 mg/day) or placebo in a three-month double-blind study.[95] At the conclusion of the study, daily off time was reduced by 2.2 hours (13.2 $\pm$ 15.1) percent in the selegiline ODT group and by 0.6 hours (3.8 $\pm$ 10.3 percent) in the placebo group.

In a 12-week, double-blind, placebo-controlled, parallel-design study of 148 patients, selegiline ODT showed no significant reduction in percentage of daily off time (11.6 versus 9.8 percent; p=NS) as compared to placebo.[96] Selegiline ODT did show a significant difference in Patient Global Impression-Improvement (PGI-I) (p=0.02). This study also suggested that selegiline was safe and well tolerated by comparing CGI-I scores (p=0.06).

DOPAMINE AGONISTS

pramipexole (Mirapex) versus levodopa (Sinemet)

A multicenter, parallel-group, double-blind, randomized, controlled trial evaluated pramipexole and levodopa/carbidopa in 301 patients, with open-label levodopa supplementation when needed.[97] Patients initially on pramipexole had a significant reduction in the risk of developing dyskinesias (25 versus 54 percent; p<0.001) and wearing-off (47 versus 63 percent; p=0.02). Patients initially receiving levodopa had a significant risk reduction for freezing (25 versus 37 percent; p=0.01). At the end of two years, disabling dyskinesias and quality of life scores were similar in both groups. The mean improvement in the total UPDRS score from baseline to two years was greater in the levodopa group than in the pramipexole group (p=0.003). Compared with placebo, pramipexole was associated with more somnolence (36 versus 21 percent, p=0.005) and edema (42 versus 15 percent, p<0.001).

The CALM-PD trial evaluated the development of motor complications in subjects with early PD randomized to initial treatment with either pramipexole or levodopa.[98] 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 four-year incidence of the development or worsening of somnolence and edema and the development of hallucinations were 35 percent, 45 percent, and 17 percent of all patients, respectively. Somnolence was associated with initial pramipexole treatment, male gender, and greater than five 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 five 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 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.[99] 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 seventeen 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 six-week period or placebo, achieving optimum levels in the four-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 ten weeks, versus placebo, UPDRS score 6.54 at ten weeks ($p=0.012$) and was similar in each group. 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.

ropinirole (Requip) versus levodopa (Sinemet)

A five-year trial of ropinirole and levodopa in early PD showed that ropinirole is associated with reduced incidence of dyskinesias.[100] 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. 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. However, the onset of dyskinesias was delayed by approximately three 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 (Requip)

Sixty patients with "de novo" idiopathic PD were randomized into one of two dopamine agonist monotherapy groups to receive oral ropinirole at 15 mg per day, or pramipexole at 2.1 mg per day.[101] Dose of the dopamine agonist could be increased in the following two 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 percent 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 percent) 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 did/did not experience wearing-off; however, UPDRS scores deteriorated similarly, and there were no differences in UPDRS scores recorded in ON conditions, between fluctuating and non-fluctuating patients, at the end of the study. Study findings provide evidence of wearing-off phenomena in patients with early PD treated with non-ergot dopamine agonist monotherapy.

ropinirole (Requip XL) versus placebo

In a double-blind, placebo-controlled, 24-week study, 393 subjects with PD were randomized to ropinirole or placebo.[102] The primary outcome measure was reduction in hours of daily off time. At week 24, the mean dose of ropinirole was 18.8 mg/day. There was a mean reduction in daily off time of 2.1 hours in the ropinirole group and 0.3 hours with placebo ($p<0.05$). Secondary outcome measures including change in hours and percent of daily on time and on time without troublesome dyskinesia, UPDRS motor and activities of daily living subscales, Beck Depression Inventory-II, PDQ-39 subscales of mobility, activities of daily living, emotional well-being, stigma and communication, and PD Sleep Scale were significantly improved at week 24 with ropinirole. Adverse events led to study withdrawal in five percent of both the active and placebo groups.

rotigotine (Neupro) versus placebo

A randomized, double-blind, multicenter, placebo-controlled study assessed the response to the rotigotine transdermal system in patients with early PD.[103] Two hundred seventy-seven patients with early PD in fifty states and Canada were eligible by means of routine clinical and neurological examinations. Patients were randomized 2:1 to receive either rotigotine at 2, 4, or 6 mg during 24 hours or placebo for 24 weeks. The main outcome measure was the percentage of patients achieving a 20 percent response or greater (reduction) as assessed with the UPDRS subtotal for activities of daily life and motor function from baseline to the end of the maintenance phase. Significant differences were observed between the rotigotine-treated and placebo groups for the 20 percent responder rate (48 percent for the rotigotine group and 19 percent for the placebo group; $p<0.001$), least squares mean change in UPDRS subtotal score (-941 for rotigotine versus -157 for placebo; $p<0.001$), and percentage changes in UPDRS subtotal score (-15.1 percent for rotigotine versus 7.3 percent for placebo; $p<0.001$). Rotigotine treatment significantly increased the patients' CGI Scale scores (57 percent for rotigotine versus 30 percent for placebo; $p<0.001$) and had a positive effect on quality of life. The most common adverse effects were application site reactions, nausea, and somnolence.

A randomized, double-blind, placebo-controlled trial (PREFER Study) was performed to assess efficacy and safety with two targeted transdermal doses of rotigotine in subjects with advanced PD with ≥ 2.5 hours of daily off time.[104] Patients were randomized to receive placebo patches (n=120) or rotigotine up to either 8 mg/24 hours (n=120) or 12 mg/24 hours (n=111). The primary efficacy measures compared changes from baseline to the end of week 24 in the number of daily hours off and responder rates for subjects achieving ≥ 30 percent reduction in off time. Compared to placebo, there were significant decreases in mean off time of 1.8 hours/day for the 12 mg/24 hours group. For rotigotine 8 and 12 mg/24 hours groups, ≥ 30 percent responder rates were 56.6 percent and 55.1 percent compared to the 34.5 percent placebo response. On time without dyskinesia after awakening was more than doubled in both rotigotine treatment groups versus placebo. Transdermal rotigotine significantly improved off time in subjects with PD not optimally controlled with levodopa and was safe and well tolerated, with typical dopaminergic side effects and occasional application site reactions.

rotigotine (Neupro) versus pramipexole (Mirapex)

A randomized, controlled trial, Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced PD, assessed the efficacy of adjunct treatment with rotigotine in comparison with placebo and with pramipexole in levodopa-treated patients with advanced PD and wearing-off type motor fluctuations.[105] Eligible patients were randomly assigned to receive rotigotine (204 patients received up to 16 mg/24 hours as a transdermal patch), pramipexole (201 patients received up to 4.5 mg/day orally), or placebo (101 patients) for six months. Most discontinuations were for adverse events. Primary efficacy variables were absolute change in total off time hours (assessed by home diaries) from baseline to end of study and responder rate (defined as the proportion of patients with ≥ 30 percent reduction in absolute off time per day). Analyses were done by intention to treat. Mean absolute change in off time from baseline was -2.5 hours with rotigotine, -2.8 hours with pramipexole, and -0.9 hours with placebo. The absolute change in off time from baseline compared with placebo was -1.58 hours (95 percent CI -2.27 to -0.9; $p<0.0001$) for rotigotine and -1.94 hours (-2.63 to -1.25; $p<0.0001$) for pramipexole. Responder rates were 67 percent for pramipexole, 59.7 percent for rotigotine, and 35 percent for placebo. As related to change in absolute off time, rotigotine was non-inferior to pramipexole. Continuous delivery of rotigotine as transdermal patches could offer similar efficacy to oral pramipexole in patients with fluctuating PD over six months of treatment.

COMT INHIBITORS

entacapone (Comtan) versus placebo

A randomized, placebo-controlled, double-blind trial enrolled 172 fluctuating and 128 non-fluctuating patients with PD to study the effect of entacapone in combination with levodopa.[106] Patients were given entacapone 200 mg with each levodopa dose or placebo. For patients with fluctuations, the proportion of on time showed a significant increase over placebo with entacapone ($p<0.05$). The absolute on time increased from 9.5 to 10.8 hours with entacapone ($p<0.001$). The improvement in on time occurred despite a reduction in daily levodopa dosage. In the non-fluctuating patients, the ADL scores of the UPDRS improved with entacapone ($p<0.001$) despite a 40 mg levodopa dose reduction ($p<0.001$). Therapy was well tolerated.

Investigators randomized 750 patients (age ≥30 years) with PD and who were responding to stable doses of levodopa-carbidopa, to receive entacapone or placebo in addition to their treatment regimen.[107] At the conclusion of the 26-week, double-blind study, there was no difference between groups in the primary efficacy variable, change from baseline in the motor subscale of the UPDRS. There was a similar significant improvement from baseline in each

group. There was no difference between groups in the secondary outcome of change in ADL subscore of the UPDRS. There were between-group differences in several quality of life measures and in CGI (physician- and patient-rated) in favor of entacapone. More patients receiving placebo (12.5 percent) required an increase in dopaminergic therapy than those receiving entacapone (8.0 percent; p=0.046).

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.[108] Between 85 and 90 percent of patients in each group completed the study. Total daily off time decreased by 21 percent (1.2 hours) with both active treatments compared to seven percent (0.4 hours) with placebo ($p \leq 0.0001$ 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 five percent in each group).

tolcapone (Tasmar) versus placebo

A study randomized 177 patients to similar treatment groups in a like manner with over 80 percent of patients in the active and placebo groups completing the three- to 12-month follow-up.[109] Tolcapone reduced off time by 26 to 32 percent compared to 11 percent with placebo (p<0.01); tolcapone increased on time by 21 percent. Levodopa doses were reduced by 16 to 18 percent in the active treatment groups compared to four percent in the placebo group. Dyskinesia developed or worsened in 37 to 53 percent of patients receiving tolcapone and 21 percent of patients receiving placebo.

In a double-blind, placebo-controlled study, tolcapone's efficacy in reducing on/off fluctuations in levodopa treated patients was evaluated.[110] Two hundred fifteen referred outpatients with PD who exhibited predictable end-of-dose motor fluctuations and were not controlled by a four-week trial of levodopa/carbidopa were randomized to receive placebo or tolcapone 100 or 200 mg three times daily in addition to their levodopa. Tolcapone reduced off time by two and 2.5 hours and increased on time by 2.1 and 2.3 hours per day for the 100 mg and 200 mg doses, respectively. Also, the authors found that significantly more patients treated with tolcapone had reduced wearing-off and symptom severity compared to placebo. Clinical improvements were seen despite a decrease in total daily levodopa dose of 185.5 mg in those treated with 100 mg of tolcapone and 251.5 mg in the 200 mg group. Adverse events were mainly nausea and dyskinesia and were levodopa-related.

Restless Leg Syndrome (RLS)

levodopa (Sinemet) versus placebo

Seven randomized, double-blind, placebo-controlled trials consistently demonstrate the efficacy of levodopa in the treatment of RLS.[111,112,113,114,115,116,117] Although these trials included a relatively small number of patients (six to 41 patients per trial), the data have resulted in the American Academy of Sleep Medicine designating levodopa as a standard for the treatment of RLS.[118]

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, 0.50 or 0.75 mg daily for 12 weeks.[119] At the end of the study, the mean 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 ($p<0.0001$); there was no significant difference between the three pramipexole dosages. Response, defined as a CGI-I score that was much improved or very much improved, occurred in 72 percent of patients receiving pramipexole and 51.2 percent of patients receiving placebo.

ropinirole (Requip) versus placebo

In a 12-week, double-blind, placebo-controlled, flexible-dose study, 381 patients were randomized to ropinirole or placebo.[120] 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 one 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. 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 were randomized to ropinirole or placebo for 12 weeks.[121] In the study, 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 was no significant difference 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.

In a third double-blind, randomized, 12-week study, 267 patients with moderate-to-severe RLS were randomly assigned to ropinirole or placebo.[122] 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.

Summary

Parkinson's Disease

PD is a progressive, debilitating disease for which medications are the primary treatment.

Although dopamine agonists are effective adjuncts to levodopa (Sinemet, Sinemet CR, Parcopa) in patients who begin to experience motor complications with the latter, evidence suggests that it is preferable to use 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), ropinirole (Requip, Requip XL), and rotigotine (Neupro), delay the need for levodopa treatment and its side effects. In general, monotherapy with these dopamine agonists is effective in a majority of patients for one year or less. A minority of patients may obtain benefits for periods as long as three years or more. In later disease, dopamine agonists increase on time and allow decreases in levodopa dose. Pramipexole and ropinirole may reduce the risk of development of dyskinesias compared to

levodopa.[123] Conceptually, it is thought that continuous dopaminergic stimulation is a means of avoidance of motor dyskinesias in PD. Until recently, frequent oral dosing regimens or invasive parenteral treatment offered the only means of achieving this phenomenon. Rotigotine transdermal system offers a significant development that allows a constant delivery of a non-ergolinic dopamine agonist.[124] In clinical trials of patients with early PD, rotigotine has decreased combined scores on the motor and activities of daily living (ADL) scores of the UPDRS for up to 85 weeks. In patients with advanced PD, rotigotine reduced mean off time when used as adjunct to levodopa.[125] Longer trials are necessary to determine if transdermal rotigotine will reduce development of dyskinesias and motor fluctuations in 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 hallucinations and psychosis. The non-ergot dopamine agonists, pramipexole and ropinirole, 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.[126] Acute adverse effects of rotigotine are similar to those of other dopamine agonists with the addition of mild-to-moderate application site reactions.[127] Pramipexole, ropinirole, and rotigotine carry bolded type warnings as patients report falling asleep while engaged in the activities of daily living.

Levodopa/carbidopa (Sinemet, Sinemet CR, Parcopa), with or without a COMT inhibitor, should be added when dopamine agonist monotherapy no longer provides adequate control of the patient's symptoms.[128] Treatment with levodopa/carbidopa is associated with decreased morbidity and mortality, and virtually all patients benefit from treatment. 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.[129,130,131] Levodopa in combination with carbidopa is available in both immediate- and controlled-release formulations. Levodopa/carbidopa should be titrated up slowly to avoid side effects such as nausea, vomiting, and hypotension.

Selegiline (Eldepryl, Zelapar) has been used as a neuroprotective agent. After a review of the literature, the American Academy of Neurology reported that although selegiline has a mild symptomatic benefit, there is no convincing clinical evidence for neuroprotective benefit.[132] Because orally disintegrating selegiline tablets avoid the first pass effect, clinical effectiveness can be achieved at lower doses than with conventional selegiline tablets. This lower dosage results in lower concentrations of amphetamine metabolites. When used as an adjunct to levodopa, rasagiline (Azilect) and selegiline do 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. A randomized clinical trial is underway to confirm preclinical and preliminary clinical data suggesting rasagiline has disease-modifying effects.[133]

The introduction of the COMT inhibitors, tolcapone (Tasmar) and entacapone (Comtan), as adjunctive therapy to levodopa provided 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 (including explosive diarrhea in up to ten percent of patients receiving tolcapone), 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. They are relatively ineffective for the more disabling features of PD, however. They are also associated with muscarinic and cognitive side effects and may be associated with withdrawal effects.

The American Academy of Neurology (AAN) recommends that entacapone be offered to patients with PD with motor fluctuations to reduce off time. Pramipexole, ropinirole, and tolcapone are recommended as alternatives to be considered, although the AAN notes that tolcapone, due to hepatotoxicity, should be used with caution and requires monitoring.[134]

For patients who continue to experience unpredictable on and off periods, a MAO-B inhibitor or amantadine (Symmetrel®) may be added to the patient's drug regimen. There is insufficient evidence to conclude that any one agent is superior to another in reducing off time.

A recent review by the Movement Disorder Society ranked the efficacy of the various treatments based on placebo-controlled trials of patients with PD.[135] In this review, levodopa, the MAO-B inhibitors, and the dopamine agonists are all rated as efficacious monotherapy in patients with early PD. The anticholinergics, as well as amantadine and bromocriptine, are rated as likely efficacious, and the COMT inhibitors are rated non-efficacious in this patient group. In patients with more severe disease, the COMT inhibitors, the dopamine agonists (with the exception of ropinirole), bromocriptine, and apomorphine (Apokyn) are all rated as efficacious adjunct therapy to levodopa. The anticholinergics and amantadine are rated as likely efficacious. The group cites insufficient evidence to rate the efficacy of the MAO-B inhibitors and ropinirole in this patient group.

RLS

The American Academy of Sleep Medicine (AASM) practice parameters for RLS state that levodopa/carbidopa (Sinemet, Sinemet CR, Parcopa) is standard therapy.[136] The AASM suggests pramipexole and ropinirole as alternatives to the older agents. Both of these drugs are now FDA-approved for the treatment of RLS. The AASM notes that amantadine and selegiline may be effective for the treatment of RLS but that the level of effectiveness has not been established.

References

[1] Benztropine (Cogentin). Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[2] Kemadrin [package insert]. Bristol, TN; Monarch; June 2003.
[3] Artane [package insert]. Pearl River, NY; Lederle Pharmaceutical Division; October 2003.
[4] Sinemet [package insert]. Princeton, NJ; BMS; October 2006.
[5] Azilect [package insert]. Kansas City, MO; Teva; May 2006.
[6] Selegiline (Eldepryl). Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[7] Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2006.
[8] Parlodel [package insert]. Suffern, NY; Novartis; May 2006.
[9] Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2007.
[10] Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2006.
[11] Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2008.
[12] Neupro [package insert]. Mequon, WI; Schwarz; May 2007.

[13] Comtan [package insert]. East Hanover, NJ; Novartis; March 2000.
[14] Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; December 2006.
[15] Stalevo [package insert]. East Hanover, NJ; Novartis; August 2007.
[16] Pahwa R, Factor SA, Lyons KE, et al. Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology. 2006; 66:983-95.
[17] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
[18] Parkinson's Disease Handbook: A guide for patients and their families. American Parkinson Disease Association, Inc. 2005.
[19] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
[20] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
[21] Marsden CD. Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol. 1994; 17:S32-44.
[22] Chen JJ. Management of wearing off in Parkinson's disease. Consult Pharm. 2005; supp B:S15-21.
[23] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
[24] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000:432-41.
[25] Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
[26] Beers MH, Berkos R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck & Co; 2000: 432-41.
[27] Hughes AJ, Ben-Shlomoa Y, Daniel SE, et al. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinical pathologic study. Neurology. 1992; 42:1142-46.
[28] Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. Lancet. 1976; 1:292-6.
[29] Obeso JA, Rodriguez-Oroz MNC, Chana P, et al. The evolution and origin of motor complications in Parkinson's disease. Neurology. 2000; 55(Suppl 4):S13-20.
[30] Lang AE, Lozana AM. Parkinson's disease. N Engl J Med. 1998; 339:1044-53.
[31] Koller WC, Silver DE, Lieberman A. An algorithm for the management of Parkinson's disease. Neurology. 1994; 44(12 suppl 10):S1-52.
[32] Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
[33] Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med. 2000; 342:1484-91.
[34]New Drug: Neupro (Rotigotine Transdermal System). Pharmacist's Letter/Prescriber's Letter. 2007; 23(6):230602.
[35] Isaacson SH. Parkinson's disease: an overview of current treatment options. Consult Pharm. 2005; supp B:S6-14.
[36] Littner MR, Kushida C, Anderson WM, et al. Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder. Sleep. 2004; 27:557-9.
[37] Benztropine (Cogentin). Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[38] Kemadrin [package insert]. Bristol, TN; Monarch; June 2003.
[39] Trihexyphenidyl (Artane). Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[40] Sinemet [package insert]. Princeton, NJ; BMS; October 2006.
[41] Parcopa [package insert]. Milwaukee, WI; Schwarz; February 2006.
[42] Selegiline (Eldepryl). Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[43] Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2006.
[44] Parlodel [package insert]. Suffern, NY; Novartis; May 2006.
[45] Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2007.
[46] Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2006.
[47] Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2008.
[48] Neupro [package insert]. Mequon, WI; Schwarz; May 2007.
[49] Comtan [package insert]. East Hanover, NJ; Novartis; March 2000.
[50] Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; December 2006.
[51] Stalevo [package insert]. East Hanover, NJ; Novartis; August 2007.
[52] Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; December 2006.
[53] Carbidopa; levodopa. Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[54] Azilect [package insert]. Kansas City, MO; Teva Neuroscience; May 2006.
[55] Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomized controlled trials. Drug Saf. 2001; 24:863-8.
[56] Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2007.
[57] Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2006.
[58] Parlodel [package insert]. Suffern, NY; Novartis; May 2006.
[59] Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2008.
[60] Neupro [package insert]. Mequon, WI; Schwarz; May 2007.
[61] Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(Suppl 5):S1-88.
[62] Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(Suppl 5):S1-88.
[63] Parlodel [package insert]. Suffern, NY; Novartis; May 2006.
[64] Mirapex [package insert]. Ridgefield, CT; Boehringer Ingelheim; November 2007.
[65] Requip [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2006.
[66] Requip XL [package insert]. Research Triangle Park, NC; GlaxoSmithKline; June 2008.
[67] Neupro [package insert]. Mequon, WI; Schwarz; May 2007.
[68] Voon V, Hassan K, Zurkowski MD, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006; 67:1254-7.
[69] Voon V, Thomsen T, Miyasaki J, et al. Factors Associated with Dopaminergic Drug-Related Pathological Gambling in Parkinson Disease. Arch Neurol. 2007; 64:212-216.

[70] Comtan [package insert]. East Hanover, NJ; Novartis; March 2000.
[71] Olanow CW, Kieburtz K, Stern M, et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. Arch Neurol. 2004; 61:1563-8.
[72] Tasmar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; December 2006.
[73] Olanow CW. Tolcapone and hepatotoxic effects. Tasmar Advisory Panel. Arch Neurol. 2000; 57:263-7.
[74] Azilect [package insert]. Kansas City, MO; Teva Neuroscience; May 2006.
[75] Eldepryl [package insert]. Tampa, Fl; Somerset Pharmaceuticals; July 1998.
[76] Waters CH, Sethi KD, Hauser RA, et al. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord. 2004; 19:426-32.
[77] Shoulson I, Oakes D, Fahn S, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: A randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. Ann Neurol. 2002; 51:604-12.
[78] Zelapar [package insert]. Costa Mesa, CA; Valeant Pharmaceuticals; June 2006.
[79]Available at www.clinicalpharmacology.com. Accessed June 2, 2008.
[80] Gottwald MD, Bainbridge JL, Dowling GA, et al. New pharmacotherapy for Parkinson's disease. Ann Pharmacother. 1997; 31:1205-17.
[81] Tourtellotte WW, Potvin AR, Syndulko K, et al. Parkinson's disease: Cogentin with Sinemet, a better response. Prog Neuropsychopharmacol Biol Psychiatry. 1982; 6:51-5.
[82]Available at www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm#105623159. Accessed June 2, 2008.
[83] Koller WC, Hutton JT, Tolosa E, et al. Immediate-release and controlled-release carbidopa/levodopa in PD: A 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology. 1999; 53:1012-9.
[84] Parkinson Study Group. A Controlled Trial of Rasagiline in Early Parkinson Disease: The TEMPO Study. Arch Neurol. 2002; 59:1937-43.
[85] Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol. 2004; 61:561-6.
[86] Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol. 2005; 62:241-8.
[87] Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1989; 321:1364-71.
[88] Parkinson Study Group. Effects of tocopheral and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med. 1993; 328:176-83.
[89] Olanow CW, Hausea RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's diseases. Ann Neurol. 1995; 38:771-7.
[90] Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. Ann Neurol. 1995; 38:771-7.
[91] Olanow CW, Calne D. Does selegiline monotherapy in Parkinson's disease act by symptomatic or protective mechanisms? Neurology. 1992; 42(Suppl 4):13-26.
[92] Brannan T, Yahur MD. Comparative study of selegiline plus L-dopa-carbidopa versus L-dopa-carbidopa alone in the treatment of Parkinson's disease. Ann Neurol. 1995; 37:95-8.
[93] Parkinson Study Group. The impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. Ann Neurol. 1996; 39:29-36.
[94] Parkinson Study Group. The impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Ann Neurol. 1996; 39:37-45.
[95] Waters CH, Sethi KD, Hauser RA, et al. Zydis selegiline educes off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord. 2004; 19:426-32.
[96] Ondo WG, Sethi KD, Kricorian G. Selegiline orally disintegrating tablets in patients with Parkinson disease and "wearing off" symptoms. Clin Neuropharmacol. 2007; 30(5):295-300.
[97] Holloway RG, Shoulson I, Fahn S, et al for the Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004; 61:1044-53.
[98] Biglan KM, Holloway RG Jr, McDermott MP, et al. Parkinson Study Group CALM-PD Investigators. Risk factors for somnolence, edema, and hallucinations in early Parkinson disease. Neurology. 2007; 69(2):187-95.
[99] Parkinson Study Group. Pramipexole in levodopa-treated Parkinson disease patients of African, Asian, and Hispanic heritage. Clin Neuropharmacol. 2007; 30(2):72-85.
[100] Rascol O, Brooks DJ, Korczyn AD, et al. 056 Study Group. Development of dyskinesias in a 5-year trial of ropinirole and L-dopa. Mov Disord. 2006; 21(11):1844-50.
[101] Thomas A, Bonanni L, Di Iorio A, et al. End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease. J Neurol. 2006; 253(12):1633-9.
[102] Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology. 2007;68(14):1108-15.
[103] Jankovic J, Watts RL, Martin W, et al. Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease. Arch Neurol. 2007; 64(5):676-82.
[104] LeWitt PA, Lyons KE, Pahwa; SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology. 2007; 68(16):1262-7.
[105] Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. Lancet Neurol. 2007;6(6):513-20.

[106] Brooks DJ, Sagar H; UK-Irish Entacapone Study Group. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomized, placebo controlled, double blind, six month study. J Neurol Neurosurg Psychiatry. 2003; 74:1071-9.
[107] Olanow CW, Kieburtz K, Stern M, et al. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. Arch Neurol. 2004; 61:1563-8.
[108] Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomized, double-blind, parallel-group trial. Lancet. 2005; 365:947-54.
[109] Baas H, Beiske AG, Ghika J, et al. Catehcol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating Parkinson's patients. J Neurol Neurosurg Psychiatry. 1997; 63:421-8.
[110] Adler CH, Singer C, O'Brien C, et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group II. Arch Neurol. 1998; 55:1089-95.
[111] Montplaisir J, Boucher S, Gosselin A, et al. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-DOPA. Sleep. 1996; 19:196-9.
[112] Kaplan PW, Allen RP, Buchholz DW, et al. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep. 1993; 16:717-23.
[113] Trenkwalder C, Stiasny K, Pollmacher T, et al. L-DOPA therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. Sleep. 1995; 18:681-8.
[114] Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. Clin Neuropharmacol. 1987; 10:69-79.
[115] Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep. 1996; 19:214-8.
[116] Benes H, Kurella B, Kummer J, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep. 1999; 22:1073-81.
[117] Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-Ldopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology. 1999; 52:285-90.
[118] Littner MR, Kushida C, Anderson WM, et al. Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder. Sleep. 2004; 27:557-9.
[119] Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology. 2006; 67:1034 -9.
[120] Bogan RK, Fry JM, Schmidt MH, et al. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc. 2006; 81:17-27.
[121] Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep. 2004; 27:907-14.
[122] Walters AS, Ondo WG, Dreykluft T, et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord. 2004; 19:1414-23.
[123] Inzelberg R, Schechtman E, Nisipeanu P. Cabergoline, pramipexole and ropinirole used as monotherapy in early Parkinson's disease: an evidence-based comparison. Drugs Aging. 2003; 20:847-55.
[124] Naidu Y, Chaudhuri KR. Transdermal rotigotine: a new non-ergot dopamine agonist for the treatment of Parkinson's disease. Expert Opin Drug Deliv. 2007; 4(2):111-8.
[125] Splinter MA. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. Ann Pharmacother. 2007; 41(2):285-95.
[126] Etminan M, Gill S, Samii A. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. Drug Saf. 2003; 26:439-44.
[127] Splinter MA. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. Ann Pharmacother. 2007; 41(2):285-95.
[128] Olanow CW, Watts RL, Koller WC, et al. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology. 2001; 56(Suppl 5):S1-88.
[129] Golbe LI. Young-onset Parkinson's disease: a clinical review. Neurology. 1991; 41:168-73.
[130] Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. Mov Disodr. 1987; 2:73-91.
[131] Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease: a community-based study. Brain. 2000; 123:1528-30.
[132] Miyasaki, JM, Martin W, Suchowersky O, et al. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2002; 58:11–7.
[133]Fernandez HH, Chen JJ. Monoamine oxidase inhibitors: current and emerging agents for Parkinson disease. Clin Neuropharmacol. 2007; 30(3):150-68.
[134] Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Neurology. 2006; 66:983-95.
[135] CG Goetz, W Poewe, O Rascol, et al. Evidence-based medical review update: Pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Movement Disorders. 2005; 20:523-39.
[136] Littner MR, Kushida C, Anderson WM, et al. Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder. Sleep. 2004; 27:557-9.

