# Antiparkinson’s Agents Review

**FDA-Approved Indications**

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Parkinson’s Disease</th>
<th>Drug-induced EPS</th>
<th>RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>benztropine (Cogentin®)(^1) generic</td>
<td>X</td>
<td>X except TD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>trihexyphenidyl (Artane®)(^2) generic</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>levodopa/carbidopa (Sinemet®, Sinemet® CR)(^3) generic</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>levodopa/carbidopa (Parcopa™)</td>
<td>generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine precursor / dopa decarboxylase inhibitor</td>
<td>rasagiline (Azilect®)(^4) Teva Neuroscience</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>selegiline (Eldepryl®)(^5) generic</td>
<td>X</td>
<td>(only as adjunct to levodopa/carbidopa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>selegiline (Zelapar™)(^6) Valeant</td>
<td>X</td>
<td>(only as adjunct to levodopa/carbidopa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAO-B inhibitors</td>
<td>bromocriptine (Parlodel®)(^7) generic</td>
<td>X</td>
<td>(only as adjunct to levodopa/carbidopa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pramipexole (Mirapex®)(^8) generic</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pramipexole extended release (Mirapex® ER(^1)(^9) Boehringer Ingelheim</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ropinirole (Requip®)(^10) generic</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ropinirole extended release (ER) (Requip XL(^1)(^1) GlaxoSmithKline</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>entacapone (Comtan®)(^1) Novartis</td>
<td>X</td>
<td>(only as adjunct to levodopa/carbidopa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tolcapone (Tasmar®)(^13) Valeant</td>
<td>X</td>
<td>(only as adjunct to levodopa/carbidopa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>levodopa/carbidopa/entacapone (Stalevo®)(^1) Novartis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EPS = extrapyramidal symptoms  
RLS = restless legs syndrome  
TD = tardive dyskinesia
Because of its effects on heart valves, the FDA withdrew pergolide (Permax®) from the market in March 2007. Monarch announced in June 2008 that they would discontinue the manufacturing of procyclidine (Kemadrin®). Rotigotine (Neupro®) transdermal system was withdrawn from the market in the United States in April 2008 following the discovery that rotigotine was prone to crystallization on the underside of the patch. The FDA has informed the manufacturer that it must find a permanent solution to a crystallization problem before the drug can be relaunched in the United States. Neupro was FDA-approved for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease and restless legs syndrome (RLS).

**Overview**

**PARKINSONISM**

Parkinson’s disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. This disease affects more than 1.5 million Americans older than 50 years of age with the incidence increasing significantly with age. The term “parkinsonism” describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait problems. 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. 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.

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. As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments. 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.

Anticholinergics were the first medications indicated for the treatment of PD. Anticholinergics such as benztropine (Cogentin) and trihexyphenidyl (Artane) 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.

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. 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. Patients may experience a "wearing-off" effect characterized by a shorter duration of benefit from each levodopa dose, causing parkinsonian symptoms to reemerge. 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"). 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 (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, Mirapex ER), 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. 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. 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) and 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. Some experts recommend the initiation of a COMT inhibitor at the onset of levodopa therapy to reduce the risk of developing motor complications.

In 2006, The American Academy of Neurology (AAN) recommended 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. For patients who continue to experience unpredictable on and off periods, a MAO-B inhibitor or amantadine 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.

An evidence-based review reported in 2005 by the Movement Disorder Society ranked the efficacy of the various treatments based on placebo-controlled trials of patients with PD between 2001 and 2004. In the 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...
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.

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. 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 and ropinirole for an indication of RLS, there has been increased focus on the use of dopamine agonists in the treatment of this disorder.

The American Academy of Sleep Medicine (AASM) 2004 practice parameters for RLS state that levodopa/carbidopa is standard therapy. The AASM suggests pramipexole and ropinirole as alternatives to the older agents.
### Pharmacology

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Half-Life (hr)</th>
<th>Metabolism</th>
<th>Excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>benztropine (Cogentin)(^{38})</td>
<td>--</td>
<td>--</td>
<td>Metabolites</td>
<td>Mostly urine</td>
</tr>
<tr>
<td>trihexyphenidyl (Artane)(^{39})</td>
<td>--</td>
<td>--</td>
<td>Metabolites</td>
<td>Urine</td>
</tr>
<tr>
<td><strong>Dopamine precursor / dopa decarboxylase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levodopa/carbidopa (Sinemet, Parcopa)(^{40,41})</td>
<td>--</td>
<td>1.5</td>
<td>Extensive</td>
<td>Urine</td>
</tr>
<tr>
<td><strong>MAO-B inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rasagiline (Azilect)</td>
<td>36</td>
<td>3</td>
<td>Two inactive metabolites</td>
<td>Urine: 62 Feces: 7</td>
</tr>
<tr>
<td>selegiline (Eldepryl)(^{42})</td>
<td>--</td>
<td>10</td>
<td>Three active metabolites</td>
<td>Urine: 45</td>
</tr>
<tr>
<td>selegiline (Zelapar)(^{43})</td>
<td>greater than conventional selegiline tablets</td>
<td>10</td>
<td>Three active metabolites – concentrations reduced 3- to 10-fold compared to conventional selegiline tablets</td>
<td></td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bromocriptine (Parlodel)(^{44})</td>
<td>28</td>
<td>15</td>
<td>Metabolites</td>
<td>Urine: 6</td>
</tr>
<tr>
<td>pramipexole (Mirapex)(^{45})</td>
<td>&gt;90</td>
<td>8 (young) 12 (elderly)</td>
<td>--</td>
<td>Urine: 90</td>
</tr>
<tr>
<td>pramipexole ER (Mirapex ER)(^{46})</td>
<td>&gt;90</td>
<td>--</td>
<td>--</td>
<td>Urine: 90</td>
</tr>
<tr>
<td>ropinirole (Requip)(^{47})</td>
<td>55</td>
<td>6</td>
<td>Inactive metabolites</td>
<td>Urine: &gt;88</td>
</tr>
<tr>
<td>ropinirole ER (Requip XL)(^{48})</td>
<td>45-55</td>
<td>6</td>
<td>Inactive metabolites</td>
<td>Urine: &gt;88</td>
</tr>
<tr>
<td><strong>COMT inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>entacapone (Comtan)(^{49})</td>
<td>35</td>
<td>2.4</td>
<td>Inactive metabolites</td>
<td>Urine: 10 Feces: 90</td>
</tr>
<tr>
<td>tolcapone (Tasmar)(^{50})</td>
<td>65</td>
<td>2-3</td>
<td>Inactive metabolites</td>
<td>Urine: 60 Feces: 40</td>
</tr>
</tbody>
</table>

The pharmacokinetics for levodopa/carbidopa/entacapone (Stalevo) are similar to the individual components of the drug.\(^{51}\)
**Contraindications/Warnings**

A boxed warning appears in the tolcapone (Tasmar) prescribing information. Three fatal cases of acute, fulminant liver failure have been reported. Patients must sign an informed consent to start therapy with tolcapone. 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.

Concomitant use of non-selective MAO inhibitors with levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR) can result in hypertensive crisis; simultaneous use of these agents is contraindicated. The MAOI must be discontinued two weeks prior to starting levodopa/carbidopa. Levodopa/carbidopa is also contraindicated in patients with narrow-angle glaucoma.

The anticholinergics, benztropine and trihexyphenidyl, should not be given to patients with narrow angle glaucoma.

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 tricyclic antidepressants is not recommended.

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 if these patients are diagnosed with pregnancy. Also it should not be used in patients with hypertensive disorders during pregnancy, such as preeclampsia, eclampsia, or pregnancy-induced hypertension. It should also 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) and ropinirole (Requip, Requip XL) 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 orders can increase the risk of excessive drowsiness or falling asleep.

In a meta-analysis, pramipexole and ropinirole were compared for the risk of somnolence. 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.

Reports have associated ropinirole 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 over a seven-day period to prevent this withdrawal.

In early 2009, warnings were added to the levodopa/carbidopa/entacapone (Stalevo) labeling regarding intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking drugs that increase central dopaminergic tone. A cause-effect relationship has not been proven, although some urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped.

Epidemiological studies have shown that patients with PD have a higher risk (two- to approximately six-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).

**Drug Interactions**

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. Dopamine agonists should be used with caution with alcohol and other central nervous system (CNS) depressants.

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

Ropinirole (Requip, Requip XL) may be potentiated by CYP1A2 inhibitors, such as ciprofloxacin.

**Adverse Effects**

**Anticholinergics**

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/carbidopa (Parcopa, Sinemet, Sinemet CR)**

The most frequently reported adverse effects with levodopa are adventitious movements, such as choreiform or dystonic movements (10 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Confusion</th>
<th>Constipation</th>
<th>Dizziness</th>
<th>Dyskinesia</th>
<th>Hallucinations</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>bromocriptine (Parlodel)</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
</tr>
<tr>
<td>pramipexole (Mirapex)</td>
<td>4-10 (1-7)</td>
<td>10-14 (6-9)</td>
<td>25-26 (24-25)</td>
<td>47 (31)</td>
<td>9-17 (3-4)</td>
<td>28 (18)</td>
</tr>
<tr>
<td>pramipexole ER (Mirapex ER)</td>
<td>nr</td>
<td>14 (2)</td>
<td>12 (7)</td>
<td>17 (8)</td>
<td>5 (1)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>ropinirole (Requip)</td>
<td>5-9 (1)</td>
<td>6 (nr)</td>
<td>40 (22)</td>
<td>$\geq$1</td>
<td>$&gt;$5</td>
<td>60 (22)</td>
</tr>
<tr>
<td>ropinirole ER (Requip XL)</td>
<td>nr</td>
<td>4 (2)</td>
<td>6-8 (3)</td>
<td>13 (3)</td>
<td>8 (2)</td>
<td>11-19 (4)</td>
</tr>
</tbody>
</table>

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. 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 ($p<0.05$).

**COMT Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anorexia</th>
<th>Diarrhea</th>
<th>Dyskinesia</th>
<th>Hallucinations</th>
<th>Orthostatic complaints</th>
<th>Nausea</th>
<th>Somnolence</th>
</tr>
</thead>
<tbody>
<tr>
<td>entacapone (Comtan)</td>
<td>nr</td>
<td>8-20 (7)</td>
<td>13-25 (11)</td>
<td>4-9</td>
<td>13 (14)</td>
<td>10-20 (12)</td>
<td>4-8 (10)</td>
</tr>
<tr>
<td>tolcapone (Tasmar)</td>
<td>19-23 (13)</td>
<td>16-34 (8)</td>
<td>42-51 (20)</td>
<td>24</td>
<td>17-24 (14)</td>
<td>28-50 (18)</td>
<td>16-32</td>
</tr>
</tbody>
</table>

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. In the 2000 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. The Practice Parameters 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase to more than twice the upper limit of normal.

**MAO-B Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Confusion</th>
<th>Dizziness</th>
<th>Dyskinesia</th>
<th>Orthostatic complaints</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>rasagiline (Azilect)</td>
<td>&gt;1</td>
<td>1 (1)</td>
<td>18 (10)</td>
<td>6-9 (3)</td>
<td>10-12 (8)</td>
</tr>
<tr>
<td>selegiline (Eldepryl)</td>
<td>3-6</td>
<td>6-12</td>
<td>34 (19)</td>
<td>reported</td>
<td>10-20</td>
</tr>
<tr>
<td>selegiline (Zelapar)</td>
<td>nr</td>
<td>11 (8)</td>
<td>6 (3)</td>
<td>≤2</td>
<td>11 (9)</td>
</tr>
</tbody>
</table>

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**

**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.

The pharmacokinetics of pramipexole (Mirapex, Mirapex ER) in children have not been evaluated. The safety and efficacy of ropinirole (Requip, Requip XL) in children have not been established.

**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. Selegiline (Eldepryl, Zelapar) is Pregnancy Category C, but it also 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 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 percent 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**

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

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

Ropinirole 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.

**Elderly**

Pramipexole clearance decreases with age, as the half-life and clearance are about 40 percent longer and 30 percent 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.
## Dosages

### Parkinson’s Disease

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Drug</th>
<th>Starting Daily Dose</th>
<th>Maximum Daily Dose</th>
<th>Recommended Dosing Schedule</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>benztropine (Cogentin)</td>
<td>0.5 mg</td>
<td>6 mg</td>
<td>one to two times daily</td>
<td>0.5, 1, 2 mg tablets</td>
</tr>
<tr>
<td></td>
<td>trihexyphenidyl (Artane)</td>
<td>1-2 mg</td>
<td>15 mg</td>
<td>three to four times daily</td>
<td>2 mg/5 mL elixir</td>
</tr>
<tr>
<td><strong>Dopamine precursor/dopa decarboxylase inhibitor</strong></td>
<td>levodopa/carbidopa (Sinemet)</td>
<td>two tablets</td>
<td>eight tablets</td>
<td>every two to five hours</td>
<td>10/100, 25/100, 25/250 mg tablets</td>
</tr>
<tr>
<td></td>
<td>levodopa/carbidopa ODT (Parcopa)</td>
<td>two tablets</td>
<td>eight tablets</td>
<td>every three to five hours</td>
<td>10/100, 25/100, 25/250 mg disintegrating tablets</td>
</tr>
<tr>
<td></td>
<td>levodopa/carbidopa (Sinemet CR)</td>
<td>two tablets</td>
<td>eight tablets</td>
<td>every four to eight hours</td>
<td>25/100, 50/200 mg sustained release tablets</td>
</tr>
<tr>
<td><strong>MAO-B Inhibitors</strong></td>
<td>rasagiline (Azilect)</td>
<td>0.5-1 mg</td>
<td>1 mg</td>
<td>once daily</td>
<td>0.5, 1 mg tablets</td>
</tr>
<tr>
<td></td>
<td>selegiline (Eldepryl)</td>
<td>10 mg</td>
<td>10 mg</td>
<td>twice daily</td>
<td>5 mg capsules; 5 mg tablets</td>
</tr>
<tr>
<td></td>
<td>selegiline (Zelapar)</td>
<td>1.25 mg</td>
<td>2.5 mg</td>
<td>once daily before breakfast and without liquid</td>
<td>1.25 mg disintegrating tablets</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td>bromocriptine (Parlodel)</td>
<td>1.25 mg</td>
<td>100 mg</td>
<td>twice daily with food</td>
<td>2.5 mg tablets; 5 mg capsules</td>
</tr>
<tr>
<td></td>
<td>pramipexole (Mirapex)</td>
<td>0.375 mg</td>
<td>4.5 mg</td>
<td>three times daily</td>
<td>0.125, 0.25, 0.5, 0.75, 1, 1.5 mg tablets</td>
</tr>
<tr>
<td></td>
<td>pramipexole ER (Mirapex ER)</td>
<td>0.375 mg</td>
<td>4.5 mg</td>
<td>once daily</td>
<td>0.375, 0.75, 1.5, 3, 4, 4.5 mg tablets</td>
</tr>
<tr>
<td></td>
<td>ropinirole (Requip)a</td>
<td>0.75 mg</td>
<td>24 mg</td>
<td>three times daily</td>
<td>0.25, 0.5, 1, 2, 3, 4, 5 mg tablets</td>
</tr>
<tr>
<td></td>
<td>ropinirole ER (Requip XL)a</td>
<td>2 mg</td>
<td>24 mg</td>
<td>once daily as a whole tablet</td>
<td>2, 4, 6, 8, 12 mg tablets</td>
</tr>
<tr>
<td><strong>COMT inhibitors</strong></td>
<td>entacapone (Comtan)</td>
<td>600 mg</td>
<td>1,600 mg</td>
<td>200 mg with each dose of levodopa/carbidopa</td>
<td>200 mg tablets</td>
</tr>
<tr>
<td></td>
<td>tolcapone (Tasmar)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>three times daily</td>
<td>100, 200 mg tablets</td>
</tr>
<tr>
<td><strong>Dopamine precursor/dopa decarboxylase inhibitor/COMT inhibitor</strong></td>
<td>levodopa/carbidopa/entacapone (Stalevo)</td>
<td>one tablet</td>
<td>six tablets</td>
<td>every three to five hours</td>
<td>50/12.5/200, 75/18.75/200, 100/25/200, 125/31.25/200, 150/37.5/200, 200/50/200 mg tablets</td>
</tr>
</tbody>
</table>

* Dosing conversion between the extended-release dopamine agonists (Requip XL, Mirapex ER) and their immediate-release counterparts can be found in the package insert of the extended-release products.83,84
Restless Leg Syndrome

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

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed 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 antiparkinsons 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.

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. 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 seven domains: social/role function, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function, plus one item of Global Health-Related Quality of Life (HRQOL).

There are a limited number of good quality direct comparative trials for the agents used in the management of PD. There are not any direct comparative trials for the agents used for RLS; current agents are only compared to placebo.
Parkinson’s Disease

ANTICHLINERGICS

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.88 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 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.89 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.90 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 entacapone (Comtan)

In an 18-week, double-blind, multicenter, randomized trial, the efficacy of rasagiline was compared to entacapone and placebo.91 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 of 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, 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, 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, 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 percent) 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.

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. The patients were followed for ten 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 percent) 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 30.0, p=0.05). Physical functioning (difference 20.8; 95% confidence interval (CI), 10.0-31.6; p<0.001) and physical summary scores (difference 5.2; 95% CI, 0.7-9.7; 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

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. The trial enrolled 301 patients with early Parkinson disease who required dopaminergic therapy to treat emerging disability. Subjects received 0.5 mg of pramipexole three times per day with levodopa placebo or 25/100 mg of carbidopa/levodopa three times per day with pramipexole placebo. The dosage was escalated during the first ten 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 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 Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to two 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 percent, p=0.005) and edema (42 versus 15 percent, 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. 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 two-year, open-label extension of the CALM-PD trial was added to the original four year trial. Of the 301 patients that originally participated in the four-year study, 222 were enrolled in the open-label two-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 didn't differ at six 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 percent for levodopa versus 50 percent 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 treatment 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 four-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. 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 \( \leq 4.5 \) 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. Adverse events occurred in 85 percent of patients on pramipexole and 69 percent on placebo. Hallucinations and insomnia were more common on pramipexole than placebo (p=0.023; 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. A total of 301 subjects with early Parkinson’s disease were randomized to either initial pramipexole or initial levodopa, and then followed every three months over a four-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 affected the results. The results indicated that all three HRQOL measures reported similar profiles over time characterized by initial improvement over the first three to six months, followed by a gradual decline in years two, three, and four. The difference in HRQOL between the treatment arms widened in favor of pramipexole in years three and four 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 (Requip) versus levodopa

A five-year trial of ropinirole and levodopa in early PD showed that ropinirole is associated with reduced incidence of dyskinesias. 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, 3.23-14.29; 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, 0.48-1.33; p=0.39). 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. 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. 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 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 (Requip) versus ropinirole ER (Requip XL)

Efficacy and Safety Evaluation in Parkinson's Disease (EASE-PD) monotherapy studied ropinirole ER and ropinirole immediate release. 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(0-24,ss)), change from baseline in Unified Parkinson's Disease Rating Scale (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(0-24,ss) was similar for both formulations, with a 60 percent to 80 percent probability of response for the exposure range studied. In patients with early PD, similar clinical benefit was achieved at AUC(0-24,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. 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 Unified Parkinson's Disease Rating Scale (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).
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. 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 three 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 one hour per day (primary efficacy measure) in 43 percent of entacapone-treated patients and 53 percent of tolcapone-treated patients, and by greater than or equal to three hours per day in 13 percent and 25 percent, respectively. The IGA indicated moderate to marked improvements in 25 percent of entacapone patients and 39 percent 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 percent with entacapone and 32 percent with tolcapone. Dyskinesia was the most common adverse event affecting 29 percent of entacapone and 31 percent 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.

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. 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<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).

Restless Leg Syndrome (RLS)

levodopa versus placebo

Seven randomized, double-blind, placebo-controlled trials consistently demonstrate the efficacy of levodopa in the treatment of RLS. 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.
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.\textsuperscript{112} 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 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.

A six-week, randomized, placebo-controlled study evaluated the efficacy of pramipexole versus placebo in RLS.\textsuperscript{113} 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 Patient Global Impression (PGI) assessment to a maximum of 0.75 mg per day if necessary. The primary endpoints evaluated at week six were the change from baseline in the International RLS Study Group Rating Scale (IRLS) and the proportion of patients reporting “much to very much improved” results with Clinical Global Impressions-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 six 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 percent for placebo and 62.9 percent 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.\textsuperscript{114} Adults with moderate or severe RLS were randomized to receive placebo or pramipexole, which was flexibly titrated from 0.25 to 0.75 mg, two to three hours before bedtime. The primary outcome measures were changes in Medical Outcomes Study (MOS) sleep disturbance score and International RLS Study Group Rating Scale (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 three-week, randomized, double-blind, placebo controlled, dose-finding study was performed in patients with moderate to severe RLS.\textsuperscript{115} 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 International RLS Study Group Rating Scale (IRLS) scores were also 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 percent reduction of IRLS score) than for placebo (61.9-77.3, versus 33.3 percent). In the pramipexole groups, 50 percent to 77.3 percent of patients rated their condition as 'much better' or 'very much better', compared with 38.1 percent of patients in the placebo group (p=0.0139 for the 0.5 mg dose). Clinical global impressions (CGI) scale ratings of 'much improved' or 'very much improved' were given to 61.9 percent to 86.4 percent of patients in the pramipexole groups, compared with 42.9 percent 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 (Requip) versus placebo

In a 12-week, double-blind, placebo-controlled, flexible-dose study, 381 patients were randomized to ropinirole (0.25-4.0 mg as needed and tolerated, once daily, 1 to 3 hours before bedtime) or placebo.116 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. Although treatment differences favoring ropinirole in daytime somnolence were observed, they were not statistically significant (p=0.10). 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 (0.25-4.0 mg per day) or placebo for 12 weeks.117 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 arousals per hour decreased from 7.0 to 2.5 with ropinirole but increased from 4.2 to 6.0 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.118 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 percent) versus placebo (57.8 percent) (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 (0.25-4.0 mg/day) or placebo, 1 to 3 hours before bedtime. 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**

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) and ropinirole (Requip, Requip XL), 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 one year or less. A minority of patients may obtain benefits for periods as long as three years or more. In advanced 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. Ropinirole ER and ropinirole demonstrated similar efficacy and safety in UPDRS motor scores in one clinical trial.

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. Pramipexole and ropinirole carry bolded type warnings as patients report falling asleep while engaged in the activities of daily living.

Levodopa/carbidopa (Parcopa, Sinemet, Sinemet CR), 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. Levodopa in combination with carbidopa is available in both immediate-release 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, 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) 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.

The COMT inhibitors, tolcapone (Tasmar) 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.

RLS

In 2004, The American Academy of Sleep Medicine (AASM) practice parameters for RLS state that levodopa/carbidopa is standard therapy. The AASM suggests pramipexole and ropinirole as treatment alternatives. Pramipexole (Mirapex) and ropinirole (Requip) are approved for the treatment of Restless Leg Syndrome.

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