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# Dopamine Agonists in Parkinson Disease: Special Focus on Pramipexole

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**ABSTRACT: Dopamine receptor agonists have played an important role in antiparkinsonian therapy since the first ergoline derivative was introduced in 1974. The non-ergoline dopamine agonists, developed later to provide the benefits of the ergolines with fewer side effects, are currently used as both monotherapy and as adjunctive therapy to treat symptoms of Parkinson disease (PD), to postpone the onset of levodopa therapy, to delay the development and minimize the severity of levodopa's complications, and to reduce the dosage of levodopa. When the effects of dopamine agonists wane and levodopa is added, patients who receive combined dopaminergic treatment still exhibit less severe motor complications than those who started antiparkinsonian therapy with levodopa. In addition to abating the core symptoms of PD (eg, akinesia and rigidity) and delaying the onset of motor complications, the dopamine agonist pramipexole has been shown to ameliorate tremor and depressive symptoms in clinical practice.**

The second most common age-related neurodegenerative disorder (after Alzheimer disease), Parkinson disease (PD) affects more than 1 million Americans. Treatments for PD have been primarily based on correcting the characteristic nigrostriatal dopamine deficiency. A number of pharmacological approaches have been introduced over the years, including agents that reduce the peripheral decarboxylation of levodopa to dopamine (carbidopa), that prolong levodopa's 90-minute half-life (controlled-release carbidopa/levodopa), that increase the amount of levodopa crossing the blood-brain barrier (catechol-*O*-methyltransferase [COMT] inhibitors), that slow dopamine's metabolic breakdown (monoamine oxidase type B [MAO-B] inhibitors), and that directly stimulate dopamine receptors in the normal striatum (dopamine receptor agonists).

Levodopa has remained the mainstay of antiparkinsonian drug therapy since its introduction in the 1960s. Unfortunately, early treatment with levodopa has been shown to lead to disabling motor fluctuations and dyskinesias; this prompted the development of alternative medications to treat PD, including dopamine agonists. The dopamine agonists represent a rational and effective alternative to levodopa for the treatment of early PD—especially in patients younger than 80 years and in older patients whose overall health is good. When disease progression finally requires the addition of levodopa, patients who are receiving combination levodopa/dopamine agonist therapy have fewer motor complications than those receiving levodopa monotherapy.

While levodopa remains the gold standard for PD therapy, dopamine agonists are being used increasingly as first-line therapy for patients with PD and have become an integral part of the disease's treatment. The initial use of dopamine agonists to forestall the onset of motor fluctuations and lessen their severity remains controversial for

some movement disorder specialists, however.

In this article, I focus on the use of dopamine agonists in early and advanced PD, with an emphasis on pramipexole.

## PATHOPHYSIOLOGY OF PARKINSON DISEASE

PD is caused by a massive loss of dopaminergic neurons in the substantia nigra, resulting in drastic depletion of dopamine levels in the striatum, to which these neurons project.[1] The loss of dopamine creates an imbalance between excitatory and inhibitory effects in the basal ganglia, resulting in hypokinetic motor behavior (**Figure 1**).[2]

Although the dopaminergic nigrostriatal tract seems to be the most important site of change, a number of other selected but heterogeneous populations of neurons are involved in the progressive cell death characteristic of PD.[3] Neurodegeneration also occurs in selected aminergic brain stem nuclei, both catecholaminergic and serotonergic; in the cholinergic nucleus basalis of Meynert; in the hypothalamus; in the small cortical neurons, particularly those in the cingulate gyrus and entorhinal cortex, as well as in the olfactory bulb and sympathetic ganglia; and in the parasympathetic neurons in the gut. These widespread degenerative changes are believed to result in the nonmotor, cognitive, and behavioral changes that are characteristic of PD.

For example, degeneration of olfactory-bulb neurons is believed to cause anosmia.[3] Degeneration of neurons in the spinal cord and sympathetic and parasympathetic ganglia and the central amygdaloid nucleus is associated with autonomic dysfunction. In addition, degeneration in the brain stem serotonergic and noradrenergic nuclei may contribute to behavioral dysfunction, including depression.

## TREATMENT OF PD: AN OVERVIEW

Levodopa continues to be the most effective agent for the symptomatic treatment of the motor effects of PD. No other drug matches its ability to suppress parkinsonian symptoms, especially in patients with advanced disease. But over time, initial benefits begin to wane; each dose is effective for progressively shorter periods and levodopa-induced side effects, such as unpredictable on-off fluctuations and the abnormal involuntary movements of dyskinesia, become increasingly prominent.

Although the pathogenesis of levodopa-related on-off fluctuations remains poorly understood, the degree of nigrostriatal degeneration and the half-life of the dopaminergic agent used to treat parkinsonian symptoms have been shown to correlate with their development.[4] The loss of striatal neurons and terminals means that activation of striatal dopamine receptors becomes increasingly dependent on the peripheral availability of the exogenously administered dopaminergic agent.[4,5] Moreover, considerable evidence now indicates that abnormal, intermittent, or pulsatile activation of brain dopamine receptors leads to the development of motor complications in PD through induction of plastic changes in striatal neurons and altered neuron firing patterns (**Figure 2**).[6-9]

Thus, it has been proposed that fluctuations in plasma levels of orally administered short-acting levodopa (half-life of 30 to 90 minutes) are not adequately buffered because of the lost dopamine terminals, causing receptors to be exposed to alternating high and low levels of activation and, in turn, to perturbations of an already abnormal basal ganglia network. Both animal and human studies have led to the concept that continuous delivery of a dopaminergic drug will prevent this pulsatile stimulation and avoid motor complications.[6-9]

In patients with early PD, several prospective, double-blind, controlled trials have shown initiation of therapy with a long-acting dopamine agonist to be associated with a lower risk of motor complications compared with initiation with levodopa (**Figure 3**).[10-13] A prospective, controlled 4-year study of 40 patients with advanced PD and severe levodopa-related motor complications showed continuous infusion of levodopa or a dopamine agonist to provide long-lasting and dramatic improvement in established motor complications.[14] However, infusions are cumbersome and may be associated with side effects at the site of administration; patients with early disease are likely to resist this treatment approach.[6] Continuous levodopa delivery by intraintestinal infusion has been shown to reduce established dyskinesia in patients with advanced disease, but the procedure requires surgery and frequent repositioning or replacement of the catheter.[15-21] On the basis of these factors, it is logical to start treatment in appropriate patients with a long-acting dopamine agonist and to add levodopa when their symptoms can no longer be satisfactorily controlled with that agent.[22,23] Factors such as the cognitive state of the patient and financial resources should be taken into account when deciding on initial therapy for PD.

Dopamine agonists fall into 2 major classes: first-generation ergot derivatives (eg, bromocriptine, pergolide [no longer marketed in the United States]) and the second-generation non-ergolines (eg, pramipexole, ropinirole).[24] A transdermal dopamine agonist, rotigotine, was recently removed from the market (see below).

All stimulate dopamine receptors directly, but the second-generation agents are not associated with retro-

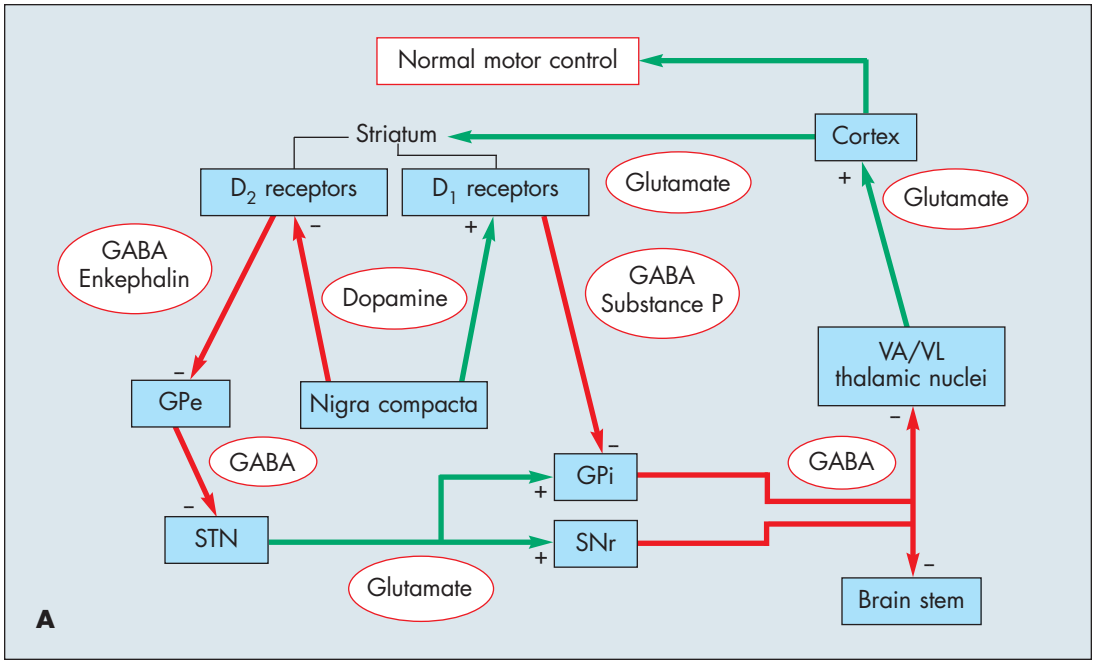
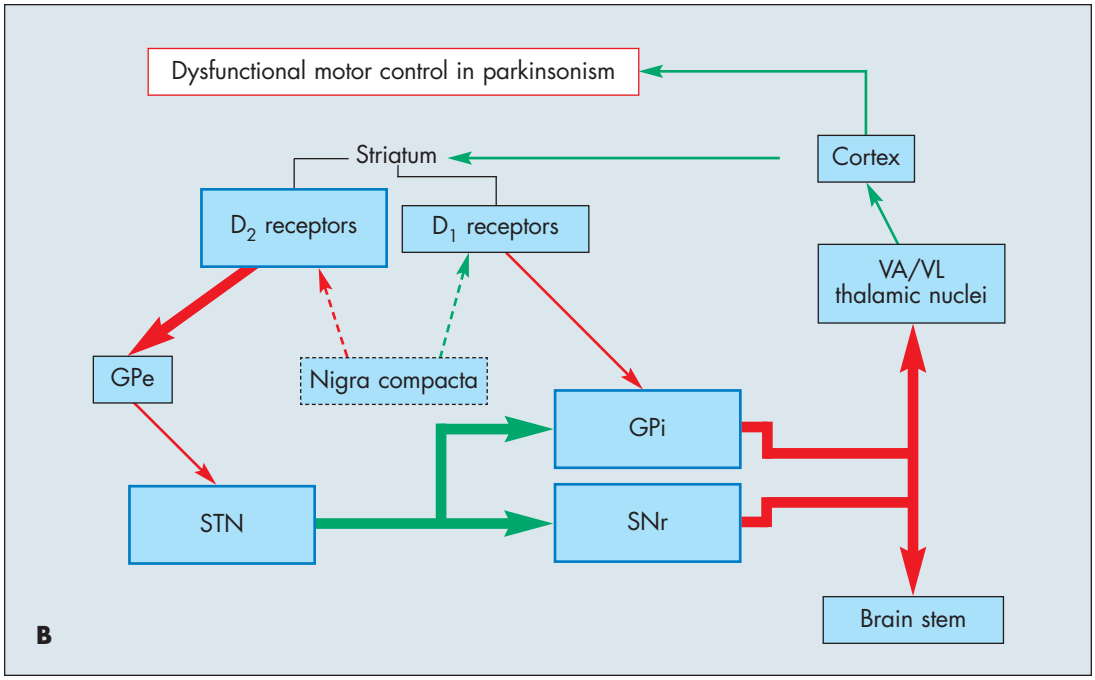



Figure 1 – Illustrated here is a simplified proposed functional model of the basal ganglia in patients with parkinsonism. In the striatum, the GABAergic output neurons projecting directly to the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr) contain a predominance of $D_1$ dopamine receptors. The neurons projecting to the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN) carry predominantly $D_2$ receptors. Dopamine has different effects on these receptors and, in turn, on the subpopulations of striatal output neurons, exciting those expressing $D_1$ receptors (green arrows, the direct striatopallidal pathway) and inhibiting those with $D_2$ receptors (red arrows, the indirect pathway).

The width of the arrows indicates degree of overall functional change in the activity of each pathway (changes in neural firing rates) compared with the normal state. The size and outlining of each box indicate the activity of the brain region compared with normal. Dashed lines and arrows indicate the dysfunctional nigrostriatal dopamine system in Parkinson disease. (Adapted from Lang AE, Lozano AM. *N Engl J Med.* 1998.[2])



peritoneal and pulmonary fibrosis and cardiac valve dysfunction, which have been reported with ergot-derived agents. The first- and second-generation agonists also show different pharmacological properties because they tend to act on different subsets of receptors. For example, the older, ergoline agents bind with high affinity to $D_2$ family receptors but also show affinity of varying degrees for $D_1$, adrenergic, and 5HT receptors. On the other hand, the non-ergolines bind only to $D_2$ and $D_3$ receptors with high affinity; pramipexole is more potent at $D_3$ binding.

When used as an adjunct to levodopa, dopamine agonists reduce both motor disability and on-off fluctuations in patients with advanced PD.[25-29] According to more recent prospective, double-blind, multicenter trials, the rate of motor complications associated with levodopa therapy is significantly reduced in patients who were randomized initially to pergolide,[30] cabergoline,[31,32] ropinirole,[10,33] or pramipexole.[11]

All dopamine agonists are associated with CNS side effects in varying degrees, which may include insomnia, somnolence, and visual hallucinations (neuropsychiatric adverse effects). Dopamine agonists can also cause GI side effects, including nausea and vomiting. Moreover, although dopamine agonists delay the introduction of levodopa, they neither prevent nor delay the development of motor complications once levodopa is initiated. The time to the development of motor complications is about the same whether the drug is used to initiate therapy or is added to supplement the waning agonist response.[10,23]

## ERGOT DOPAMINE AGONISTS

**Bromocriptine.** This dopamine agonist directly stimulates both pre- and postsynaptic receptors, with a high affinity to $D_2$ receptors (it is also

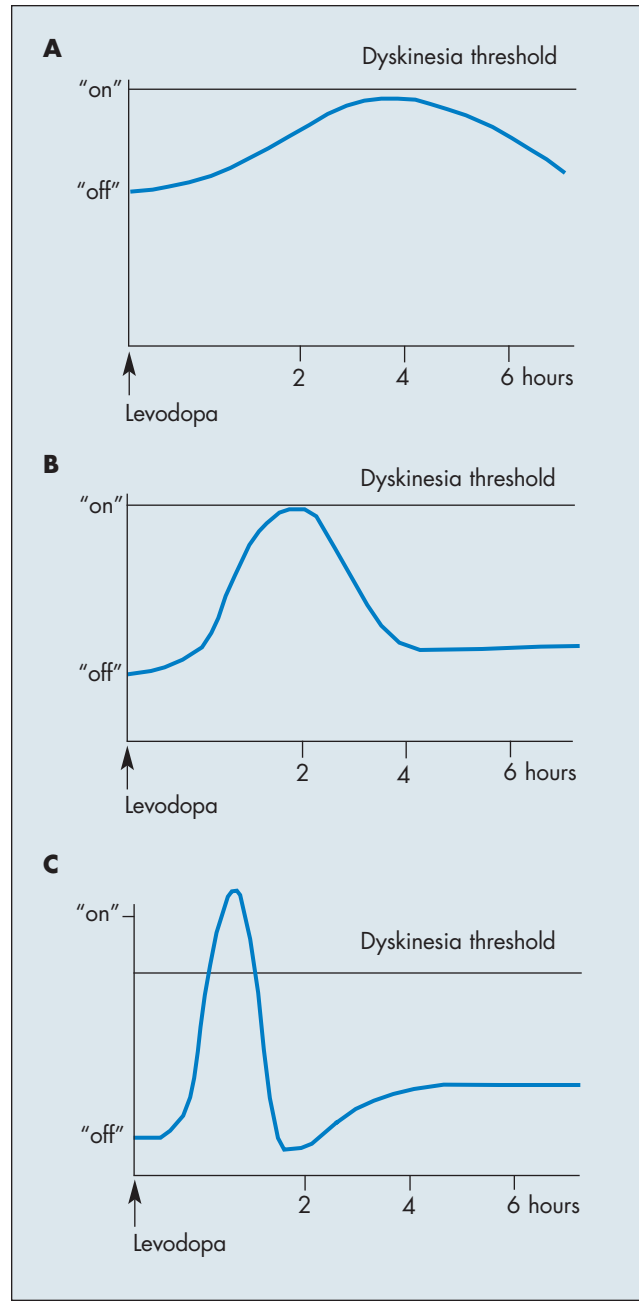



Figure 2 – Illustrated here is the pharmacological response to a levodopa challenge in patients with mild (A), moderate (B), and severe (C) PD. In the early stage, response is slow in onset, has small magnitude, and a long duration. In the intermediate stage, the severity of motor dysfunction in the off state has increased and the response is of greater magnitude and shorter duration. Dyskinesias may be elicited at this stage. In the late stage, motor response is abrupt and has a very large magnitude, but the duration is short and the threshold for dyskinesia is reduced.

(From Olanow CW, Obeso JA, eds. In: *Dopamine Agonists in Early Parkinson's Disease*. 1997.[6])

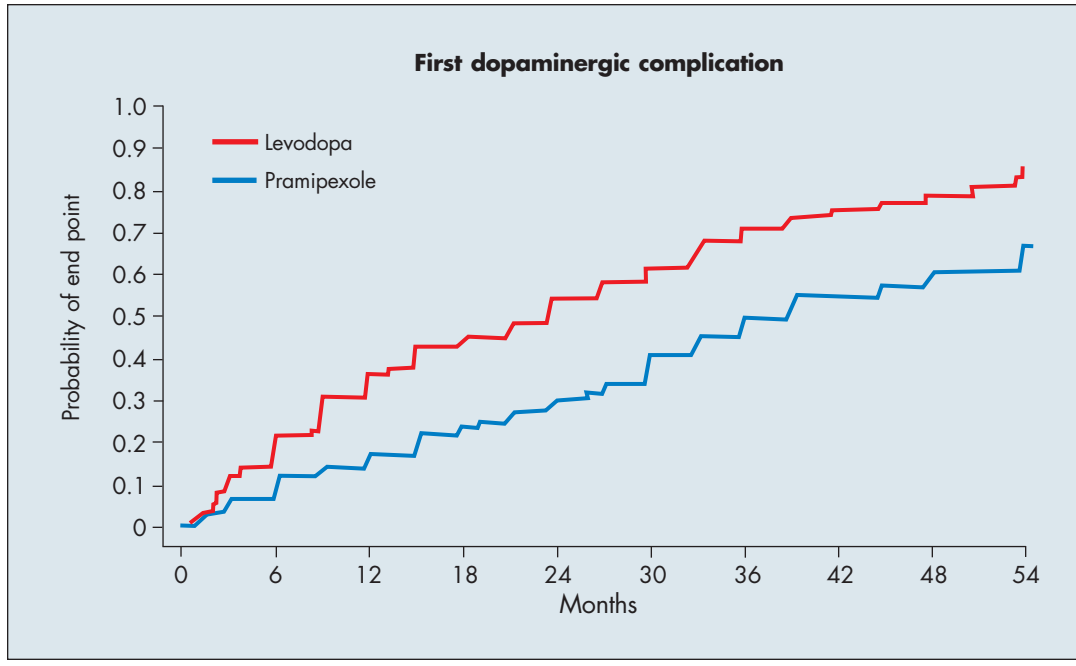



Figure 3 – Time to first dopaminergic complications[a] for initial therapy with either levodopa or the dopamine agonist pramipexole.

[a] Wearing-off, dyskinesias, on-off fluctuations. Levodopa supplementation was allowed for both groups after 10 weeks.

(From Holloway RG et al. *Arch Neurol*. 2004.[11])

a partial antagonist of $D_1$ receptors). In a 42-month study of levodopa monotherapy versus levodopa plus bromocriptine (as partial substitution for more than 30% of levodopa) in de novo patients with early PD, the severity and extent of motor dysfunction was significantly less in those receiving combination therapy.[34] However, the usefulness of bromocriptine has been tempered by a lengthy titration schedule (weeks to months)[35] and by reports of retroperitoneal fibrosis in patients receiving long-term therapy at high dosages.[36] The introduction of non-ergoline agents with more rapid titration schedules and greater tolerability has also superseded bromocriptine in the treatment of levodopa-induced dyskinesia and on-off phenomena.

**Pergolide.** A strong $D_2$ and a weak $D_1$ receptor agonist, pergolide is effective in reducing motor complications as both monotherapy[30] and adjunctive therapy to levodopa.[27,30]

Four earlier reports of retroperitoneal, pericardial, or pleural fibrosis and valvular insufficiency in patients treated with high-dose pergolide[37-40] were followed in 2003 by one report of pergolide-associated valvular heart disease.[41] A year later, echocardiographic evidence of valvular insufficiency was reported in 10 patients who were receiving high-dose pergolide.[42] At least 4 more studies have described the association of pergolide with valvular heart disease.[43-46] In 2007 the US FDA announced that the manufacturers of pergolide were voluntarily withdrawing it from the market.

## NON-ERGOT DOPAMINE AGONISTS

**Ropinirole.** A highly selective non-ergoline $D_2$ agonist, ropinirole is effective as early monotherapy and as an adjunct to levodopa. A study of ropinirole as monotherapy in patients with early-stage PD demonstrated a 24% improvement in motor function at 6 months in the monotherapy group compared with a 3% worsening in the placebo group ($P < .001$).[47]

The safety and efficacy of ropinirole and of levodopa were compared in a 5-year double-blind, randomized, multicenter study of patients with early PD who required dopaminergic therapy.[10] The primary outcome measure was the occurrence of dyskinesia. A total of 268 de novo patients were randomized to receive either levodopa (89 patients) or ropinirole (179 patients). Patients could receive supplementary levodopa in an open-label fashion if symptoms were inadequately controlled. At 5 years, the cumulative incidence of dyskinesia, regardless of levodopa supplementation, was 20% in the ropinirole group and 45% in the levodopa group. The investigators concluded that early PD can be managed successfully for up to 5 years with a reduced risk of dyskinesia by initiat-

ing treatment with ropinirole alone and supplementing it with levodopa if necessary.

The 2-year, double-blind Requip As Early Therapy Versus L-dopa—Positron Emission Tomography (REAL-PET) study compared the rates of loss of dopamine-terminal function in 162 de novo patients randomized with either levodopa or ropinirole, with levodopa supplementation if necessary.[12] The primary outcome measure was reduction in putamen (18)F-dopa uptake between baseline and 2-year PET scans. A significantly slower reduction in (18)F-dopa uptake in the putamen was seen over the 2 years with ropinirole (−13.4%) than with levodopa (−20.3%). However, direct pharmacological effects of the study medications or compensatory mechanisms induced by them cannot be excluded as alternative explanations for these results. Of note, levodopa supplementation was allowed in both groups. Although dyskinesia developed in 3% of patients taking ropinirole compared with 27% of those taking levodopa, patients who received levodopa showed significantly greater motor improvement.

Ropinirole is also effective as an add-on therapy to levodopa. In one study, 27.7% of ropinirole-treated patients had at least a 20% reduction in levodopa dose as well as a 20% reduction in off time, compared with 11% in the placebo group.[48]

**Rotigotine.** This dopamine agonist was developed for administration via a silicone-based transdermal patch.[49-51] This agent was recently removed from the market, however, because of crystal formation on the patches that diminished the amount of available drug. For this reason, this agent will not be discussed further here.

**Pramipexole.** This non-ergot synthetic amino-benzathiazol derivative binds to $D_3$ receptors with 7-fold greater affinity than it does to either $D_2$ or $D_4$ receptors.[52] Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers.[53] In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. Pramipexole should be titrated gradually with doses increased every 5 to 7 days to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth. Starting with 0.125 mg tid, a suggested ascending dosage schedule increases to an individualized effective and well-tolerated maintenance dose. Inhibitors of cytochrome P-450 enzymes would not be expected to affect the elimination of pramipexole because it is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole is effective as both monotherapy and in combination with levodopa in the treatment of PD.

An early 24-week multicenter, randomized, double-blind study of pramipexole's safety and efficacy that included 335 patients with early PD concluded that the drug was safe and significantly improved motor function and activities of daily living, compared with placebo.[54] In the assessment of adverse events, nausea, insomnia, constipation, somnolence, and visual hallucinations occurred more frequently in the pramipexole group than in placebo recipients.

The Comparison of the Agonist Pramipexole With Levodopa on the Motor Complications in Early PD (CALM-PD) trial was the first controlled study to compare long-term outcomes with dopaminergic therapy.[55] This randomized, multicenter, parallel-group, double-blind clinical trial involved 301 patients who required antiparkinsonian therapy to treat emerging disability. Subjects were randomized to active pramipexole or levodopa monotherapy; starting at week 11, addition of open-label supplemental levodopa was allowed in both treatment groups. The primary outcome measure was the time to the first occurrence of any of 3 dopaminergic complications: wearing off, dyskinesias, or on-off motor fluctuations.

Patients treated initially with pramipexole had significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with those taking levodopa (51%) (hazard ratio, 0.45; 95% confidence interval [CI], 0.30 to 0.66; $P < .001$). However, there was a greater mean improvement in total UPDRS score from baseline to 23.5 months in the levodopa group compared with the pramipexole group (pramipexole, 4.5 [12.7]; levodopa, 9.2 [10.8]; $P < .001$). Somnolence, peripheral edema, and hallucinations were more common in pramipexole than in levodopa-treated patients (32.4% vs 17.3%; $P = .003$). At the end of the study, patients treated with levodopa had greater improvement in UPDRS motor scores than those treated with pramipexole (pramipexole 3.4 [8.6]; levodopa 7.3 [8.6]; $P < .001$). Nevertheless, mean changes in quality-of-life scores did not differ between the treatment groups.

The question of whether pramipexole could actually slow disease progression was examined in the CALM-PD-CIT substudy, in which 82 patients with early PD underwent dopamine transporter imaging at baseline and at 22, 34, and 46 months as an index of remaining dopamine neurons.[56] Single photon emission CT (SPECT) showed that the mean percentage loss in striatal uptake from baseline was significantly reduced in the pramipexole group compared with the levodopa group (**Figure 4**). However, direct pharmacological effects of the medications or compensatory mechanisms induced

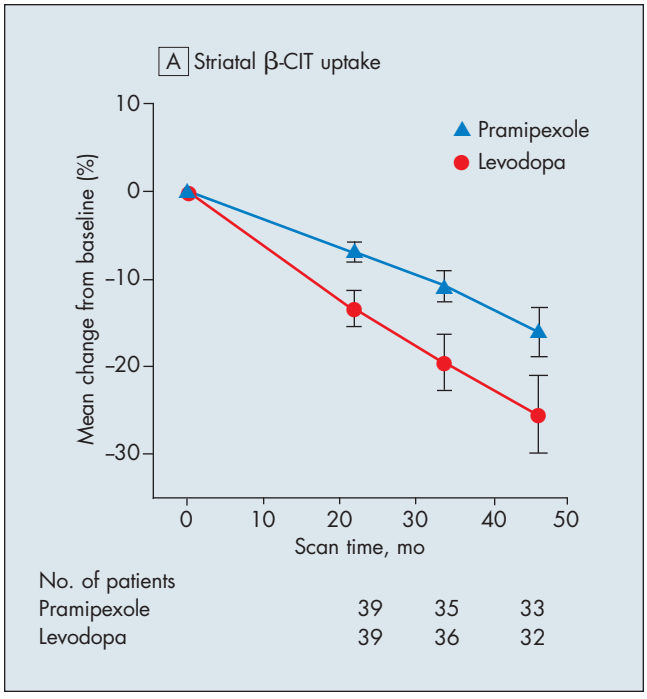



Figure 4 – The rate of decline in striatal uptake from baseline, measured by single photon emission CT (SPECT), was significantly reduced in the pramipexole compared with the levodopa group.

(Adapted from Parkinson Study Group. *JAMA*. 2002.[56])

by them cannot be excluded as possible alternative explanations for the difference.

One double-blind, placebo-controlled study compared the efficacy, safety, and tolerability of pramipexole with placebo in 291 patients with advanced PD who were treated with levodopa and who were experiencing motor fluctuations.[28] There was improved motor function in pramipexole-treated patients during "on" and "off" periods compared with those patients treated with placebo, as well as decreased time spent in "off" periods and a reduction in the severity of "off" periods. The use of pramipexole also permitted a reduction in levodopa dosage. Adverse effects were similar to those usually attendant on dopamine agonists.

Another double-blind, placebo-controlled study in 354 patients with PD who had motor fluctuations and who were taking levodopa found that pramipexole treatment improved UPDRS parts II and III (activities of daily living and motor examination) scores by 30% and reduced off times by roughly 2.5 hours per day.[57] There were significant differences between treatment groups at a relatively low daily dose of pramipexole (0.75 mg/d). An open-label extension phase of this study provided data for up to 57 months and confirmed the long-term safety and efficacy of pramipexole. Post hoc analysis of these findings further showed that in the subgroup of patients with a UPDRS I score of greater than 0 at inclusion, decreases in this score with pramipexole were mainly caused by significant improvements in motivation/initiative and depression.

In addition to its efficacy in treating rigidity and akinesia, pramipexole reduced parkinsonian tremor in 16 patients with advanced PD and marked rest tremor during the on period.[58] Subjects represented a subgroup of patients recruited by one center to participate in a placebo-controlled, randomized, double-blind, multicenter European phase 3 trial of pramipexole's efficacy and safety. Eleven patients received pramipexole; 5 received placebo.

The first effects were seen with a pramipexole dose of 0.75 mg/d, with a reduction of tremor item on the UPDRS (part III rest tremor parameters, during on periods) of 35% and of rigidity and akinesia of 22%. With the highest dose, 4.5 mg/d, tremor score was improved by 61% over baseline and the sum of rigidity and akinesia items was improved by 65%. The 5 patients who received placebo did not show any improvement of motor function except at dose levels of 3.57 and 4.5 mg/d. At 3.57 mg/d UPDRS scores were 136% of baseline for tremor and 139% for rigidity and akinesia. Correspondingly, placebo patients' UPDRS scores did not change significantly after washout from the study's double-blind phase.

Another double-blind, randomized, placebo-controlled study compared the tremorlytic properties of pramipexole with those of placebo as add-on medication in 84 patients with PD who had marked drug-resistant tremor.[59] Patients were taking optimized antiparkinsonian medication at the time of study entry, and they were randomized to either pramipexole (n = 44) or placebo (n = 40) as adjunct medication. The primary end point of the study was the change in tremor score (the sum of tremor-related items 16, 20, and 21 on the UPDRS in the "on" state).

Pramipexole significantly reduced tremor compared with placebo, with a 34.7% reduction in tremor scores ($P < .0001$). The visit-by-visit analysis of the change in tremor score showed that the improvement under pramipexole increased in a dose-dependent manner during the

ascending dose interval and seemed to remain stable between the beginning and end of the maintenance period (**Figure 5**). The mean daily dose of pramipexole during the maintenance phase of the study was 4.1 mg (SD, 0.9). Long-term electromyographic recordings were performed as an objective measure of tremor; significant improvement was noted in pramipexole-treated patients. There were also improvements in investigators' and patients' assessments of tremor. Patients who were treated with pramipexole had more fatigue, insomnia, nausea, abdominal pain, and headache than patients who were treated with placebo.

**Apomorphine.** This potent nonergot dopamine agonist exerts strong activity at both the $D_1$ and $D_2$ dopamine receptors of the striatum, thus mimicking the action of dopamine more closely than any other available agent.[60] The efficacy of apomorphine is identical to that of levodopa and substantially greater than that of any other orally administered dopamine agonist. Because of extensive first-pass hepatic metabolism when taken orally, apomorphine can be administered only parenterally, resulting in a half-life of about 40 minutes, with clinical effects that last about an hour. When given by intermittent subcutaneous injection, the most common route, in doses ranging from 2 to 10 mg, apomorphine produces adequate blood and cerebrospinal levels within 7.5 to 10 minutes, resulting in robust antiparkinsonian effects.[60,61] Thus, apomorphine is well suited for the purpose of "rescue," the rapid termination of levodopa-induced fluctuations, including tremor, bradykinesia, and limb rigidity.[62]

Given the relatively brief clinical response to its short half-life, apomorphine will not have an additive effect when used with longer-acting oral drugs. Furthermore, because the drug does not accumulate in the brain, dyskinesias do not typically increase later in the day when it is initiated during off periods; this is in contrast to the accentuation of dyskinesias associated with levodopa when used as-needed for off states.[60]

Because one of the most common side effects of apomorphine is nausea and vomiting, all patients should be pretreated for at least 3 days with an antiemetic (domperidone in Europe; trimethobenzamide, 250 to 300 mg tid, in the United States) before the first injection.

The pivotal trial for the approval of subcutaneous apomorphine injectable in the United States assessed its efficacy in patients with advanced PD who had at least 2 hours of off time daily despite optimized oral antiparkinsonian medications.[63] Of 29 patients recruited, 20 were randomized to receive titrated doses of subcutaneous apomorphine (2 to 10 mg) and 9 were to receive placebo during an inpatient and 1-month outpatient phase. The average levodopa equivalent dose of apomorphine was 5.4 ± 0.5 mg, and mean placebo dose was 1 mL. Phase 1 consisted of an inpatient assessment of PD symptom reversal with apomorphine after withholding antiparkinsonian medications overnight; phase 2, a 4-week outpatient treatment trial, assessed drug effectiveness in terms of reversal of spontaneous off episodes and total time off.

Mean inpatient UPDRS motor scores were reduced by 23.9 (62%) and 0.1 (1%) points by apomorphine treatment and placebo, respectively ($P < .001$). Twenty-five subjects (17 active and 8 placebo) completed phase 2 and were allowed to administer up to 5 doses of apomorphine daily. The active group self-administered 2.5 doses per day; the placebo group, 2.3 doses per day. The active group reported a 95% rate of off-state events arrested compared with 23% in those taking placebo. The apomorphine group reported a median of 2 hours less off time per day, whereas the placebo group reported no change. A significantly greater frequency of yawning and drowsiness was reported with apomorphine. Nausea occurred in 35% of apomorphine patients compared with 11% of

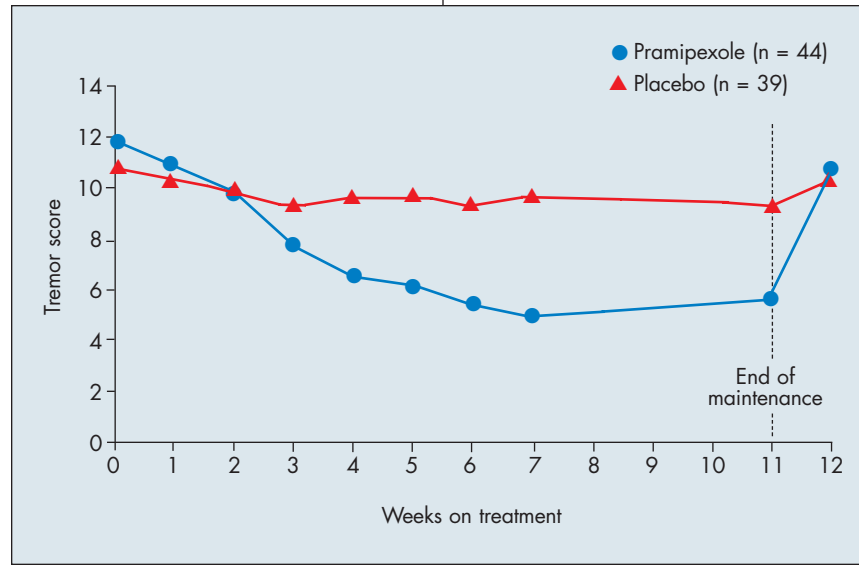



Figure 5 – Shown here is the development of mean tremor score (sum of UPDRS items 16, 10, and 21) per week with pramipexole and placebo from baseline, through weeks 1 to 7 (ascending dose interval), weeks 7 to 11 (maintenance period), to weeks 11 and 12 (dose reduction). (Adapted from Pogarell O et al. *J Neurol Neurosurg Psychiatry*.2002.[59])

placebo patients, but the difference was not significant. No other significant changes were seen in symptoms, physical findings, ECGs, or blood test results.

Following antiemetic treatment, the initial dose of apomorphine should always be given under nurse or physician supervision because of the possibility of acute orthostatic hypotension.[60] The patients should be in an off state, and baseline blood pressure should be measured in both the standing and supine positions. A test dose of 2 mg should be given with repeated measurement of orthostatic blood pressures at 20, 40, and 60 minutes. The 2-mg dose for reversal of spontaneous off states can be prescribed for patients who respond with motor improvement and without an acute adverse event. Those who do not respond to the 2-mg test dose but have no acute adverse reaction may be given an additional test dose of 4 mg (2 hours after the initial test), and if the response is positive, they may be discharged with a 3 mg prescription.

Most patients respond to doses of 3 to 6 mg; the average frequency of dosing in the apomorphine development program was 3 times daily.[60] Experience with dosing frequencies greater than 5 times per day or total daily doses exceeding 20 mg is limited.

## OTHER DOPAMINE RECEPTOR AGONISTS

A number of ergot and non-ergot dopamine agonists are available in Europe but are either not available or not indicated for PD in the United States. These agents include the ergoline derivatives cabergoline,[64-71] dihydroergocryptine,[72,73] and lisuride,[74-82] and the non-ergoline piribedil.[83-89]

## SIDE EFFECTS OF DOPAMINE AGONISTS

Ergoline dopamine agonists may cause retroperitoneal and pleuropulmonary fibrosis, albeit very rarely.[82] In addition, they may give rise to Raynaud syndrome and erythromelalgia.[90] The ergoline derivatives in high doses have also been associated with valvular heart disease, most recently in a study that found echocardiographic changes with cabergoline and pergolide,[91] the latter now withdrawn from the market. The non-ergolines pramipexole and, to a lesser degree, ropinirole have been associated with sudden sleep attacks or at least somnolence.[92,93] According to a large European survey, the non-ergolines have a slightly higher tendency towards somnolence than the ergolines.[94] The propensity for levodopa and the dopamine agonists to cause psychosis or neuropsychiatric symptoms in patients with PD, including hallucinations[95] and compulsive symptoms such as pathological gambling or stereotyped behaviors (termed punding), has been reported.[96,97]

**Sleepiness and sleep attacks.** Patients with PD are known to have disordered sleep architecture, including vivid dreaming, nocturnal vocalization, excessive daytime sleepiness, and altered sleep-awake cycles, as well as movement disorders specific to sleep. Virtually all dopaminergic antiparkinsonian medications may contribute to sleep problems, but somnolence, excessive daytime sleepiness, and sleep attacks appear to be more common in patients with PD who are treated with dopamine agonists than in those treated with other agents.[93] Somnolence caused by dopamine agonists may be dose related and occurs most frequently during the dose-escalation phase of therapy. Sleep attacks, described as sudden, irresistible, overwhelming sleepiness without awareness of falling asleep, may be triggered by down-regulation of dopaminergic input to the reticular activating system, possibly by the action of the agents on presynaptic receptors.[90] Sleep attacks can occur with all dopaminergic drugs, including alpha-dihydroergocryptine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, and ropinirole, with no significant difference between ergot and non-ergot agents.[87,93]

**Psychosis.** This is defined as a disturbance of perception and thought and commonly includes hallucinations, delusions, paranoid beliefs, agitation, and delirium.[96] Psychotic symptoms are common in patients with PD and dementia but are also observed as a drug-induced phenomenon in patients without obvious cognitive dysfunction.[10,98,99] Early drug-induced psychosis has been observed in up to 16% of patients treated with dopamine agonists and has been associated with an increased risk of the development of dementia later on.[96] Visual hallucinations are the most common clinical manifestations and have been observed in about 30% of patients over the course of PD.[100,101] Up to 16% of patients exposed to dopamine agonists or combinations of dopamine agonists with levodopa have been observed to develop symptoms of drug-induced psychosis.[96]

In an animal study of the relative propensity of clinically available dopaminergic drugs (levodopa, pergolide, ropinirole, and pramipexole) to induce neuropsychiatric symptoms, levodopa-treated 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset models of psychosis-like behavior in parkinsonism were administered doses of study agents that produced an equivalent full reversal of parkinsonism.[102] All drugs significantly reversed peak-dose parkinsonian disability and induced peak-dose psychosis-like behaviors (agitation, stereotypies, and hallucinatory-like and obsessive-compulsive behaviors). These findings suggest that the nature of the dopaminergic agent employed may not be a major factor in determining the degree of the comparative neuropsychi-

atric adverse events of antiparkinsonian therapies, although no similar study in humans exists.

**Impulse control and dopamine dysregulation disorders.** A number of reports in the literature suggest that impulse control disorders (ICDs) and dopamine dysregulation disorders, including pathological gambling,[103] pathological hypersexuality,[104] punding,[105] binge eating,[106] compulsive shopping,[107] and compulsive dopaminergic medication use,[108] may occur in patients with PD and are possibly associated with dopaminergic stimulation. In a survey of patients with PD, ICD during the course of PD was seen in 6.6% of patients, while 4.0% of patients had an active ICD.[109] Another study found the lifetime prevalence of these impulse-control behaviors was 6.1% and increased to 13.7% in patients receiving dopamine agonists.[110]

The precise pathophysiology of ICDs is unknown, but appears to involve alterations in specific neurotransmitter systems, brain regions, and neural circuits. Dopamine function is important in the mediation of reward and reinforcement behavior.[111] For example, the prefrontal cortex, ventral striatum, and amygdala mediate aspects of impulsivity.

Several explanations for an association between ICDs in PD and treatment with dopamine agonists have been proposed, which include:

- The loss of dopamine influences dopaminergic cortical-subcortical circuits, leading to cognitive and emotional impairment that can predispose to the development of psychiatric disorders, including ICDs.[109]
- Patients who have PD may display executive function deficits[112] linked to degeneration in the frontal-striatal tracts secondary to cell loss within the $SN_c$.[113]
- In addition to activating $D_1$ and $D_2$ receptors in the dorsal striatum that are associated primarily with their motor effects, agonists also bind to the $D_3$ receptors,[114] which are localized to limbic areas and may mediate psychiatric manifestations of dopamine receptor stimulation.[115]

*Gambling.* In a prospective screening study (using a modified South Oaks Gambling Scale) of 297 patients with PD who attended a tertiary clinic, lifetime prevalence of pathological gambling was 3.5% and prevalence while taking any dopamine agonist was 7.2%.[103] (The *DSM*-defined pathological gambling prevalence in the patients' area was 1%.) Pathological gambling was associated with earlier onset of PD and with dopamine agonists but not with agonist subtype or doses. The $D_1/D_2$ (pergolide) and the $D_2/D_3$ (ropinirole and pramipexole) agonists were equally implicated. As a point of comparison, a recent general-population survey in California found the overall lifetime prevalence of problem or pathological gambling was 3.7%; the rate was higher among people who were disabled or unemployed.[116]

*Hypersexuality.* This condition has not been associated with any specific agonist, and it has been reported in patients receiving levodopa monotherapy as well.[104,110] Among 297 patients who completed systematic screenings and met rigorous definitional criteria, 7 reported behaviors consistent with diagnostic criteria for hypersexuality.[110] In 2 patients, hypersexuality occurred either while receiving levodopa monotherapy or before the initiation of adjunctive agonist therapy. The lifetime prevalence of pathological hypersexuality was found to be 2.4% and that of compulsive shopping to be 0.7%. Six of 7 patients had comorbid depression, but whether it was secondary to the behavior, the result of similar pathophysiological substrates, or as mediator of the behavior is unknown. Timing of the depression in relation to the onset of the hypersexuality was not clearly established.

*Punding.* This refers to engaging in complex, prolonged, purposeless, and stereotyped behavior.[105] A questionnaire survey found that Punding Scale scores were higher among 141 patients with PD than among 103 controls (11.88 vs 10.21, respectively; $P < .001$). Of 14 clinical, demographic, and medication factors investigated as predictors of punding, daily use of dopamine-receptor agonists was 1 of 9 independent predictors of a higher score. The largest independent predictors, however, were age at onset of PD, score on the Barratt Impulsivity Scale, and Parkinson's Disease Questionnaire–39 score. The authors note that dopamine-agonist use was higher in patients with an earlier onset of PD.[105] Another study of 45 patients found that punding was associated with severity of dyskinesias but not with dopamine agonist use.[117] A review of compulsive and punding behaviors associated with dopaminergic treatment in PD places punding in obsessive-compulsive spectrum disorders, noting that OCD is conceptualized as a disorder of corticostriatothalamo-cortical circuitry.[118]

## INITIATING TREATMENT WITH PRAMIPEXOLE

In all clinical studies, dopamine agonists were initiated at a subtherapeutic level to avoid side effects, particularly orthostatic hypertension. Thus, in patients with normal renal function, pramipexole is initiated at a starting dose of 0.125 mg tid (0.375 mg/d) for 1 week, 0.25 mg tid for the second week, and 0.50 mg tid for the third week, with further incremental dose adjustments of 0.25 mg tid per week based on patient response, up to 1.50 mg tid (**Table**).[119]

**Pramipexole in monotherapy.** Pramipexole has demonstrated efficacy and is well tolerated over a dosage range of 1.5 to 4.5 mg/d, with

or without levodopa at approximately 800 mg/d.[119] A fixed-dose study using 1.5, 3, 4.5, and 6 mg/d showed no significant therapeutic benefit beyond that achieved at 1.5 mg/d. However the frequency of some dose-related adverse events (postural hypotension, nausea, constipation, somnolence, and amnesia) was 2-fold greater than that of placebo at pramipexole dosages greater than 3 mg/d.

**Pramipexole in combination therapy.** When pramipexole is used in combination with levodopa, reduction of the levodopa dosage should be considered. A controlled study of patients with advanced PD found that the dosage of levodopa was reduced by an average of 27%.[28] In this trial, pramipexole was initiated by incremental titration over a 7-week period.

## SWITCHING DOPAMINE RECEPTOR AGONISTS

Switching dopamine agonists may be necessary because of tolerability issues, potential for fibrotic adverse events, control of non-motor symptoms of PD, such as hallucinations and depression; or because the efficacy of an agonist wanes.[120,121] Soon after the non-ergoline dopamine agonists were introduced, one of the first studies to look at how best to switch from an ergot to a new non-ergot agent, pramipexole, involved 16 patients receiving stable regimens of carbidopa/levodopa and bromocriptine or pergolide.[120] An end-equivalency pramipexole dose was calculated using a daily milligram conversion of 1:1 for pergolide and of 10:1 for bromocriptine. Patients were randomized to 2 titration schedules: the slow schedule (8 patients), following the early package insert, which could take up to 8 weeks to reach an equivalent dose; or rapid titration, with patients receiving the full converted dose the day after stopping the former agonist, with subsequent weekly adjustments. Both groups showed equivalent and statistically significant improvement after the switch to pramipexole.

The mean time to reach a UPDRS score superior to baseline without increased adverse effects was significantly shorter for the rapid-titration group. Moreover, with slow titration, 2 patients experienced enhanced parkinsonian side effects (falls with fractures) requiring hospitalization.

In a later open-label trial, 217 patients with advanced PD who were not optimally controlled by levodopa and a stable dose of bromocriptine (58 patients), pergolide (125), or ropinirole (34) were converted overnight to pramipexole.[121] The switch was made according to the following dose equivalency scheme: 1 mg of pramipexole = 1 mg of pergolide = 10 mg of bromocriptine = 4 mg of ropinirole. Clinical assessments were performed just before conversion and after 2, 6, and 12 weeks of treatment, when an optimal dose of pramipexole was achieved.

Mean levodopa dose was slightly reduced in all groups, and UPDRS activities of daily living, motor examination, and complications of therapy (parts II, III, and IV) scores were reduced by 26% to 30% in all patients. No serious or unexpected side effects were reported. The investigators concluded that switching from the 2 ergot dopamine agonists or 1 non-ergot dopamine agonist to pramipexole on an overnight schedule was safe, and that the observed clinical improvement may be related to a placebo effect, to the use of low doses of dopamine agonists, or to a direct effect of pramipexole. ■

**Table – Ascending dosage schedule for pramipexole**

| Week | Dosage (tid) | Total daily dose (mg) |
|---|---|---|
| 1 | 0.125 | 0.375 |
| 2 | 0.25 | 0.75 |
| 3 | 0.5 | 1.50 |
| 4 | 0.75 | 2.25 |
| 5 | 1.0 | 3.0 |
| 6 | 1.25 | 3.75 |
| 7 | 1.5 | 4.50 |

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