## Role of Pramipexole in the Management of Parkinson's Disease

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**Abstract (word count 229)**

The non-ergot dopamine agonist pramipexole was first approved for the treatment of Parkinson's disease (PD) in 1997 in the US and 1998 in most European countries. Since then it has become the most prescribed dopamine agonist for the treatment of PD and is currently indicated for the treatment of the signs and symptoms of idiopathic PD, both as monotherapy and as adjunct to levodopa. A new extended release formulation of pramipexole has now also been launched in Europe and the US to improve ease-of-use, compliance and provide a more continuous effect over 24 hours. Before initiating any treatment, the benefit-risk ratio to the individual patient must be considered. For pramipexole in the treatment of PD, this means taking into account the available evidence regarding its symptomatic efficacy, effect on delaying long-term levodopa-related motor complications, benefit on non-motor symptoms such as depression, and its safety and tolerability profile. Studies have shown that pramipexole is effective as monotherapy in early PD and as adjunctive therapy in advanced disease. Trials further suggest that the benefits of pramipexole may extend beyond the relief of motor symptoms (akinesia, rigidity and tremor at rest) to amelioration of depressive symptoms in PD. Pramipexole is generally well-tolerated however, compared to levodopa treatment with pramipexole is associated with a higher rate of some dopaminergic side effects.

## Introduction

The non-ergot dopamine agonist pramipexole was first approved for the treatment of Parkinson's disease (PD) in 1997 in the US and 1998 in most European countries. Since then it has become the most prescribed dopamine agonist for the treatment of PD and is currently indicated for the treatment of the signs and symptoms of idiopathic PD, both as monotherapy and as adjunct to levodopa. It is also currently indicated for the treatment of moderate-to-severe primary restless legs syndrome (RLS).

Since its introduction there has been a widespread move in the PD field to use dopamine agonists as first-line treatment for PD and some patients remain on a dopamine agonist through the entire course of their disease [1, 2]. This means there is now considerable experience, both in trials and in clinical practice with pramipexole. Here we review the overall drug profile of pramipexole, noting that a new formulation – Pramipexole Extended Release is now available. This review examines the evidence for both the immediate- and extended-release formulations of pramipexole and discusses the role of pramipexole in the management of PD.

The review of the literature involved performing searches with specific search terms (pramipexole, pramipexole extended release, mirapexin, mirapex, dopamine agonist) of Medline (1966–May 2010) and the central database in the Cochrane Library (1948–2009). Papers were considered if they were published in the English peer-reviewed literature. In addition, reference lists published in review papers were systematically checked for relevant references, regulatory publications issued by the European Committee of Proprietary Medicinal Products and the US Food and Drugs Administration were reviewed and recent releases of information (congress abstracts and press releases) from major PD clinical trials were considered.

## Basic pharmacology and pharmacokinetic profile of pramipexole

Pramipexole is a synthetic, non-ergot, aminothiazole dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D2 subfamily of dopamine receptors, binding with higher affinity to D3 than to D2 or D4 receptor subtypes [3]. The relevance of D3 receptor binding in Parkinson's disease is unknown but it is suggested that the preferential affinity of pramipexole for the D3 receptor subtype could contribute to efficacy in the treatment of psychiatric symptoms of PD like depression [4]. Unlike the ergot dopamine agonists, pramipexole has little or no interaction with adrenergic or serotonergic receptors [3], which as will be discussed later, means that pramipexole does not appear to exert any fibrotic effects.

Pramipexole shows linear pharmacokinetics. It is rapidly and completely absorbed with peak levels appearing in the bloodstream within 2 hours of oral dosing. It has a high absolute bioavailability of >90% and can be administered without regard to meals (time to peak concentration is 3-4 hours

with food although the extent of absorption remains unaffected) [5]. Pramipexole excretion is primarily renal and there is negligible metabolism of pramipexole [5]. Of particular note is the fact that pramipexole is the only dopamine agonist not appreciably metabolized by the P450 system. This lack of hepatic metabolism has been suggested to minimize drug-drug interactions, which may be clinically relevant as PD predominantly affects the older generation who are often prescribed multiple medications [6].

A new extended release 'once-daily' formulation of pramipexole was developed in an effort to improve ease-of-use, compliance and provide a more continuous effect over 24 hours. In a Phase I trial, where pramipexole immediate release and prolonged-release tablets were assessed in fasted state, the minimum and peak plasma concentration (Cmin, Cmax) and exposure (AUC) of the same daily dose of pramipexole extended-release tablets given once daily and pramipexole immediate release tablets given three times a day were equivalent. Moreover, once daily administration of pramipexole extended-release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of pramipexole immediate release tablets. Maximum plasma concentrations occur at about 6 hours after administration of pramipexole extended-release tablets and a steady state of exposure is reached at the latest after 5 days of continuous dosing [7].

**Therapeutic efficacy in early PD**

Clinical trials of pramipexole have included over 1,200 patients in the early stages of Parkinson's disease (disease durations up to 2.4 years), with 698 patients receiving pramipexole for up to 4 years (Table 1). Following a period of dose titration lasting 6 to 7 weeks, the maintenance dose in all but one of the studies was standardized between 0.375 and 4.5 mg of salt) per day [8-12]. These studies have consistently shown pramipexole efficacy in treating the symptoms of early PD with significantly different changes versus placebo in UPDRS scores of up to 3 points in UPDRS Part II (activities of daily living), up to 5 points in UPDRS Part III (motor) scores and up to 6.5 points in Total-UPDRS scores [8, 9, 11]. Thus, even in the early stages of the disease, where baseline UPDRS scores are lower, pramipexole provides clinically relevant efficacy [13].

Importantly, the Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) trial, compared initial treatment with pramipexole (0.5 mg three-times daily) versus levodopa (100mg three-times daily), followed by open-label levodopa supplementation as required [10, 12]. The primary outcome measure was the time to the first occurrence of dopaminergic complications, which included wearing-off, dyskinesias, ON–OFF fluctuations and freezing. Secondary outcome measures were changes in UPDRS scores and quality of life. The results of the study at 2 years showed that initial pramipexole treatment resulted in significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%)

compared with levodopa (51%) (hazard ratio, 0.45; 95% confidence interval [CI], 0. 30-0.66; P<0.001). Interestingly, almost half (47%) of patients were maintained on pramipexole monotherapy over two years [10]. The benefits of initial pramipexole treatment on motor complication risk were maintained at 4 years where initial pramipexole treatment resulted in a significant risk reduction versus levodopa (52% vs. 74% had developed motor complications at 4 years; hazard ratio, 0.48; 95% CI, 0.35-0.66; P<0.001). By 4 years, 72% of patients in the pramipexole group had required supplemental levodopa therapy and the majority of the dopaminergic complications developed after initiating open-label levodopa treatment. By contrast, the majority of complications in the levodopa group had occurred prior to initiating open-label levodopa treatment [12]. Health-related quality of life (HRQOL) was assessed by EQ-5D in 301 subjects of the CALM-PD study (early randomization to either initial pramipexole or initial levodopa). HRQOL measures improved over the 6 months with a gradual decline in years 2-4. However, the deterioration of HRQOL in years 3 and 4 was greater in patients treated with levodopa compared with those treated with pramipexole (P < 0.05). The incremental effectiveness of pramipexole might be mediated through nonmotor functions, whereas levodopa improved primarily motor domains of HRQOL [14].

Recently, six-year follow-up data for 222 of 301 patients originally randomised to the CALM PD trial continued to show reduced overall dyskinesia rates for those patients initially randomised to pramipexole. Dopaminergic motor complications (wearing off, on-off effects, or dyskinesias) were more common in the initial levodopa group (68.4%) than in the initial pramipexole group (50.0%) (P = 0.002). Interestingly, at this time point, mean changes from baseline in the Total-UPDRS score did not significantly differ between the initial pramipexole (2.4) and initial levodopa (0.5) groups (P = 0.11) [15].

Since motor complications with levodopa can severely limit a patient's quality of life [16], the results from CALM-PD were a major contributor to the international move towards prescribing dopamine agonists as first-line therapy. It must be noted however, that secondary analyses from the study also showed that the mean improvement in total UPDRS score from baseline to 23.5 months was greater in the levodopa group than in the pramipexole group (9.2 vs 4.5 points; P<0.001) [10]. This smaller magnitude of change compared to levodopa is similar to results seen in clinical trials of other dopamine agonists [17, 18] and it is generally agreed that patients who present with more severe symptoms should be prescribed levodopa as first-line therapy [1, 2].

**Therapeutic efficacy in advanced PD**

Several randomized placebo-controlled trials have assessed the efficacy of pramipexole as adjunct to levodopa in patients suffering from levodopa motor fluctuations (Table 2) [19-25]. These studies consistently showed significant improvements of UPDRS motor and ADL scores versus placebo

and Total-UPDRS were improved by 20-40% versus baseline (compared with 4-13% with placebo). At the same time, the introduction of pramipexole adjunct therapy meant that patients could reduce their levodopa dose by an average of 30%. Retrospective analyses of randomized, placebo-controlled trials with pramipexole, pergolide, ropinirole, tolcapone or entacapone as adjuvant therapies to levodopa revealed that the reduction in levodopa dose was most significant for pramipexole and entacapone ($p < 0.0001$). In addition, the most significant reduction in OFF duration was with pramipexole (approximately 30% reduction) and entacapone ($p <0.001$) [26].

Pogarell et al assessed the efficacy of adjunct pramipexole specifically in 84 patients with drug-resistant tremor [27]. Many of these patients had received adjunctive therapy with other agents (including other dopamine agonists) without a satisfactory response. In this study, pramipexole was significantly superior to placebo with a difference between groups in the mean absolute change in UPDRS tremor score (sum of UPDRS items 16, 20 and 21 in the ON state) of -4.4 (95% CI -6.2 to -2.5; $p<0.0001$), corresponding to a difference in the mean percentage change of -34.7% in favour of pramipexole [27].

There have only been a very few randomized, controlled studies comparing the efficacy of pramipexole with other dopamine agonists. One 9-month study also included a bromocriptine arm. In this study, the median percent change in UPDRS II from baseline was -27% with pramipexole, -14% with bromocriptine, and -5% with placebo. Similarly, the median percent change in UPDRS III from baseline was -35% with pramipexole, -24% with bromocriptine and -6% with placebo. However, although there was a clear trend for pramipexole to be more effective than bromocriptine, the study was not powered for between-group comparisons for active treatments and no significant difference between dopamine agonists could be shown [20]. More recently the efficacy of the rotigotine patch was compared to pramipexole (as an active comparator) and placebo. In this study both active therapies showed similar efficacy in reducing OFF time, and were superior to placebo. Responder rates and reduction in OFF-time were in absolute numbers higher for pramipexole, but not enough to show any statistically significance [28]. Finally Reichmann et al conducted a study in 1202 levodopa-treated PD patients who were switched to adjuvant therapy with pramipexole from any other oral dopamine agonist because of insufficient effectiveness on motor performance, tremor, and mood (depression, anhedonia). In this study, the switch to pramipexole led to improvement of all symptoms. Resting tremor improved more than postural tremor [29].

**Neuroprotection or disease modifying effects**

As discussed above, a major advantage of the dopamine agonists, including pramipexole, is that they can delay the motor complications (dyskinesia, wearing-off) that are seen with chronic levodopa use. Studies in early PD with the initiation of therapy using pramipexole, ropinirole, or cabergoline have all demonstrated a reduction in the rate of development of motor complications

[10, 17, 30]. This is observed when the dopamine agonists are used alone as initial monotherapy and when levodopa is added. The basis for the reduced motor complication rate with early agonist use is not fully known. However, dyskinesias themselves are probably related to the degree of striatal denervation, the total dose and duration of levodopa treatment and, importantly, the half-life of the dopaminergic drug used [31, 32]. Levodopa has an increased propensity to cause motor complications as it has a short half-life of 60-90 minutes [33]. By contrast, the half-life of pramipexole is 9–12 hours. There is therefore a consensus that continuous dopaminergic stimulation, with agents such as pramipexole, decreases the risk for these motor complications.

It is also suggested that pramipexole and other dopamine agonists have 'neuroprotective' effects that may be mediated through a number of complementary mechanisms [34-36]. One proposed mechanism is decreased dopamine turnover. By interacting with the dopamine autoreceptors, dopamine agonists decrease the turnover of dopamine and therefore the free radical production associated with its metabolism. For example, pramipexole has been shown to produce a dose-dependent decrease in dopamine concentration when it is incubated with cultured dopaminergic neurons [37]. The antioxidant activity of dopamine agonists is another potential mechanism for neuroprotection. *In vitro* studies have shown that pre-treatment with pramipexole (5-20 μMol) protects the dopaminergic cell line MES 23.5 against dopamine, 6-hydroxydopamine (6-OHDA), and hydrogen peroxide (H2O2)-induced cytotoxicity. Moreover, it was shown that such neuroprotection was not blocked by selective D2 or D3 antagonists, indicating a neuroprotective effect that is independent of its dopamine receptor agonist properties [38]. Another proposed mechanism is the protection of basal ganglia neurones from glutamatergic excitotoxicity. In support of this, pramipexole has been shown to attenuate the loss of tyrosine hydroxylase-positive cells in primary mesencephalic cultures exposed to levodopa. Pramipexole was effective at a concentration of 500 pMol but pergolide, bromocriptine and the inactive stereoisomer of pramipexole were not neuroprotective in this model in this study, suggesting that pramipexole was mediating its neuroprotective effect in this model via D3 receptor activation [39, 40].

The clinical relevance of these protective effects shown *in vitro* is unclear and interpretation is hindered by the absence of placebo controls and of a direct measure of neuroprotection. Moreover, the majority of *in vitro* studies that have shown a neuroprotective effect of pramipexole have required pre-treatment with pramipexole (before toxic insult) and a relatively high concentration of drug [34]. In order to clinically evaluate the neuroprotective potential of pramipexole, the CALM-PD study also included subgroup of patients receiving either levodopa or pramipexole (with or without levodopa) who had ß-CIT SPECT scans before and during the treatment program [10]. Early analysis did not show any significant difference at 2 years in the imaging between the two groups. However, later evaluation using more sensitive quantitation did reveal a significant difference with the patients initiated on pramipexole had significantly greater ß-CIT uptake, implying greater

neuronal density and therefore less nigral loss [10]. At the 3- and 4-year time points, there remained a significant difference in that those initiated on pramipexole continued to have a higher ligand uptake and presumed greater neuronal density, thus implying increased neuronal survival [41].

There has been much debate about the clinical relevance of this substudy (and a similar study with ropinirole [42]) as the lack of a placebo group means that the study cannot confirm whether the result demonstrates protection provided by pramipexole or toxicity caused by levodopa. It has also been widely suggested that the study results could have been due to differences in the pharmacologic effect of pramipexole on the biomarker rather than on cell survival [43]. The recent INSPECT study refutes this latter argument as it failed to detect regulatory or other effects of pramipexole on DAT binding using ß-CIT SPECT [44].

The results of the PRamipexole On Underlying Disease (PROUD) delayed-start study have recently been reported in preliminary format [45]. In this study, 261 patients with early PD were randomized to 6 to 9 months of pramipexole 1.5 mg/day (early treatment group) and 274 patients took a placebo during this phase, and then all of the patients took pramipexole 1.5 mg/day up to 15 months. During the study's first 6–9 months, early initiation of pramipexole (as expected) provided significant benefits versus placebo as demonstrated by a significant difference in the mean slope of change in UPDRS total score from month 4 to month 9. However, at 15 months, there was no significant difference in clinical benefit between the two groups. Furthermore, results of the neuroimaging substudy found no significant difference between the groups' mean 15-month decrease in striatal [$^{123}$I]FP-CIT uptake. Although the study failed to show a disease modifying effect, it is becoming apparent that a number issues with the delayed-start design need to be considered when interpreting the results. For example, the recent delayed-start study with rasagiline (ADAGIO) in which the lower 1 mg, but not the higher 2 mg dose, met the study's primary endpoints leading the authors to conclude that evidence for rasagiline disease-modifying effect is not definitive [46]. The ADAGIO authors discussed the possibility that the more potent a drug is in terms of symptomatic response, the greater may be its capacity to mask any disease modifying effect, especially in a population of patients with only mild symptoms. We believe that, if this were the case for rasagiline, it would hold true for pramipexole, which provides a greater magnitude of symptomatic benefit in earlier disease.

**Non-motor symptoms**

Depression is a common psychiatric non-motor symptom of PD and negatively affects patients quality of life and disability [47]. In a prospective study, Hughes et al. reported that presence of depression and dementia were important predictors of mortality in PD subjects followed for over 11 years [48]. Several clinical studies have provided data that the clinical benefit of pramipexole may

go beyond improvement of motor symptoms to improve depression often associated with PD.

In an Italian randomized trial including 67 PD patients with major depression and without motor complications, pramipexole was compared with sertraline in respect to recovery from depression (using the Hamilton depression scale). Twelve weeks treatment with pramipexole led to recovery in 60.6% of patients, which was significantly higher compared with sertraline (27.3%) [49]. Another 8-month randomized study compared the effects of pramipexole with the ergot agonist pergolide as add-on to levodopa therapy on depression in 41 non-demented patients suffering from both mild–moderate depression and advanced PD. A significant decrease in mean Montgomery and Asberg Depression Rating Scale (MADRS) scores was present only in the pramipexole group. The average UPDRS scores decreased significantly with no statistical difference between both groups at the comparable average total daily dose of both preparations [50]. A large, double-blind, placebo-controlled clinical trial conducted in PD patients suffering from depression has been recently reported. In this study, treatment with pramipexole significantly reduced depressive symptoms in PD and improved quality of life. Pramipexole was also well-tolerated, with fewer AE-related discontinuations of treatment than in the placebo group. Use of pramipexole in PD patients with depressive symptoms may be a practical treatment approach to improving motor and depressive symptoms [51].

In a recent meta -analysis of the effects of mood and motivational symptoms in patients with PD, data were extracted from randomized, double-blind, placebo-controlled trials of pramipexole in the manufacturer's database (i.e. authors had access to unpublished data) that included part I of the UPDRS as an outcome measure [52]. Only patients with baseline scores >0 (range, 0-4) on item 3 (mood) and item 4 (motivation) were included. Of the seven trials (N = 1296), six included patients with levodopa motor fluctuations and one study included patients who did not yet require levodopa. In the pooled data set, 480 patients had a baseline score >0 on item 3 (mood). These mood symptoms improved in 64.7% of patients treated with pramipexole and 43.4% of those receiving placebo (odds ratio weighted by trial = 2.41; $P < 0.001$). Five hundred seventy patients had a baseline score >0 on item 4 (motivation). These motivational symptoms improved in 63.2% of patients treated with pramipexole and 45.0% of those receiving placebo (odds ratio weighted by trial = 2.06; $P < 0.001$). Thus the authors concluded that pramipexole has a beneficial effect on mood and motivational symptoms in PD patients who did not have major depressive disorder [52].

The effects of pramipexole specifically on anhedonia were also measured in 657 PD patients using the self-rated Snaith-Hamilton-Pleasure-Scale (SHAPS-D) [53]. At the same time, depression was assessed by the observer-rated Short-Parkinson's-Evaluation Scale (SPES). At baseline anhedonia was present in 45.7% of all patients and in 79.7% of the depressed patients with PD. Mild depression was present in 47% and moderate to severe depression was present in 22% of the

patients. At the end of the study period of 9 months, the frequency of depression (moderate to severe: 6.8%, mild: 37.6%) and anhedonia (25.5%), as well as motor deficits were significantly reduced during treatment with pramipexole [53].

**Tolerability**

The acute side effects of pramipexole are similar to those observed with other dopamine agonists and levodopa and include nausea, vomiting and postural hypotension. These tend to occur with the initiation of treatment and to abate as tolerance develops. In clinical studies, an approximately equal percentage of patients in the pramipexole and placebo groups discontinued due to an adverse event. Qualitatively, as compared to levodopa, pramipexole and other dopamine agonists have been associated with a higher rate of some dopaminergic side effects, including oedema, hallucinations, somnolence and sudden-onset-sleep as well as impulse control disorders [10, 12, 19, 54].

*Oedema*

Oedema is a common yet poorly understood complication of dopaminergic therapy and occurs as a complication of most dopamine agonists (ergot and non-ergot) as well as levodopa [54]. Most studies have found that pedal oedema with pramipexole abates with discontinuation of the drug. However, it is less clear if there is a relationship between the dose of pramipexole and the intensity of the oedema. Whereas one study in 17 patients (15 PD, 2 RLS) showed a clear dose relationship [55], a retrospective medical record review of 237 pramipexole treated patients could not show any relationship between the dose of pramipexole and the incidence or severity of pedal oedema [56]. A *post-hoc* analysis of the CALM-PD trial recently found the 4-year incidence of leg oedema to be 45% in patients who were initially randomized to pramipexole. Importantly, the oedema mainly emerged after at least two years of continuous therapy, suggesting that studies of shorter duration are likely to underestimate this complication [57].

*Sleepiness*

Depending on the methodology used, excessive daytime sleepiness (EDS) has been found in 16 – 51 % of all PD patients [54]. Sudden onset sleep (SOS) as a side effect from non-ergolinic dopamine agonists like pramipexole and ropinirole was first reported by Frucht et al [58] and may occur between 4 and 6 % of PD patients exposed to dopaminergic therapy [59, 60]. In a retrospective chart review of 40 patients involved in clinical trials at one research center, 6 out of 22 patients assigned to double-blind treatment with pramipexole reported somnolence as an adverse event (1 moderate, 5 mild) compared with 2 out of 18 patients assigned to placebo (1 severe, 1 moderate) [61]. In the open-label extension studies 57% of patients treated with pramipexole reported somnolence as an adverse event; 30% patients reported moderate somnolence and 8% patients reported severe somnolence. For patients with moderate or severe

somnolence, the onset of worst-reported somnolence occurred at a mean pramipexole dose of 4.0 mg (range, 0.75-4.5 mg) per day. Patients had been taking pramipexole for a total of 10.0 months (range, 0.03-22 months). Structured interviews revealed that seven patients had fallen asleep while driving and two reported minor motor vehicle accidents caused by falling asleep. Most patients reported relatively continuous drowsiness that led to falling asleep without acute warning during periods of inactivity. Three patients reported discreet waves of irresistible sleepiness heralded by prodromal symptoms occurring against a background of normal wakefulness [61]. The 4-year results of the CALM-PD study showed that more somnolence was reported in the pramipexole group at 4 years; 12 subjects (8%) in the pramipexole group withdrew because of somnolence versus 1 subject (0.7%) in the levodopa group. Eight of these 12 subjects (66%) described their somnolence as “sudden” or “unexpected” and 5 (41%) reported that these episodes occurred while driving. Two serious adverse events related to driving were reported in the levodopa group and 5 in the pramipexole group. Somnolence seemed to occur mostly during the escalation phase of pramipexole [12]. Further analysis of this data found that initial treatment with pramipexole in patients with early PD almost doubled the risk for developing somnolence [57]. The increased risks of somnolence with pramipexole and other dopamine agonists means that physicians should make all dopamine agonist treated patients aware of this potential problem. Routine assessments should be performed and management should include proper sleep hygiene, ruling out underlying sleep disorders, and using the lowest dose that provides satisfactory clinical control. Patients who have excessive daytime somnolence should not drive until the problem has been resolved.

*Impulse control disorders*

Dopaminergic therapies of particularly PD have been associated with behavioural abnormalities including the dopamine dysregulation syndrome (DDS), abnormal repetitive non-goal oriented behaviours (punding) and reward or incentive-based compulsive actions. Whereas DDS and punding have been associated in particular to treatment with high-dose levodopa, impulse control disorders (ICDs) are more frequent in PD patients treated with dopamine agonists. Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age ( ≤ 65 years), not being married and self-reported family history of gambling behaviours. Furthermore, patients and caregivers should be aware of the fact that other behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/tapered discontinuation should be considered. In PD, typical ICDs include hypersexuality, gambling, compulsive shopping and compulsive eating all of which can have significant impact on the patients daily life [62-64].

Three systematic studies of the prevalence of ICDs in PD found that 6–13% of patients met criteria for an ICD [65-67]. In these studies pramipexole was used in a significant proportion of the patients suffering from an ICD (up to 50% of all dopamine agonist use). However, it must be noted that in

the US (where most studies have been conducted) and in many EU countries, pramipexole is the most widely prescribed dopamine agonist and therefore such observational studies will tend to report more cases of ICD with pramipexole as there is more patient exposure to the drug. Furthermore, no significant differences could be found between the different dopamine agonists in their association with ICDs [65].

*Fibrotic reactions*

Whereas the use of ergot derived dopamine agonists pergolide and cabergoline is significantly limited by the risk of developing the serious conditions of retroperitoneal and pleuropulmonary fibrosis, pramipexole does not appear to exert any fibrotic effects [68]. Indeed, studies of dopamine agonists and valvular heart disease have either reported no cases with pramipexole or frequencies similar to the age-matched control group [69, 70]. This is in line with pramipexole's lack of affinity to serotoninergic receptors, which are thought to be involved in the development of these problems with the ergot agonists.

**Pramipexole extended release**

There are several potential advantages of the pramipexole extended release compared to the immediate release formulation. These include maintaining more consistent dopaminergic activity with steadier plasma levels, increased tolerability, greater compliance from a simpler once-daily dosing regimen and ease in dose titration. Data from two large studies have been so far been presented.

The first study was conducted in PD patients with early disease [71]. In this study, patients were randomized (2:2:1) to double-blind pramipexole extended-release (0.375-4.5 mg, once daily), immediate-release (0.125-1.5 mg tid), or placebo. Patients were flexibly titrated to an effective dose over 7 weeks, then maintained for an additional 26 weeks. A pre-planned interim analysis at week 18 confirmed superiority of pramipexole extended-release over placebo, and in the final analysis at Week 33, non-inferiority was demonstrated between the two pramipexole formulations with an adjusted mean change in UPDRS II+III score of -8.6 points for ER (n=213) and -8.8 points for IR (n=207). The second study was conducted in patients with advanced disease [72]. In this study, patients with advanced PD taking levodopa plus a dopa decarboxylase inhibitor were randomized (1:1:1) to pramipexole extended release (0.375-4.5 mg qd), or immediate-release (0.125-1.5 mg tid), or placebo. Patients were flexibly titrated to an effective dose over 7 weeks, then maintained for an additional 26 weeks. The adjusted mean change in UPDRS II +III at Week 18 was -11.0 points for pramipexole extended-release, -12.6 points for pramipexole immediate-release, and -6.3 points for placebo ($P<0.0002$ and $P<0.0001$ vs placebo, respectively). The adjusted mean change in percentage off-time was -13.3 for pramipexole extended-release, -15.7 for pramipexole immediate-release, and -9.0 for placebo ($P=0.0174$ and $P<0.0001$ vs placebo,

respectively), corresponding to an absolute placebo-corrected improvement of –0.5 hour for pramipexole extended-release and –1.0 hour for pramipexole immediate-release.

**Dosage and administration**

Pramipexole is typically initiated at a dose of 0.25 mg and gradually titrated to 1.5 mg TID depending on patient's response. It should be noted that in dosing studies, the group receiving 0.5 mg TID had benefits comparable with those receiving higher doses, but with fewer side effects. It is therefore suggested to titrate patients to 0.5 mg TID and use higher doses on an individual basis rather than as part of a routine titration schedule.

Pramipexole extended-release tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time. Doses of pramipexole extended release should be increased gradually from a starting dose of 0.26 mg of base (0.375 mg of salt) per day and then increased as needed every 5 - 7 days up to a daily dose of 1.05 mg of base (1.5 mg of salt). If a further dose increase is necessary the daily dose should be increased by 0.52 mg of base (0.75 mg of salt) at weekly intervals up to a maximum dose of 3.15 mg of base (4.5 mg of salt) per day. Studies have shown that patients already taking pramipexole tablets may be switched to pramipexole extended-release tablets overnight, at the same daily dose [73]. After switching to pramipexole extended-release tablets, the dose may be adjusted depending on the patient's therapeutic response.

**Conclusion**

Current evidence favours therapy initiation in PD with a dopamine agonist, such as pramipexole, except for elderly patients or those presenting cognitive abnormalities at onset. However, levodopa should not be withheld from patients in whom adequate symptomatic control cannot be otherwise obtained. The choice of initial therapy will depend on the individuals need for symptomatic efficacy, the degree of motor impairment and the risks of adverse effects. Pramipexole has been shown to have additional benefits in treating tremor [27] anhedonia and depression [49, 51, 52] and may be the drug of choice for patients with these problems. Patients and their caregivers should be made aware of all the potential risks and benefits of the chosen medication, and advice should be given at the outset regarding simple measures such as the importance of taking their medications at the correct times of day and maintaining good sleep hygiene. In more advanced disease, when levodopa therapy is complicated by the emergence of wearing-off and other complications, a dopamine agonist (such as pramipexole) may be initiated or the current dose increased to reduce severity of OFF periods and to allow reduction of levodopa doses. Finally, more complex therapeutic strategies should be considered according to the individual needs of the patient [74].

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Table I: Pramipexole trials in early Parkinson's disease

| Study | Study design | Treatment arms | Primary Endpoint | Primary Endpoint Findings |
|---|---|---|---|---|
| Hubble 1995 | Multicenter, randomized, double-blind, placebo-controlled, Phase II, parallel group, 8 week study | Pramipexole up to 4.5 mg/day<br><br>Placebo | UPDRS II and III scores | Pramipexole group showed significant improvement placebo on UPDRS II score at the end of 9 weeks (p The groups were not significantly different on UPDR score but pramipexole group had a greater improver placebo (p=0.10). |
| Shannon 1997 | Multicenter, randomized, double-blind, placebo-controlled, 31 week, parallel group study | Pramipexole up to 4.5 mg/day<br><br>Placebo | UPDRS II and III scores | UPDRS II and II scores were significantly lower in th pramipexole group vs. placebo starting from the third the titration phase until the end of the maintenance p (week 31) (p<0.001). |
| Wright 1997 | Multicenter, randomized, double-blind, placebo-controlled, 31 week, parallel group study | Pramipexole up to 4.5 mg/day<br><br>Placebo | UPDRS II and III scores | UPDRS II and II scores were significantly lower at th the maintenance phase in the pramipexole group vs (p≤0.022). |
| Kieburtz 1997 | Multicenter, randomized, placebo-controlled, double-blind, 11 week study | Pramipexole 1.5, 3.0, 4.5 or 6.0 mg/day<br><br>Placebo | UPDRS III score | At 10 weeks, patients treated with pramipexole show significant improvement compared to placebo of abo in the total UPDRS score compared with baseline (p |
| Parkinson Study Group 2000 | Multicenter, randomized, placebo-controlled, double-blind, parallel group 4 year study | Pramipexole 1.5, 3.0 or 4.5 mg/day<br><br>carbidopa/levodopa 75/300, 112.5/400 or 150/600 mg/day in 3 doses | Occurrence of the first motor complication (wearing off at end of dose, "on-off" fluctuations, dyskinesia) | Results after 2 years<br>At the end of the maintenance phase (23.5 months patients in the pramipexole group had motor comp vs. 51% of patient in the levodopa groups (p<0.00<br>Results after 4 years<br>At the end of 4 years 52% of patients in the pramip group had the first motor complications vs. 74% of in the levodopa groups (p<0.0001). |
| Navane 2003 | Multicenter randomized, double-blind, placebo-controlled 3 month study | Pramipexole up to 1.0 mg three times a day.<br><br>Pergolide<br><br>Placebo | Tremor Index and UPDRS III score | Both pramipexole and pergolide had significantly gre effects than placebo on tremor and UPDRS III vs. pl No significant difference was found between the two treatment groups. |

Table II. Pramipexole Trials in Advanced Parkinson's Disease

| Study | Study design | Treatment arms | Primary Endpoint | Primary Endpoint Findings |
|---|---|---|---|---|
| Wermuth 1998 [21] | Multicenter randomized, double-blind, placebo-controlled, 11 week study | Pramipexole up to 5.0 mg/day<br><br>Placebo | Total UPDRS score | At the end of the maintenance period, the total UPDRS was significantly improved in pramipexole group as cor to placebo (p=0.0184) |
| Lieberman 1997 [19] | Multicenter randomized, double-blind, placebo-controlled, 31 week study | Pramipexole doses of 0.35-4.5 mg/day.<br><br>Placebo | UPDRS II mean "on" and "off" periods and UPDRS III score mean "on" periods | At 31 weeks, UPDRS II (p<0.0001) and III (p=0.01) sco were significantly lower in the pramipexole group vs. pl |
| Pinter 1999 [22] | Multicenter randomized, double-blind, placebo-controlled, 11week study | Pramipexole up to 5.0 mg/day<br><br>Placebo | Total UPDRS score | At the end of the maintenance period, the total UPDRS was significantly improved in pramipexole group vs. pla (p=0.0002) |
| Guttman 1997 [20] | Multicenter, randomized, placebo-controlled, double-blind, 9 month study | Pramipexole up to 4.5 mg/day<br><br>Bromocriptine up to 30mg/day<br><br>Placebo | UPDRS II and III score | At the end of the maintenance period, the UPDRS II (p=0.0002) and III (p=0.0006) scores were significantly improved in the pramipexole group vs. placebo |
| Mizuno 2003 [23] | Multicenter randomized, placebo-controlled, double-blind, Japanese 12 week study | Pramipexole up to 4.5 mg/day<br><br>Bromocriptine up to 22.5mg/day<br><br>Placebo | UPDRS II mean "on" and "off" periods and UPDRS III score mean "on" periods | At the end of the maintenance period, the UPDRS II an scores were significantly improved in the pramipexole a bromocriptine groups vs. placebo (P<0.001) |