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EXPERT REVIEW

Pramipexole and its Extended Release Formulation for Parkinson's Disease

Paul S. Fishman

Department of Neurology, University of Maryland School of Medicine, Baltimore, MD 21201, USA.
Corresponding author email: pfishman@umaryland.edu

Abstract: Pramipexole has been a widely used dopamine agonist for the last decade. Recently an extended release formulation of pramipexole has been introduced as both monotherapy for patients with early Parkinson's disease as well as for patients with more advanced disease, as an adjunct to L-DOPA. Along with the enhanced patient compliance seen with once a day dosing, there are other potential advantages of extended release preparations of dopamine agonists. Patients initiated on pramipexole have a lower incidence of developing motor fluctuations including dyskinesia than those initiated on L-DOPA. Pramipexole requires a prolonged dose titration compared to L-DOPA, and generally does not have the efficacy of L-DOPA. The extended release form of pramipexole shows comparable mean and peak serum levels with once a day dosing as seen with three times a day dosing of the immediate release preparation. The extended release preparation has been studied in randomized multicenter clinical trial against both placebo and the immediate release preparation in the setting of early Parkinson's disease as monotherapy and in more advanced patients with motor fluctuations on L-DOPA. In both settings the extended release preparation was superior to placebo and comparable to the immediate release form in efficacy with a similar side effect profile including nausea, sleepiness, leg edema, dyskinesias, hallucinations and impulse control disorders.

Keywords: dopamine agonist, dyskinesia, restless leg syndrome, impulse control disorder, pharmacokinetics

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Introduction

Dopaminergic pharmacotherapy remains the mainstay of the treatment of motor symptoms of Parkinson's disease more than 50 years since its introduction. Agonists of the dopamine receptor are the second most widely used medications after levo-dopa (L-DOPA) for patients with Parkinson's disease, particularly the more recently introduced non-ergot agonists, pramipexole and ropinirole.[1] A controlled release form at ropinirole was introduced in 2008, and more recently a controlled release form of pramipexole was approved in the United States for treatment as monotherapy in early Parkinson's disease (PD), and as adjuvant therapy along with L-DOPA for treatment of more advanced PD.

Before discussing the rationale, properties and clinical utility of pramipexole extended release (ER) it is worthwhile to review the pros and cons of the use of dopamine agonist therapy in general and for pramipexole in particular for PD as well as other conditions.

Pramipexole (Immediate Release) in Parkinson's Disease

Pramipexole's original indications were for both monotherapy in early PD and adjunctive therapy with L-DOPA in more advanced PD. Significant improvement over placebo was seen in pivotal studies in both settings. The commonest primary outcome measure was the Unified Parkinson's Disease Rating Scale (UPDRS), both the total score which includes patient symptom information as well as a rating of disability, and part II the motor score which is based on a standardized neurological exam. For patients with dose fluctuation on L-DOPA another outcome measure commonly included is the duration of the walking day that a patient rated themselves as "on" (motor symptoms relieved) versus "off" (motor symptoms not relieved) over the week previous to the evaluation, using a patient recorded daily diary. Relief of motor symptoms by pramipexole in clinical studies is on the order of reduction of moderately severe to mildly severe scores, and is comparable to the changes seen with L-DOPA for patients with early PD.[2,3] Nausea is the commonest side effect of pramipexole, as it is for all dopamine agonists, particularly in monotherapy trials for early PD.[4] This side effect is reduced with a dose titration strategy. With immediate release pramipexiole dosing is initiated with 0.125 mg three times daily, and increased to 0.25 mg after one week followed by increases of 0.25 mg three times daily each week until symptoms are adequately controlled, or until a total daily dose of 4.5 mg is attained. Side effects of pramipexole that appear to occur more frequently than seen with other dopamine agonists are sleepiness and leg edema.[5,6]

For patients with motor fluctuations on L-DOPA, adjuvant treatment with pramipexole results in improvement in motor function particularly in the off state with reduction in off time duration and reduction in total daily L-DOPA dosage.[7] Common side effects in this older and more severely affected population included hallucinations and increased reports of dyskinesia during the treatment period.[8,9] Dyskinesias are usually reduced at the end of most dopamine agonist studies including those of pramipexole, through a reduction of total daily L-DOPA dose.[10] A clear conclusion from the original pivotal studies is that pramipexole is effective and safe as monotherapy in patients with motor symptoms of Parkinson's disease (PD) of mild to moderate severity, and in PD patients with motor fluctuations as an adjunctive therapy along with L-DOPA.

Long Term Studies and the Rationale for Pramipexole Treatment of Early Parkinson's Disease

Pramipexole is one of the six[6] direct acting dopamine agonist for the treatment of PD and the first of the non-ergot derived dopamine agonists approved in the US. The rationale for the development of these agents was initially threefold. 1) As medications with significantly longer serum half-lives than L-DOPA they would be useful in the management of fluctuation of motor response seen with L-DOPA alone. 2) On the basis of their longer half-lives they would be less likely to induce abnormal involuntary movements (dyskinesia) seen after years of treatment than L-DOPA. 3) On the basis of their differences in metabolism, they might have an effect on the natural progression of Parkinson's disease. Thanks to large long term clinical trials of both pramipexole and ropinirole there is data regarding the potential validity of each of these assumptions.

A long term comparison between patients initiated with pramipexole and those initiated on L-DOPA

(Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease, known by the acronym CALM-PD) demonstrated that the pramipexole initiated group had no only less wearing off, but a significantly lower rate of initiation of dyskinesia after years of treatment.[11] This reduction in rate of development of dyskinesia was seen in the pramipexole group even in the months and years after L-DOPA was added to the treatment of this group, when the clinical investigator deemed it necessary for adequate relief of motor symptoms.[11] Patients with PD rarely developed dyskinesias while taking pramipexole alone during the study.[11] These results were comparable to a long term trial of ropinirole with a similar design.[12] This observation is consistent with animal model data (MPTP treated primates) that show an inverse correlation between the half-life of a dopaminergic medication and its capacity to induce dyskinesia.[13] Long-term follow-up of CALM-PD patients found that the development of dyskinesia correlated with total L-DOPA dose/duration of treatment in both L-DOPA and pramipexole initiated treatment groups.[14] An interpretation of these studies provides a rationale for the initiation of the dopamine agonists as monotherapy rather than L-DOPA in an effort to reduce the likelihood of a patient with PD developing dyskinesias. An alternative approach would be initiation of L-DOPA therapy first, with pramipexole added later in the course of the disease as adjuvant therapy, usually with the onset of end of dose deterioration (wearing off). Longer term studies of patients on both agents (greater than 5 years) although less well controlled suggest that the prevalence of dyskinesias may be similar between L-DOPA and dopamine agonist initiated groups.[15] These initial studies did not assess the functional impact of dyskinesia, and the relative contribution of this symptom to overall disability and quality of life for PD patients is still controversial.[16]

Although pramipexole reduces motor symptoms of PD, in the head to head comparison performed in early PD in CALM-PD, pramipexole patients in general had less relief of motor symptoms than L-DOPA, which was at some time points statistically significant.[11] Both in pramipexole pivotal adjunctive trials and in CALM-PD, patients taking pramipexole had reduced off time in spite of taking significantly less L-DOPA per day. Assessments of disability and quality of life were not significantly different between the two groups, suggesting a trade-off between reduction in severity of PD motor symptoms and reduction in frequency and duration of motor fluctuations.[11]

In general pramipexole is not considered as effective as L-DOPA in relief of PD motor symptoms. This difference is usually not significant in patients with early or mild Parkinson's disease, where patients can be maintained on monotherapy with pramipexole for an average of approximately three years.[17] The relatively equivalent efficacy of pramipexole monotherapy compared to L-DOPA in mild but not severe Parkinson's disease may in part be a reflection of the contribution of tremor to overall motor signs and symptoms at different stages of PD. Tremor plays a much greater role as a sign and symptom in early PD while rigidity and bradykinesia are the major source of motor disability and symptomatology in more advanced PD.[18] Improvement in early PD by pramipexole appears to be in part driven by its efficacy in relief of tremor, which can be superior to that of L-DOPA in some patients. This observation is supported by evidence that pramipexole is one of very few agents that has been shown to significantly improve tremor in PD that has been refractory to L-DOPA.[19]

Neuroprotection and Pramipexole

On the basis of its differences in metabolism from L-DOPA, this has been long standing interest in the possibility that dopamine agonists such as pramipexole may have the capacity to slow the progressive worsening of motor symptoms, related to dopaminergic neuronal degeneration in PD. Laboratory studies in cell culture models and the MPTP animal model of PD support this view on the basis of reduced dopamine degradation with a reduction of associated oxidative injury, usually in comparison with L-DOPA.[20,21] There is also evidence from similar laboratory studies of a direct neuroprotective effect.[22] Clinical evidence indirectly supporting a neuroprotective role of both pramipexole and ropinirole comes from neuroimaging sub-studies that were part of the larger long term studies of patient begun on either L-DOPA or dopamine agonist described earlier. These studies using either a fluoro-DOPA PET ligand or a dopamine transport SPECT ligand serially imaged PD patients who had begun treatment on either a dopamine

agonist or L-DOPA. Both studies found a significantly slower rate of loss for ligand uptake in the striatum of patients who were begun on an agonist compared to those begun on L-DOPA.[23,24] Contraversy still exists as to whether these observations represent a slowing of loss of dopaminergic terminals from the striatum or simply a long term change in binding or uptake by the experimental dopaminergic ligand between the two groups.[25]

Another form of clinical trial that has been used to detect a possible disease modifying effect of a medication in PD is the so-called "delayed start" design. In this type of trial one group of early PD patients is begun on the putative neuroprotective agent immediately upon entry into the trial, while a second group of patients receives the test agent only after several months into the observation period. The two treatment groups are compared at the end of the study—several months after both groups have received treatment. This design is particularly useful for agents known to relieve motor signs of PD, but may also have a long-term disease modifying effect. The rationale behind this trial design is the assumption that a drug with both a symptomatic and neuroprotective effect will show both improvement in motor signs within a short period after initiation (usually one month), but superiority of the early start group at the end of the trial suggests a long term benefit of the drug on disease progression.

With the demonstration of a small but significant difference between patients initiated earlier rather than nine months later on the monoamine oxidase inhibitor rasagiline, (Attenuation of Disease Progression with Azilect Given Once-daily, known as ADAGIO) there has been interest in re-evaluation of early treatment with pramipexole.[26] In a recently completed large study, patients begun initially on pramipexole were compared to those who had a delayed start of drug in a design similar to that of the previous rasagiline study.[27] The pramipexole study (PRamipexole On Underlying Disease, known by the acronym PROUD) was similar to ADAGIO in that patients were enrolled at a very early stage of PD, but was somewhat smaller (approximately 1100 compared to 500 patients) which may have reduced its capacity to detect a small difference in UPDRS score at endpoint seen in ADAGIO (1.7 points). Unlike ADAGIO, the PROUD study also used dopamine transport ligand SPECT scanning both to improve accuracy of diagnosis of early PD, and as a secondary endpoint similar to previous pramipexole neuroprotection studies. PROUD also did not permit so called "rescue" therapy with L-DOPA, in an effort to avoid other complicating effects of symptomatic treatment. The results of this study have been presented, and at this point are available only in abstract form, but report a negative result. Timing of initiation of pramipexole between the two groups (which differed by nine months) did not appear to influence severity of symptoms of PD when evaluated several months later at study end point, and did not support a disease modifying effect for pramipexole in early PD.[28] While the pramipexole initiated group was clearly superior to the placebo group (by –4.8 points on the UPDRS, $P < 0.0001$) during the initial phase, consistent with a symptom reducing effect, that superiority was not significant (by –0.4 points on the UPDRS, $P = 0.65$) when both groups had completed pramipexole treatment.[28] No significant difference was seen between the two group in the 123 subjects who underwent serial SPECT scans (15.1% decline in early and 14.6% decline in delayed treatment, $P = 0.84$). Curiously although no claim of neuroprotection can be made for pramipexole in PD at this time, an isomer of pramipexole with no dopaminergic agonist activity is under study as a potential disease modifying neuroprotectant in ALS.[29]

Rationale for Extended Release Preparations of Dopamine Agonists

The extended release (ER) form of pramipexole is the third dopamine agonist introduced in some form of extended release formulation including a trans-dermal patch formulation of rotigotine and an extended release oral form of ropinirole. Since immediate release forms of pramipexole and ropinirole are used three times daily, once a day ER forms offer patients a more convenient alternative. Medication compliance is a clear issue in PD, particularly for patients with more advanced disease who tend to be older with more medical co-morbidities and with complex poly-pharmacy drug regimens. Compliance with single daily dosing has been shown to be superior over there times daily dosing, particularly the setting of polypharmacy.[30] Extended release forms of either pramipexole or ropinirole can also be used as monotherapy in early Parkinson's disease and potentially combined with rasageline, the only other form of once a day monotherapy for PD with good compliance.

This strategy would be particularly useful in younger, early onset patients who are likely to be employed, where compliance with a mid day dose during work may be particularly problematic. This younger onset group is also the population most at risk of developing clinically significant dyskinesias over the course of the disease, where dopamine agonists may have clear benefit.[31] The overall value of once a day dosing with regard to patient convenience and compliance is more complex where dopamine agonists are used as adjunctive therapy for more advanced PD. These patients usually already have a complex drug regimen including L-DOPA taken at least three times a day. These forms of complex drug regime are highly associated with reduced compliance in PD patients.[32] In a clinical research setting, the degree of correspondence of physician instructions with how patients take medications is usually referred to as adherence rather than the compliance, which is felt by some to be an overly judgmental term regarding the intent of patient behavior.[33] Most errors in adherence in PD patients are negative, with patients failing to take their medications on time or at all.[34] Such negative adherence with complex drug regimens can be severe enough to lower both functionality as well as quality of life.[35] Within a complex drug regimen, pramipexole ER would be expected to have superior adherence than three times a day dosing with immediate release pramipexole.[32] The overall impact on PD treatment and quality of life of improved compliance solely of the dopamine agonist, while other medications including L-DOPA treatment remains on a complex schedule has yet to be directly assessed. Single daily dosing of pramipexole can be part of a comprehensive plan to improve adherence in PD patients, including patient education, and identification and treatment of concurrent depression.[36]

There are other potential advantages of extended release preparations that are somewhat specific to dopamine agonist therapy. Unlike L-DOPA, dopamine agonists including pramipexole require several weeks of multi-stepped dose titration to achieve comparable efficacy and tolerance. The mantra "start low go slow but aim high" has been heard in instructions on the use of dopamine agonists since the introduction of bromocriptine in the 1970's. Prolonged dose titration is required to minimize nausea in particular, the most common side effect of dopamine agonists including pramipexole. This strategy is particularly important in countries such as the United States where the dopamine antagonist domperidone is not FDA approved or readily available. Unlike more widely used dopamine antagonist anti-emetics such as metoclopramide, domperidone does not cross the blood-brain barrier and can be used without the risk of worsening the motor aspects of PD.[37] Prolonged dose titration allows for development of tolerance by the dopamine receptors of the area postrema of brainstem's "vomiting center" and reduction of the risk of nausea or vomiting with these medications.[38] Stimulation of this center and provocation of nausea relates not only to serum levels of dopamine agonists but also to fluctuations in serum levels. Extended release preparations of dopamine agonists such as pramipexole with a longer time to peak serum level (Tmax) and a lower peak serum level (Cmax) than their immediate release counterparts and may potentially have a lower incidence of nausea. Such a lowered potential for nausea could translate into the capacity for a more rapid rate of dose titration, allowing patients to achieve an effective dose and relief of motor symptoms in a shorter period of time. The prolonged dose titration needed to achieve adequate relief of Parkinsonian symptoms remains one of the limitations to use of these agents, particularly in comparison with L-DOPA.

As discussed earlier, both animal model studies and clinical data suggest that short serum half life and so called "pulsatile" stimulation of dopamine receptors relates to the potential to induce dyskinesias with prolonged usage of dopaminergic therapies. Studies such as CALM-PD show a clear difference in the capacity to induce dyskinesias between L-DOPA with a serum half-life of 90 minutes and dopamine agonist such as pramipexole and ropinirole, which even as immediate release preparations have serum half-lives of several hours. There are no clinical studies similar to CALM-PD comparing the intermediate half life dopamine agonists noted above and older agonists such as pergolide with longer serum half lives hours with regard to eventual induction of dyskinesia. It will be of interest in the future to follow PD patients who have been initiated on the new extended release preparations such as pramipexole ER to see if the rate of development of dyskinesias is lower than that seen with intermediate release preparations.

A similar issue is involved for patients treated with dopamine agonists for the restless leg syndrome (RLS). This condition characterized by unpleasant sensations in the legs with an urge to constantly move the legs when at rest, is highly prevalent and a major source of interference with sleep.[39] Although a wide array of dopaminergic and non dopaminergic medications are used for RLS the only approved treatment in the US are the immediate release forms of pramipexole and ropinirole. Prior to the introduction of these dopamine agonists L-DOPA was commonly used to treat RLS.[40] Although far less well described than dyskinesia associated with PD, chronic use of L-DOPA in RLS resulted in an apparent change in sensitivity to treatment termed augmentation, where RLS symptoms progressively occurred earlier in the evening, spread to involve a greater area of the leg or body, and required increasing L-DOPA dosage for adequate symptom relief.[41] The high incidence of augmentation is a major limitation in the use of L-DOPA for RLS. Limited longer term studies of patients with RLS treated with dopamine agonist such as immediate release pramipexole suggest that the incidence of augmentation is much lower than that seen with L-DOPA, but the phenomenon still clearly occurs at a readily detectable rate.[42] Even the lower rate of augmentation associated with immediate release pramipexole is problematic because of the very long duration of potential treatment for RLS patients, who tend to be much younger than those with Parkinson's disease. Augmentation appears to be unique to treatment of RLS with dopaminergic agents. It has been proposed that augmentation may represent a similar type of hypersensitivity phenomenon as dopamine induced dyskinesia in PD, and that serum half life may also be a factor in development of augmentation.[43] It will be of interest to follow the results of future studies of pramipexole extended release in RLS patients noting the incidence of augmentation. If the serum half life and resulting decrease in "pulsatile" dopamine receptor stimulation has a role of development of augmentation, extended release preparations may provide a real improvement in RLS treatment.

Extended Release Pramipexole: Pharmacology

Pramipexole binds to most forms of dopamine receptors including the functionally important D2 subtype with a highest affinity for the D3 subtype with modest binding to other neurotransmitter receptors.[44] ER formulations have been directly compared to the IR formulation in healthy males ranging in age from 18–50 years over a range of doses from 0.375 to 4.5 mg 1 day.[45] Results are summarized in Table 1 comparing three times daily dosing of IR to single daily ER dosing.

These healthy volunteer studies demonstrated a level of comparability between IR and the several ER preparations tested, with the optimal ER formulation of a matrix tablet showing bioequivalence in Cmax, Cmin and AUC in spite of the once a day for ER versus three times a day dosing for IR. Bioequivalence was shown in both fasting state and well as with a meal. The profile and incidence of adverse effects was also very similar in the healthy male population over several doses. Both preparations have a bioavailability greater than 90%. Both preparation also have limited binding to plasma proteins (less than 20%) and have predominantly (90%) renal clearance.

Clinical Trials of Pramipexole ER in Parkinson's Disease

Pramipexole ER has been studied in comparison to both placebo and pramipexole IR in large multicenter manufacturer sponsored studies in early PD patients without L-DOPA treatment, as well as in more advanced PD patients on L-DOPA with dose fluctuations.

Pramipexole ER in Early PD

Early PD patients (Hoehn and Yahr stage 1–3) were randomized to ER, IR or placebo in a 33 week

Table 1. Pharmacokinetics of pramipexole.

	IR	ER
Peak-Trough Fluctuation (%)	104 (26)	57–101
AUC (ng · h/m1) 0–24 hr	16.0 (26.7)	17.4*
Tmax (h)	1.27 (24.8)	4.32–9.12
Cmax (ng/m1)	0.22 (16.3)	0.25–0.30
Single dose		
Cmax (steady—state)	1.090	0.967*
Cmin (steady—state)	0.383	0.455*

Notes: For IR values are mean and ( ) are percent coefficient of variance. For ER values are range of mean values a several prototype formulations. *Optimal formulation of ER.

study (539 patients).[46] The primary end point was the total of motor and disability (ADL) scores of the UPDRS (parts II and III). Secondary end points included percentage of patients rated as responders on the Clinical Global Impression of Improvement (CFI-I). Safety assessments not only included incidence of adverse events and associated withdrawals but specific assessment of two problematic side effects of pramipexole as well as other dopamine agonists. Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS). The modified Minnesota Impulsive Disorder Interview (mMIDI) subscale for compulsive behavior was employed to capture potential adverse events such as compulsive gambling, shopping, eating, or sexual behavior seen with dopamine agonist treatment, and recently reported to occur at a surprisingly high frequency.[47]

Although all groups including placebo treated patients improved over baseline scores, both IR and ER formulations were superior to placebo in improvement in UPDRS scores after both 18 and 33 weeks of treatment. Differences between IR and ER treated patients were not statistically different at either time point (at 33 weeks 8.8 point improvement from baseline for IR, 8.6 point improvement for ER). The magnitude of the difference in improvement for both treatment groups compared to placebo (5.0 point superiority for IR and 4.8 point superiority for ER at 33 weeks) is not only statistically significant but also likely clinically meaningful.[48] Both preparations were also demonstrated to be superior to placebo when evaluating the secondary outcome of frequency of response to therapy at 33 weeks. 46% and 43% of patients treated with IR and ER preparations respectively were rated as responders using the CGI-I compared to 29% of placebo patients. Similar although less robust differences were obtained using a patient rather than clinician based global rating scale (33% response for IR, 34% for ER, 21% for placebo patients). Tolerance and adverse event profile were also comparable between the two preparations, and were consistent with previous studies of pramipexole. Both treatment groups had a higher percentage of patients who experienced at least one treatment emergence adverse event (80.8% for IR, 84.8% for ER) than placebo (77.7%). Somnolence, nausea, constipation, fatigue, hallucinations, dry mouth, muscle spasms and peripheral edema were the most common adverse events for ER treated patients. Discontinuation of treatment due to an adverse event was more likely in the pramipexole treated groups than placebo (4%), and were similar between IR (9%) and ER (11%) Nausea was still the commonest cause of discontinuation for ER treated patients, who also showed increased ESS scores (1.8 for ER, 1.2 for IR, 0.3 for placebo) Abnormal behavior or urges as measured by the mMIDI were similar for all groups and (2.8% for IR, 2.2% for ER, 2.0% for placebo).

Pramipexole ER in Advanced PD

Pramipexole ER has also been compared to both pramipexole IR and placebo in patients with more advanced PD (HY stages 2–4) as an adjuvant treatment along with L-DOPA. The design of the clinical trial was similar to that for early PD with 485 patients completing 33 weeks of treatment.[49] Efficacy as measured by change in total II and III components of the UPDRS scores from baseline were superior for both treatment groups (11.3 for IR, 11.3 for ER) compared to placebo (7.0) at 33 weeks. Significant difference in UPDRS scores were present at the earlier time point of 18 weeks as well (12.8 or IR, 11.0 for ER, 6.1 for placebo).

Advanced Parkinson's patients have an increased prevalence of problematic fluctuations of motor response with L-DOPA treatment, which is the rational for the secondary end point of percentage of the waking day spent in the off state, where motor symptoms are not felt to be relieved. Both forms of pramipexole resulted in a significant reduction in percent off time (15.9% for IR, 13.3% for ER compared to 8.8% for placebo) after 18 weeks of treatment. In this older population with more severe disease and more medical co-morbidity, there was little difference between treated and placebo groups with regard to treatment emergent adverse events (64.0% for IR, 54.9% for ER, 55.6% for placebo). Little difference was also seen in the percentage of patients who discontinued study treatment by 18 weeks due to an adverse event (5% for IR, 5% for ER, 4% for placebo). Fewer patients completed 33 weeks of treatment with the ER preparation (117) than with IR (131) or placebo (137). As expected in this more

advanced PD population, hallucinations were the commonest side effect resulting in discontinuation of the ER preparation (1%) along with nausea (1%). Adverse events reported by more than 5% of treated patients included both those seen in early patients (nausea, constipation) as well as adverse events seen frequently in this population (hallucinations, dyskinesia, headache and anorexia).

The clear conclusion of both studies is that pramipexole ER is an effective treatment of motor symptoms of Parkinson's disease, both as monotherapy in patients with early PD and as adjunctive therapy for more advanced PD patients on L-DOPA with a fluctuating response. It is comparable to the IR preparation in efficacy and has a very similar level of tolerance and profile of adverse events.

Titration and Use of Pramipexole ER

In spite of the pharmacokinetic differences between the IR and ER preparations as single equivalent doses, tolerance for pramipexole and the incidence of treatment emergent nausea was similar for the two preparations when ER is dosed once a day and IR is dosed three times a day. In both studies weekly titration schedules for both preparations were the same, as are the manufacturer's recommendations. Treatment is initiated with a single daily dose of 0.375 mg with weekly single daily dose increases of 0.375 mg per day until adequate control of motor symptoms or a maximal daily dose of 4.5 mg/day is attained. Tablets of 0.375, 0.75, 1.5, 3.0, 4.5 mg strength are available and unlike previous brand name preparations of pramipexole are labeled with both the mg strength and ER designation. The majority of patients who have been switched from the IR preparation to ER have done so without the need for a dose adjustment, even when the switch has been done on an overnight basis.[50]

The ER preparation carries with it the same warnings with regard to possible side effects such as sudden onset of sleep, reports of disorder of impulse control and compulsive behavior as well as hallucinations and potentiation of dyskinesias.

Pramipexole ER is a reasonable choice for patients with Parkinson's disease who are candidates for either monotherapy with a dopamine agonist or as an adjunct to treatment with L-DOPA. It is particularly suited for patients who would benefit from a schedule of a single daily dose to enhance compliance and quality of life. Although there are potential theoretic advantages in the use of pramipexole ER over the IR preparation with regard to tolerance and induction of dyskinesia and other long term complication of dopaminergic therapy, these advantages have not been demonstrated at this time using once a day dosing.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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