Pramipexole: new use for an old drug – the potential use of pramipexole in the treatment of restless legs syndrome

Gulcin Benbir
Christian Guilleminault

Sleep Medicine Program, Stanford University, CA, USA

Abstract: Restless legs syndrome (RLS) is characterized by paraesthesias–dysesthesias and motor restlessness worsening at rest–in the evening, with at least temporary relief by activity. Its etiology is unknown, though it could be secondary to various conditions. It is well known, however, that dopamine plays a crucial role in the pathophysiology of RLS, as dopaminergic agonists achieve marked improvement. Pramipexole is a nonergoline compound with selectivity for D3 dopamine receptors. This drug is very effective in the treatment of idiopathic and secondary RLS and in treatment-resistant patients, as shown by double-blind, placebo-controlled studies in adults. In children, studies are much more limited, and RLS is often misdiagnosed as "growing pain" or attention deficit hyperactivity disorder. Pramipexole has been successful in open studies, eliminating clinical symptoms. This medication has the advantage of being free of the frequently encountered problems seen with ergot derivatives. The side-effects are limited, particularly at the dosages usually prescribed for RLS treatment: They are much lower than in Parkinson's disease, and inappropriate sleepiness and sleep attacks, particularly while driving, or compulsive behavior have not been seen. Compared with the adverse reactions of levodopa, including tolerance, rebound, and augmentation phenomena in RLS, which led to usage of dopamine agonists as first line of treatment for RLS, pramipexole has had one of the best profiles. Augmentation can still be noted with the drug, but after longer usage time compared with many other dopamine agonists. Although excessive daytime sleepiness has been noted, sleep attacks have not been encountered in RLS patients treated with pramipexole.

Keywords: pramipexole, restless legs syndrome, polysomnography, adults, children

About pramipexole

Pramipexole, a nonergoline aminobenzothiazole compound, was approved by the Food and Drug Administration for the treatment of Parkinson's disease (PD) in 1997 (Montplaisir et al 1994; Lin et al 1998; Hubble 2000). Pramipexole is a full dopamine agonist with particular selectivity for D2 dopamine receptor family, and has a 5- to 7-fold higher affinity for D3 receptor subtypes than for either D2 or D4 receptors (Parkinson Study Group 1997; Lin et al 1998; Hubble 2000). It has a moderate opioid affinity, only minimal alpha2-adrenoceptor activity, but no other beta-adrenergic or serotonergic activity (Hubble 2000; Saletu et al 2002).

It is rapidly and well absorbed and not influenced by food. The peak levels of the drug appear in the bloodstream within 2 hours of oral administration with an absolute bioavailability of more than 90%, indicating its good absorption and little presystemic metabolism (Lin et al 1998; Hubble 2000). Binding to plasma proteins is low (Montplaisir et al 2000a).

Its elimination half-life ranges from 8 to 12 hours (Wright et al 1997; Lin et al 1998). Pramipexole is excreted unmetabolized largely through the kidney, with little or no interaction with other drugs eliminated by hepatic cytochrome P450 enzymes

Corresponding author: Christian Guilleminault
Sleep Disorders Program, 401 Quarry Road, suite 3301,Stanford, CA 94305, USA
Tel +1 650 723 6601
Fax +1 650 725 8910
Email cguil@stanford.edu

or other related metabolic pathways (Hubble 2000; Montplaisir et al 2000a). It can therefore be safely used in patients with hepatic failure or in patients using multidrugs. It is a "category C" drug in pregnancy (Comella 2002).

About restless legs syndrome

Restless legs syndrome (RLS) was first described by Thomas Willis in the 17th century, and labeled as a psychosomatic disease, anxietas tibiarum, by Whittmack in the 19th century (Whittmack et al 1861; Willis 1685). The first report on RLS as a sensorimotor and sleep disorder, however, was written by Ekbom in 1945 (Ekbom 1945). RLS is characterized by leg paraesthesias–dysesthesias and motor restlessness worsening at rest and in the evening, with at least temporary relief by activity (Walters 1995). The diagnosis of RLS is based on clinical criteria established by the International RLS Study Group (IRLSSG), and has recently been modified (Walters 1995; Allen et al 2003) (Table 1). RLS was found to be the fourth leading cause of insomnia (Coleman 1982) particularly at sleep onset.

The overall prevalence of RLS is approximately 10% (Rothdach et al 2000) with variation between 6% and 11%, depending on the general population survey and the geographic location of the considered country. The symptoms are often progressive and tend to worsen with aging (Comella 2002). The mean age of onset of RLS symptoms was found to be 27 years (Montplaisir et al 1997). Although most subjects are not diagnosed for many years, 38%–45% of adult RLS subjects have onset of symptoms before age 20 years (Montplaisir et al 1997; Walters et al 1996; Restless legs syndrome Study Group 2000), with 13% of patients reporting symptoms before the age of 10 (Montplaisir et al 1997). Familial aggregation of RLS is known to be more common in early onset of symptoms (Allen et al 2003).

The recognition of RLS in childhood is complex. In 1832, Duchamp observed some children suffering aches and pains, termed "growing pains" (Duchamp 1832). Walters and colleagues (Walters et al 1994; Walters 1995) and Ekbom (Ekbom 1975), on the other hand, have stated that some of these children might actually have RLS. RLS in childhood may therefore be more common than appreciated. It is now well known that RLS may begin in childhood (Picchietti et al 1998, 1999; Walters et al 2000). It was important to have well defined clinical criteria for the recognition of RLS in childhood. The IRLSSG proposed such criteria (Walters 1995; Allen et al 2003) (see Table 2), but a validation on a general population children group is needed, despite the fact that this is currently the best document on the matter.

The etiology of RLS remains unknown. It could be idiopathic, 50%–92% of which has familial occurrence with autosomal dominant mode of inheritance (Montplaisir et al 1994; Walters 1995; American Sleep Disorders Association 1997; Comella 2002). Three different genetic loci, 12q, 14q13-21, and 9p (RLS-1, RLS-2, and RLS-3), have been reported with a recessive (RLS-1) and autosomal dominant (RLS-2, RLS-3) mode of inheritance, respectively (Desautels et al 2001; Bonati et al 2003; Winkelmann et al 2005). RLS can also be secondary to various conditions, including central and peripheral nervous system disorders, metabolic disturbances, pregnancy, anemia, and so forth (Collado–Seidel et al 1998; Happe and Trenkwalder 2004).

The most important development in the understanding of the pathophysiology of RLS was achieved by the demonstration of dopaminergic hypofunction by Akpinar (1982), who demonstrated the relief of RLS symptoms by levodopa treatment. The marked improvement achieved with dopaminergic agonists, exacerbation of RLS symptoms with dopamine antagonists, and increased frequency of RLS in patients with PD suggests that dopamine plays a crucial role in the pathophysiology of RLS (Comella 2002). In addition, imaging studies using ligands showed that dopaminergic activity in the central nervous system, particularly in the striatonigral system, is reduced in patients with RLS (Turjanski et al 1999; Ruottinen 2000).

Why pramipexole in RLS

The pharmacological treatment of RLS has developed greatly since Akpinar (1982) reported complete resolution of RLS symptoms with levodopa. Later studies consistently showed the beneficial effects of levodopa given with a peripheral decarboxylase inhibitor in both primary and also secondary RLS patients (Brodeur et al 1988; Von Scheele and Kempi 1990; Trenkwalder et al 1995). Levodopa was the first drug of choice in RLS, as it is usually well tolerated in most patients (Chesson et al 1999; Hening et al 1999). On the other hand, some adverse reactions have limited its use (Guilleminault et al 1993; Collado–Seidel et al 1999; Hening et al 1999).

Rebound phenomenon, worsening of symptoms at the end of a dosing period leading to late-night or morning recurrence of symptoms (Guilleminault et al 1993; Ferini-Strambi 2002), is seen in approximately 25% of patients on

Table 1 Clinical features of the restless legs syndrome (RLS) in adults[a] (Walters 1995; Allen et al 2003)

Diagnostic features

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or occur only in the evening or night

Supportive clinical features

1. Positive family history
2. Positive response to dopaminergic therapy
3. Presence of periodic limb movements (during wakefulness or sleep)

Associated features of RLS

1. Variable clinical course, but typically chronic and often progressive
2. Physical examination normal in idiopathic–familial forms
3. Sleep disturbance is a common complaint in more affected patients

[a]Diagnostic features are those mandatory for a definite clinical diagnosis. Supportive clinical features are those which may increase the probability of a diagnosis in doubtful cases, such as is common in children. Associated features are typical, but do not contribute to diagnosis.

levodopa for RLS (Comella 2002). It has been reported that 35% of RLS patients treated with levodopa for long periods developed morning restlessness, which resolved within 1 week upon discontinuation (Guilleminault et al 1993). This complication is most commonly seen when the regular-release formula of levodopa–carbidopa is used (Ferini-Strambi 2002). This rebound restlessness may be overcome by an additional levodopa dose during daytime, but may also decrease the compliance (Guilleminault et al 1993; Montplaisir et al 1999).

Augmentation is seen in more than 80% of RLS patients with long-term use of levodopa, leading to apparent worsening of symptoms (Allen and Earley 1996; Restless legs syndrome Study Group 2000; Comella 2002; Saletu et al 2002). In the augmentation phenomenon, symptoms progressively increased in severity have an earlier onset in the day involving the other parts of the body beyond the legs (Restless legs syndrome Study Group 2000; Earley and Allen 1996). If augmentation is taken to be a decrease in drug efficacy, as the dosage is increased, greater augmentation is seen. Augmentation is more common in severe RLS patients with a higher dose of medication (Ferini-Strambi 2002).

Another complication of long-term levodopa treatment is tolerance, the need for larger doses to maintain the original effect. Allen and Earley (1996) showed that following about 21 months of treatment, 59% of patients with RLS needed to increase their levodopa dose. However, the increase in dosage may also be due to the development of augmentation.

Due to the abovementioned complications of levodopa, dopamine agonists, with prolonged duration of action, have become the primary treatment for RLS. It has been shown in many studies that all dopamine receptor agonists licensed for PD can also be used effectively in the treatment of RLS (Brodeur et al 1988). Therefore, dopamine agonists are now being used as the first choice of treatment, especially in moderate-to-severe RLS, and in the presence of daytime symptoms or augmentation (Brodeur et al 1988). In secondary RLS, the underlying condition should first be addressed, but dopaminergic drugs may also be helpful (Comella 2002). However, although D2-receptor agonists of ergot derivatives, such as bromocriptine (Walters et al 1988) and pergolide (Earley and Allen 1997), are shown to be effective in RLS, some major and frequent side-effects limit their usefulness. Some degree of augmentation with these dopaminergic agonists was also reported between 9% and 18% in different studies (Montplaisir et al 2000b; Silber et al 2001; Ferini-Strambi 2002). The augmentation with pergolide, for instance, was shown to affect 15%–25% of patients (Earley and Allen 1996; Silber et al 1997). Moreover, it has also been reported that some degree of symptoms persists even after treatment with these agents.

Pramipexole, being selective for the D3 receptor and also a nonergot compound, does not have the frequently encountered problems seen with dopamine agonists of ergot derivative (see below). An initial pramipexole follow-up study in 7 RLS patients showed that none had augmentation after a mean period of 7.8 months (Montplaisir et al 2000b). Even if these initial long-term results have not be confirmed in all cases and presence of augmentation has been shown with all dopamine agonists tried to date on RLS, pramipexole

Table 2 Diagnostic criteria for childhood restless legs syndrome(RLS) (Walters 1995; Allen et al 2003)

Definite childhood RLS

1. The child meets all 4 essential adult criteria for RLS (see Table1), and
2. The child relates a description in his or her own words that is consistent with leg discomfort

or

1. The child meets all 4 essential adult criteria for RLS (see Table 1), and
2. Two of 3 following supportive criteria are present:
   (a) Sleep disturbance for age
   (b) A biological parent or sibling has definite RLS
   (c) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep.

Probable childhood RLS

1. The child meets all essential adult criteria for RLS, except criterion #4 (the urge to move or sensations are worse in the evening or at night than during the day), and
2. The child has a biological parent or sibling with definite RLS

or

1. The child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs, the discomfort has characteristics of adult criteria 2, 3, and 4 (ie, is worse during rest and inactivity, relieved by movement, and worse during the evening and at night), and
2. The child has a biological parent or sibling with definite RLS.

has been commonly used without problem for many months. In addition, pramipexole in the treatment of the symptoms of RLS has been shown to be very effective.

In rare cases, benzodiazepines, opioids, and anticonvulsants have also be given, particularly in cases of treatment failure with dopaminergic agents (Hening et al 1999; Saletu, Anderer, et al 2000; Saletu, Gruber, et al 2000; Saletu et al 2001). The question of the potential role of IV infusion of iron as an intermittent treatment or supplemental treatment of RLS is currently under investigation (Early et al 2005).

Studies with pramipexole in adult RLS and periodic limb movements in sleep (PLMS) patients

Pramipexole in RLS and PLMS

RLS and PLMS

The studies with pramipexole performed in adult patients have clearly shown that the drug is effective in the treatment of RLS in placebo-controlled, double-blind studies (Table 3). Compared with levodopa, which improved leg restlessness by about 40% in a blind-designed study, pramipexole improved RLS symptoms by about 80% (Brodeur et al 1988; Happe and Trenkwalder 2004), which suggests that pramipexole is more potent than levodopa. However, to compare two different studies with different diagnostic criteria used in selection of the population questions this statement, revealing the need for head-to-head comparative studies. Pramipexole also has a major effect on PLMS index and PLMS-related arousals when associated with RLS (Montplaisir et al 1999). Pramipexole has also been compared with another nonergot dopamine agonist, the drug ropinirole, which has demonstrated a similar positive effect on PLMS index. Ropinirole, with a shorter half-life, has been reported to improve sleep efficiency less (Saletu, Gruber, et al 2000; Saletu et al 2002). The efficacy of pramipexole on secondary RLS has also been reported in many studies, including uremic RLS in dialysis patients (Miranda et al 2004) (Table 3). All dopaminergic agents, including pramipexole, are effective in secondary forms of RLS–PLMS (Boivin et al 1993; Trenkwalder et al 1995; Manconi et al 2003; Miranda et al 2004). The drug can thus be used to treat RLS and PLMS associated with underlying conditions.

Based on both short- and long-term observational and controlled studies, some also with polysomnography, the recommended dosage of pramipexole ranges normally between 0.375 and 0.75 mg/day (Montplaisir et al 1999). A very low initial optimal therapeutic dose of pramipexole (0.25 mg/day) was reported to have a very rapid efficacy in 66% of RLS patients (Comella 2002). About 50% of the studied patients were reported to have moderate or marked improvement after the first to third administration of such dosage. This rapid action of pramipexole even at low dosages is hypothesized to indicate a more specific role of D3 receptors of the mesolimbic system in the pathophysiology of RLS (Trenkwalder et al 1996; Comella 2002).

Sleep

Most of the sleep laboratory studies showed that there is no effect of pramipexole on total sleep time, number of awakenings, sleep continuity, or sleep efficiency (Montplaisir et al 1999; Miranda et al 2004). Similar results were also reported in levodopa trials in RLS patients (Brodeur et al 1988; Kaplan et al 1993; Trenkwalder et al 1995). It has been found, however, that pramipexole may delay REM sleep latency and decrease total percentage of REM sleep (Montplaisir et al 1999). Acute administration of pramipexole, 0.25mg, has been shown to increase sleep stages NREM-1 and 2 and stage shifts, while slow-wave and REM sleep decreased significantly compared with placebo (Saletu et al 2002). The dopamine agonist pergolide has also been reported to significantly improve total sleep time (TST), total sleep period, and sleep efficiency, and also increase the number of spontaneous awakenings in stage 2 nonREM sleep, and decrease stages 3+4 with the alteration in the distribution of non REM sleep towards more light sleep (Wetter et al 1999; Saletu, Gruber, et al 2000) but with an improvement of subjective sleep quality. Moreover, a partial antidepressive effect of pramipexole has also been found, supporting a dopaminergic dysfunction in the pathogenesis of these two disorders (Saletu et al 2002).

Studies with pramipexole in childhood RLS and PLMS

There are few studies on RLS in children, and fewer with pramipexole. But it is now known that RLS is much more common in children than previously assumed.

Clinical presentations in children

Growing pains

The most common misdiagnosis of childhood RLS is growing pains (Walters et al 1994). A study of 112 children diagnosed as having growing pains showed that some children had sensation of cramps or creeping very similar to RLS (Walters 2002). A polysomnographic (PSG) study in 10 children with growing pains showed they all met clinical criteria for definite RLS (Rajaram et al 2004). Interestingly, the positive family history of growing pains was also more common in these children (51.0% vs 12.5% of children without growing pains) (Walters 2002). In addition, 7 of 60 patients with age of onset of RLS symptoms before 20 years reported that they had the diagnosis of growing pains (Montplaisir et al 1997).

Attention deficit hyperactivity disorder (ADHD)

High prevalence of RLS symptoms in children with ADHD and PLMS has also been reported (Picchietti et al 1998). Many children with ADHD have RLS symptoms (eg, leg paraesthesias) due to their ADHD symptoms (Walters et al 1994). On the other hand, some children with ADHD signs and symptoms might actually have RLS (Picchietti and Walters 1994). In addition, many of the parents of children with ADHD and RLS–PLMS were also shown to have RLS symptoms or PLMS in some studies (Picchietti and Walters 1994).

To explain the close relationship between ADHD and RLS–PLMS, a genetic linkage between these two disorders has been hypothesized, with the possibility that they might share a common deficit in dopaminergic pathways (Picchietti et al 1999). This hypothesis is supported by well-known therapeutic response of RLS–PLMS to dopaminergic agents (Lin et al 1998; Ondo 1999), as well as the evidence that ADHD, in some cases, is genetically linked to the dopaminergic system (La Hoste et al 1996; Waldman et al 1998).

Iron deficiency, low serum ferritin levels (Kryger et al 2002; Kotagal and Silber 2004), diabetes mellitus type 1 (Happe et al 2005), and RLS-like symptoms possibly associated with streptococcal or *Mycoplasma pneumoniae* infections (Matsuo et al 2004) have also been reported as etiological factors in children with secondary RLS.

Treatment studies

Treatment of childhood RLS remains largely unexplored. There are some reports on children with ADHD and RLS–PLMS treated with carbidopa–levodopa and clonidine with moderate benefit (Walters et al 1994; Rajaram et al 2004), and clonazepam with no benefit (Picchietti and Walters 1994; Walters et al 1994). Another study was performed on 7 children with RLS–PLMS treated with prescription dopaminergic drugs, either levodopa or pergolide. The children had shown no benefit from prior stimulant therapy, but demonstrated long-term improvement in RLS, PLMS, and the associated arousals, along with objective and subjective improvements in ADHD (American Sleep Disorders Association 1997). However, the effect of improvement in ADHD symptoms on the amelioration of RLS–PLMS cannot be excluded. Finally, a study of PLMS performed in children indicated association of the polysomnographic findings of PLM with many etiologies, including association with RLS and with ADHD (Martinez and Guilleminault 2004)

Table 3 Studies with pramipexole in adult RLS patients

Study	Trial/study design	Measures	Patients	Duration	Dosage	Primary outcomes	Secondary outcomes
Lin et al (1998)	Open-label	Visual analog scale	15 out of 16 patients (94%) completed study Symptomatic RLS Treatment-resistant RLS	2–3 mo	Mean dose 0.3 mg/d	Suppresses RLS symptoms	Suppresses daytime augmentation
Becker et al (1998)	Open-label clinical	Short IRLSSG	23 moderate to severe resistant RLS patients (primary and secondary) (19 completed trial)	1–5 mo	Single dose of 0.125 mg (nighttime symptoms); 0.125 mg bid/tid (daily symptoms) Mean dose of 0.35+0.15 mg/d (Dallas); 1.6+1.0 mg/d (Houston)	Significant improvement	
Montplaisir (1999)	Double-blind, randomized, crossover with placebo control	RLS severity home questionnaire Polysomnogram	10 out of 11 subjects completed trial	4 wk of trials with 2-wk washout period	0.375 mg/d increased up to 1.5 mg/d vs placebo	Effective in treating sensory and motor symptoms of RLS 0.375–0.75 mg completely eradicated RLS in 9 patients Decrease in PLMS by 98%	No improvement in sleep continuity, efficiency, sleep latency, TST, number of awakenings
Galvez-Jimenez et al (1999)	Observational	IRLSSG	4 resistant RLS patients (primary and secondary)	Mean of 8.9 mo (1.5–12 mo)	Average dose of 0.75 mg/d	Control of symptoms without any significant side-effects or need of medication adjustment	Difficulty initiating or maintaining sleep unimproved
Montplaisir (2000b)	Follow-up for long-term efficacy	Home questionnaire	7 RLS patients	Mean follow-up duration of 7.8 mo	0.25 mg/d increased to optimal dose	Efficacy throughout 24 h with a single dose at bedtime	Long-lasting beneficial effect on RLS symptoms
Saletu et al (2002)	Single-blind, placebo-controlled crossover	IRLSSG Polysomnography Psychometry	11 patients with primary RLS 10 patients completed 4-week follow-up	After night (acute) 4-wk follow-up	Acute after night dose of 0.27 mg/d 4 wk trial mean dose of 0.28±0.1 mg/d	Total scores of the IRLSSG improved Significant decrease in PLMs/h	Improved sleep efficiency and quality compared to placebo Significant decrease in PSQI–QOL

Abbreviations: d, day; h, hour; IRLSSG, International RLS Study Group questionnaire; mo, months; NS, not significant; PLMS, periodic leg movement during sleep; PLMA, periodic leg movements sleep arousal index; PLMW, periodic leg movements while awake; PSQI–QOL, Pittsburgh Sleep Quality Index -quality of life; RLS, restless legs syndrome; TST, total sleep time; wk, weeks.

Table 3 *Continued*

Study	Trial/study design	Measures	Patients	Duration	Dosage	Primary outcomes	Secondary outcomes
		Zung Depression and Anxiety Scale					Daytime sleepiness and depression improved
		Quality of Life Index					
		Pittsburgh SleepQuality Index					
		Epworth Sleepiness Scale					
Silber et al (2003)	Retrospective review		60 consecutive RLS patients	Mean of 27.2 mo	Median initial dose of 0.38 mg/d	Completely effective in 2 out of 3 patients; ineffective in 7%	
Manconi et al (2003)	Open-label without placebo-control group	Suggested Immobilization Test	24 never treated primary (20) and secondary RLS patients	30–60 d (mean 39 d) after optimal dosage	0.25–0.50 mg/d	Significantlyimproved the subjective RLS symptoms and IRLSSGRS scores	Significant decrease in mean movement index
		IRLSSG					
Ondo et al (2004)	Follow-up	Subjective report by patients	52 out of 83 patients with nonuremic RLS	39.2+20.9 mo (7–101 mo)	0.79+0.55 mg/d	Effectively treat RLS	
Stiasny-Kolster et al (2004)	Short-term open label	IRLSSG	17 patients with severe primary RLS	4 wk	0.125-0.75 mg/d (a mean of 0.3+0.2 mg)	Rapid complete or pronounced relief of RLS symptoms	Significantly improved sleep by reduction in sleep onset latency, increase in TST, increase in sleep efficiency
		Polysomnography	(13 patients resistant to levodopa)			Worsening of RLS symptoms under levodopa recovered	
						Significant improvement in PLM index, PLMA index	
Miranda et al (2004)	Follow-up	IRLSSG	10 uremic RLS patients	1 mo	Mean dose of 0.25 mg/d (0.125–0.5 mg/d)	Decrease in mean severity scale score	No changes in sleep latency, TST, number of awakenings, or sleep efficiency
		Polysomnography (8 patients)				Decrease in PLMW index	
Partinen et al (2004)	Large randomized double-blind, placebo-controlled, dose-finding		109 patients with RLS	NS	0.5–0.75 mg/d vs placebo	Significant decrease in severity of symptoms	

Abbreviations: d, day; h, hour; IRLSSG, International RLS Study Group questionnaire; mo, months; NS, not significant; PLMS, periodic leg movement during sleep; PLMA, periodic leg movements sleep arousal index; PLMW, periodic leg movements while awake; PSQI–QOL, Pittsburgh Sleep Quality Index -quality of life; RLS, restless legs syndrome; TST, total sleep time; wk, weeks.

There are only 2 studies with pramipexole usage in childhood RLS–PLMS, both of which were performed at the Stanford sleep center. The first was carried out in prepubertal children with sleep disorders. Six children with PLMS and 2 with RLS and PLMS were given pramipexole, and 5 out of these 6 had a complete disappearance of their PLMS demonstrated by follow-up polysomnography and were able to well tolerate the drug (Martinez and Guilleminault 2004). These 5 children have been followed now for a minimum of 3 years. One of the 2 children with PLM and RLS has developed augmentation after close to 3 years of pramipexole intake. Another had drug intake terminated by family concerned about long-term intake of a dopamine agonist, and 3 children are still taking the dopaminergic agent without side-effects. The 6th child developed side-effect very soon after initiation of treatment and was switched to levodopa, and after 2 years to ropinirole. Parents stopped usage of any drugs after 6 years of treatment again because of concern about the effect of long-term drug intake. The other study, of 84 children (5 with sleep terrors and 79 with both sleep terrors and sleepwalking) with a control group of 36 healthy children, revealed that 2 sleepwalkers had accompanying RLS. These 2 children had disrupted sleep during the first sleep cycle. The nocturnal sleep disruption associated with the RLS–PLM was hypothesized to possibly be a factor in the occurrence of sleepwalking events. Each child was treated for RLS with pramipexole. Follow-up recording showed absence of PLMS and no report of symptoms of RLS. There was simultaneous observation of complete absence of confusional arousals at long-term follow-up with no parasomnia reported since treatment (Guilleminault et al 2003). These 2 children have been followed for either 2 or 3 years. RLS symptoms and parasomnia have not been reported at recent follow-up but increase in drug intake has been necessary in both cases due to reports of reappearance of mild symptoms of RLS 7 and 9 months ago, respectively. All children studied (n=7) were all started with the recommended lowest effective daily dosage, ie, 0.25mg. The first week, each child was started with 0.125mg taken at evening meal. When absence of any side-effect at the end of the first week was observed, each child's daily dosage was increased to 0.25mg. The rationale to select the same dosage as in adults was that dopamine agonists have been used in children with abnormal movements at higher dosage; and child metabolism, overall, is faster than adult metabolism. The current maximum daily dosage administered to a child is 0.50mg at evening meal. Observation of side-effects led to immediate interruption of drug administration, and all children had a general pediatric examination every 6 months and a simple blood test evaluation every year.

Side-effects of pramipexole in patients with RLS

Augmentation–rebound phenomena

As mentioned, augmentation and rebound phenomena are the main problems that limit the usefulness of levodopa. It was in the first trials on pramipexole that augmentation or rebound were reported to be absent with the continunation of benefits of pramipexole therapy (Montplaisir et al 2000b). Montplaisir (2000b) had followed 7 RLS patients taking pramipexole with a mean daily dose 0.125mg for a mean of 7.8 months without augmentation. On the other hand, subsequent studies have shown that augmentation with pramipexole, although rare, could be seen. Ferini-Strambi et al (2002) found that only 9 of 102 RLS patients (9%) had augmentation after at least 6 months of pramipexole treatment. Silber et al (2001) reported augmentation with pramipexole occurring in 18% of 50 RLS patients who had failed previous dopaminergic treatment. However, nearly two-thirds of those patients had developed augmentation with either levodopa or pergolide. An observational study reported augmentation in 8.5% of patients during long-term treatment with pramipexole (Ferini-Strambi et al 2001), very close to the percentage (8.3%) found in another study (Ferini-Strambi 2002). However, a very high rate of subjects developing augmentation, 32%, was reported in another study (Winkelman and Johnston 2004), similar to the ratio reported for augmentation seen with pergolide (Silber et al 2003), but still lower than the 50% reported in patients treated with levodopa (Earley and Allen 1996). The authors who reported the need to increase the initial therapeutic dose of pramipexole in 32% of their cases mentioned that the increase could also be due to some degree of tolerance to the drug or increasing severity of RLS, in addition to RLS augmentation (Silber et al 2003). Factors such as natural progression of RLS, fluctuations in underlying disease severity, or different study designs in terms of inclusion criteria for patients might be responsible for the discrepancy noted in the different reports (Winkelman and Johnston 2004). But in this specific study (Winkelman and Johnston 2004) anatomical extension of symptoms was found in only 5% (3/59) of patients, and this percentage involved only patients who presented augmentation or tolerance.

The investigations on the possible risk factors associated with the appearance of augmentation revealed that it was not related to medication dosage or severity of RLS before the onset of pramipexole treatment (Ferini-Strambi 2002). Two factors most likely to affect augmentation were reported as: (a) pretreatment with levodopa, and (b) secondary RLS compared with idiopathic RLS (Ferini-Strambi 2002; Winkelman and Johnston 2004). Patients with a positive family history and normal electromyographic examination results were also reported as predictors for augmentation (Ondo et al 2004).

The risk of observing augmentation was found to be highest soon after starting treatment, mostly within the first 4 months of treatment (Ferini-Strambi 2002). The shortest time to augmentation was reported to be 2 months after initiation of treatment (Silber et al 2003). In the first year of treatment, about 20% of patients experienced augmentation, and in the second year, 10% of patients. After 2.5 years, it has been said that no previously unaffected patient developed augmentation (Silber et al 2003).

A comparison of carbidopa–levodopa or pergolide augmentation with pramipexole augmentation revealed that it was significantly less common with pramipexole (Silber et al 2003). It is reasonable that augmentation would be less frequent and less severe with pramipexole than with levodopa. For a similar reason, morning rebound and nocturnal penetrations of RLS symptoms were rare. In general, augmentation with pramipexole appears to be less severe, and is easily managed by earlier medication dosing (Silber et al 2003; Winkelman and Johnston 2004).

Sleep attacks

The excessive daytime somnolence in the form of sudden sleep attacks that are involved even in motor vehicle accidents was first reported by Frucht et al (1999), with the use of pramipexole and ropinirole in patients with PD. Since then, there have been reports of sudden, irresistible sleep episodes as an adverse effect with dopaminergic agents (Becker et al 1999) in PD patients. However, this adverse effect was not encountered in RLS patients treated with pramipexole (Ferreira et al 2000; Stiasny et al 2000).

Becker et al (1998, 1999) reported daytime somnolence in 4 out of 16 patients taking pramipexole for RLS. In another study, excessive daytime sleepiness was noted in 5% of patients (Silber et al 2003). None of these patients had sleep attacks. However, in this study, 3 patients with excessive daytime sleepiness with no sleep attacks felt the need to discontinue the medication (Silber et al 2003). Stiasny et al (2001) also found that 1 of 24 patients described sleepiness with no sleep attacks. The lower risk of sleepiness with pramipexole, especially while driving, could be related to the differences in dose and timing of medication compared with PD patients (Parkinson Study Group 2000; Silber et al 2003). This opinion has been emphasized in one study by comparing doses, as RLS patients are mostly treated with a mean dose of 0.37 mg/day (Stiasny et al 2000), while PD patients with sleep attacks had been given pramipexole at a mean dose of 2.9 mg/day (Ferreira et al 2000).

Other side-effects

The other more common but less serious side-effects of pramipexole noted in the drug trials for RLS relief include nausea or dyspepsia, constipation, anorexia, insomnia–alertness, sleepiness or stiffness during the day, fatigue, headache, dizziness, fluid retention–edema, and tachycardia (Weimerskirch and Ernst 2001; Comella 2002; Saletu et al 2002; Hening et al 2004). But these side-effects are reported as usually affecting a low number of subjects and usually not causing the drug trial to be interrupted. Although about 40% of patients were reported to have side-effects with the medication (Silber et al 2003) (Table 4), they occurred at initiation, and were only mild, tolerable, and transient, disappearing within 1 week (Montplaisir et al 1999; Weimerskirch and Ernst 2001; Silber et al 2003). In addition, one must emphasize that studies that are not placebo-controlled might overestimate the adverse reactions. Pramipexole is believed to have fewer adverse effects than pergolide. Side-effects were reported in 60%–68% of patients taking pergolide for RLS (Silber et al 1997, 2001; Stiasny et al 2001).

Table 4 Side-effects in rest legs syndrome (RLS) patients treated by pramipexole (Silber et al 2003)

Side-effect	Number of patients affected (%)
Insomnia	8 (13)
Nausea or dyspepsia	7 (12)
Postural lightheadedness	6 (10)
Excessive daytime sleepiness	3 (5)
Nasal stuffiness	3 (5)
Limb numbness or pain	2 (3)
Headache	1 (2)
Anxiety	1 (2)
Depression	1 (2)
Peripheral edema	1 (2)
Constipation	1 (2)
Palpitations	1 (2)

Table 5 Treatment-emergent adverse events in early Parkinson's disease (combined data from: Parkinson Study Group [1997]; Pogarell et al [2002]; Wong et al [2003])

Adverse events	Pramipexole (n=388)	Placebo (n=235)
Asthenia	14	12
General edema	5	3
Malaise	2	1
Reaction unevaluable	2	1
Fever	1	0
Nausea	28	18
Constipation	14	6
Anorexia	4	2
Dysphagia	2	0
Peripheral edema	5	4
Decreased weight	2	0
Dizziness	25	24
Somnolence	22	9
Insomnia	17	12
Hallucinations	9	3
Confusion	4	1
Amnesia	4	2
Hypesthesia	3	1
Dystonia	2	1
Akathisia	2	0
Thinking abnormalities	2	0
Decreased libido	1	0
Myoclonus	1	0
Vision abnormalities	3	0
Impotence	2	1

It must be emphasized that Martinez and Guilleminault (2004) report a child treated for PLMS with pramipexole who had treatment terminated soon after beginning of drug intake due to increased daytime sleepiness and behavior changes that included "blunted affect" and personality change with "strangeness" as verbalized by parents. These effects were seen at 0.25 mg/day. Interruption of treatment led to return to normal behavior within 3 days.

Overall potential side-effects of pramipexole

Side-effects of pramipexole have been well published previously for its usage in PD, a pathology not considered here. Patients with either early or advanced PD were enrolled in clinical trials. Patients with early disease had no concomitant levodopa therapy, while patients with advanced PD received a combined treatment of levodopa along with pramipexole.

In double-blind, placebo-controlled trials of patients with early PD, the most commonly observed adverse events were reported as nausea, dizziness, somnolence, constipation, asthenia, and hallucinations (Parkinson Study Group 1997; Pogarell et al 2002; Wong et al 2003) (Table 5). Approximately 12% of 388 patients with early PD discontinued treatment due to adverse events, compared with 11% of 235 patients taking placebo. The most common adverse events associated with discontinuation were found to be hallucinations, dizziness, somnolence, extrapyramidal syndrome, headache, confusion, and nausea. It must be remembered that not only the dosage but also the

Table 6 Treatment-emergent adverse events in Advanced Parkinson's Disease (Lieberman et al 1997; Kunig et al 1999; Pinter et al 1999).

Adverse events	Pramipexole (n=260)	Placebo (n=264)
Accidental injury	17	15
Asthenia	10	8
General edema	4	3
Chest pain	3	2
Malaise	3	2
Postural hypotension	53	48
Constipation	10	9
Dry-mouth	7	3
Peripheral edema	2	1
Increased creatinin PK	1	0
Arthritis	3	1
Twitching	2	0
Bursitis	2	0
Myasthenia	1	0
Dyskinesia	47	31
Extrapyramidal syndrome	28	26
Insomnia	27	22
Dizziness	26	25
Hallucinations	17	4
Dream abnormalities	11	10
Confusion	10	7
Somnolence	9	6
Dystonia	8	7
Gait abnormalities	7	5
Hypertonia	7	6
Amnesia	6	4
Akathisia	3	2
Thinking abnormalities	3	2
Paranoid reaction	2	0
Delusions	1	0
Sleep disorders	1	0
Dyspnea	4	3
Rhinitis	3	1
Pneumonia	2	0
Skin disorders	2	1
Accommodation abnormalities	4	2
Vision abnormalities	3	1
Diplopia	1	0
Urinary frequency	6	3
Urinary tract infection	4	3
Urinary incontinence	2	1

neurological lesions are very different between RLS and PD.

An interesting side-effect of pramipexole, pathological gambling in PD patients, was recently reported in 2 studies (Driver-Dunckley et al 2003; Dodd et al 2005). Out of a total of 1884 PD patients, 529 were treated with pramipexole, 421 with ropinirole, and 331 with pergolide (Driver-Dunckley et al 2003). Seven men and 2 women were found to have symptoms of obsessive or excessive gambling. Of these 9 subjects, 8 were on pramipexole (mean dosage 4.3 mg/day, range 2–8 mg/day) and 1 was on pergolide (4.5 mg/day) at the onset of symptoms. In the second paper (Dodd et al 2005), pramipexole was the agonist in 9 of 11 PD patients who developed pathological gambling within 3 months of treatment or more, with demonstrated resolving of the gambling problem after discontinuation of the drug. A survey very recently performed on 32 of our RLS patients who took pramipexole on a daily basis for over a year did not elicit any indication of obsessive behavior change since the start of medication, but considering the very large number of patients with PD necessary to demonstrate presence of this side-effect, our sample is most likely too small.

In double-blind, placebo-controlled trials with pramipexole and concomitant levodopa in patients with advanced PD, the most common adverse events were orthostatic hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency (Lieberman et al 1997; Kunig et al 1999; Pinter et al 1999) (Table 6). Approximately 12% of 260 patients discontinued treatment due to adverse events compared with 16% of 264 patients receiving placebo. The events most commonly causing discontinuation were noted as hallucinations, dyskinesia, extrapyramidal syndrome, dizziness, and confusion orthostatic hypotension.

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Disclosures

The authors have no conflicts of interest and nothing to disclose.

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