Fighting Needle Fear in Diabetes Helps Compliance

BY KATE JOHNSON
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Needle fear can complicate many doctor-patient relationships, but in the case of patients with insulin-dependent diabetes, fear of needles can become a serious barrier to compliance.

Studies show that up to one-quarter of people with diabetes have needle anxiety (Diabetes Res. Clin. Pract. 1999;46:239-46), and that extreme needle phobia exists in about 1% of patients (J. Psychsom. Res. 2001;51:665-72).

If these issues are not properly addressed, they can lead to skipped doses and poor glycemic control, according to Dr. Mary Korytkowski, of the division of endocrinology and metabolism at the University of Pittsburgh, and director of its center for diabetes and endocrinology.

"I've had people tell me it takes them an hour to give the shot," Dr. Korytkowski said in an interview. "They break out in a cold sweat, they just can't face it, and they have to work themselves up to giving it."

"For someone with diabetes to have needle fear, and then have to take four shots a day, that's a little bit of an overwhelming request," commented Dr. H. Peter Chase, professor of pediatrics at the University of Colorado, Denver, and clinical director emeritus of the Barbara Davis Center for Childhood Diabetes, Aurora. "I've had kids [who were] ready to go to college, and the parents were still giving the shot because the kids were so scared of it."

According to Dr. Korytkowski, needle anxiety can arise not only in first-time insulin users, but also in experienced patients in whom the injection routine has become well established.

Although some patients are clearly focused on their fear of pain or injury, others have psychological issues that are more complex. "Sometimes it is an emotional response to going on insulin," she said. "Now

Mirapex® (pramipexole dihydrochloride) **Brief Summary of Prescribing Information**
0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg tablets
INDICATIONS AND USAGE
Parkinson's Disease: MIRAPEX tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.
Restless Legs Syndrome: MIRAPEX tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).
CONTRAINDICATIONS: MIRAPEX tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.
WARNINGS: Falling Asleep During Activities of Daily Living
Patients treated with Mirapex® (pramipexole dihydrochloride) have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on MIRAPEX tablets, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as one year after the initiation of treatment.
Somnolence is a common occurrence in patients receiving MIRAPEX tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75 mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients (see ADVERSE EVENTS). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.
Before initiating treatment with MIRAPEX tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX tablets such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine – see PRECAUTIONS, Drug Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX tablets, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.
Symptomatic Hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, both Parkinson's disease patients and RLS patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see **PRECAUTIONS, Information for Patients**).
In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to Mirapex® (pramipexole dihydrochloride) tablets than among those assigned to placebo. This result, especially with the higher doses used in Parkinson's disease, is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.
While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing.
Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX tablets, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX tablets and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX tablets compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.
Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.
In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.
PRECAUTIONS
Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication. **Renal:** Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing Mirapex® (pramipexole dihydrochloride) tablets to patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION** in full Prescribing Information). **Dyskinesia:** MIRAPEX tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.
Retinal Pathology in Albino Rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved (see **ANIMAL TOXICOLOGY**).
Events Reported with Dopaminergic Therapy: Although the events enumerated below may not have been reported in association with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date. ***Withdrawal-Emergent Hyperpyrexia and Confusion:*** Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. ***Fibrotic Complications:*** Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.
Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.
A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the post-marketing experience for Mirapex® (pramipexole dihydrochloride) tablets. While the evidence is not sufficient to establish a causal relationship between MIRAPEX tablets and these fibrotic complications, a contribution of MIRAPEX tablets cannot be completely ruled out in rare cases. ***Melanoma:*** Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. MIRAPEX tablets are one of the dopamine agonists used to treat Parkinson's disease. Although MIRAPEX tablets have not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using MIRAPEX tablets for any indication should be made aware of these results and should undergo periodic dermatologic screening.
Impulse Control/Compulsive Behaviors: Cases of pathological gambling, hypersexuality, and compulsive eating (including binge eating) have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.
Rebound and Augmentation in RLS: Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a shifting of symptoms to the early morning hours, referred to as rebound. Rebound was not reported in the clinical trials of MIRAPEX tablets but the trials were generally not of sufficient duration to capture this phenomenon. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. In a controlled trial of MIRAPEX tablets for RLS, approximately 20% of both the Mirapex- and placebo-treated patients reported at least a 2-hour earlier onset of symptoms during the day by the end of 3 months of treatment. The frequency and severity of augmentation and/or rebound after longer-term use of MIRAPEX tablets and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.
Information for Patients (also see Patient Package Insert): Patients should be instructed to take MIRAPEX tablets only as prescribed.
Patients should be alerted to the potential sedating effects associated with MIRAPEX tablets, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with Mirapex® (pramipexole dihydrochloride) tablets to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX tablets and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine).
Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease. In clinical trials, patients with RLS treated with pramipexole rarely reported hallucinations.
Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines to treat Parkinson's disease or RLS, including MIRAPEX tablets. These include pathological gambling, hypersexuality, and compulsive eating (including binge eating). If such behaviors are observed with MIRAPEX tablets, dose reduction or treatment discontinuation should be considered.
Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX tablets.
Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see **PRECAUTIONS, Pregnancy**).
Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.
If patients develop nausea, they should be advised that taking MIRAPEX tablets with food may reduce the occurrence of nausea.
Laboratory Tests: During the development of MIRAPEX tablets, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.
Drug Interactions: *Carbidopa/levodopa:* Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours. *Selegiline:* In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole. *Amantadine:* Population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole. *Cimetidine:* Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12). *Probenecid:* Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12). *Other drugs eliminated via renal secretion:* Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole. *CYP interactions:* Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 µM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day (1.5 mg TID). *Dopamine antagonists:* Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Mirapex® (pramipexole dihydrochloride) tablets.
Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX tablets and laboratory tests.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day [0.3, 2.2, and 11 times the Maximum Recommended Human Dose (MRHD) (MRHD of 1.5 mg TID on a mg/m² basis)]. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs were 0.3, 2.5, and 12.5 times the AUC in humans at the MRHD). No significant increases in tumors occurred in either species.
Pramipexole was not mutagenic or clastogenic in a battery of assays, including the in vitro Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus assay.
In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.
Pregnancy: Teratogenic Effect: Pregnancy Category C: When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the MRHD on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.
There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.
Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: The safety and efficacy of Mirapex® (pramipexole dihydrochloride) tablets in pediatric patients has not been established.
Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies with Parkinson's disease patients, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPEX tablets was increased in the elderly. In clinical studies with RLS patients, 22% of patients were at least 65 years old. There were no apparent differences in efficacy or safety between older and younger patients.
ADVERSE EVENTS
Parkinson's Disease: During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.
Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.
Early Parkinson's Disease: In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.
Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX tablets who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX tablets vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX tablets vs 1% on placebo]; somnolence [1.6% on MIRAPEX tablets vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX tablets vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placebo]); and gastrointestinal system (nausea [2.1% on MIRAPEX tablets vs 0.4% on placebo]).
Adverse-event Incidence in Controlled Clinical Studies in Early Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.
The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.
Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=388) vs placebo (N=235), respectively. ***Body as a whole:*** asthenia (14% vs 12%), general edema (5% vs 3%), malaise (2% vs 1%), reaction unevaluable (2% vs 1%), fever (1% vs 0%). ***Digestive system:*** nausea (28% vs 18%), constipation (14% vs 6%), anorexia (4% vs 2%), dysphagia (2% vs 0%). ***Metabolic and nutritional system:*** peripheral edema (5% vs 4%), decreased weight (2% vs 0%). ***Nervous system:*** dizziness (25% vs 24%), somnolence (22% vs 9%), insomnia (17% vs 12%), hallucinations (9% vs 3%), confusion (4% vs 1%), amnesia (4% vs 2%), hypesthesia (3% vs 1%), dystonia (2% vs 1%), akathisia (2% vs 0%), thinking abnormalities (2% vs 0%), decreased libido (1% vs 0%), myoclonus (1% vs 0%). ***Special senses:*** vision abnormalities (3% vs 0%). ***Urogenital system:*** impotence (2% vs 1%).
Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

that we have other injectable medications that are not insulin, I find that some people will accept them more readily. There's something specific about the insulin."

The psychological implications of reaching insulin dependency may not figure as prominently in needle fear among children or adolescents, whose primary concerns focus more on pain—both physical and social, Dr. Chase said in an interview.

"Only about a third of teenagers are currently in the range recommended by the ADA [American Diabetes Association] for good glycemic control," he said. There are lots of reasons for this, and fear of needles is one of them.

In fact, Dr. Chase's group recently completed a study looking at the effect of reducing needle pain by fitting pediatric diabetes patients (aged 5-7 years) with a subcutaneous injection port (presented at the 2006 ADA annual meeting). EMLA cream was used for placement of the port, which could then stay in place for 3-5 days. Patients' multiple daily needles (mean, 4.5) were then administered through the port's catheter without piercing the skin. After 6 months, compared with 22 patients in both a control group and a second group who received regular dose-reminder alarms, the 17 patients fitted with the injection ports reported a reduction in pain, which was reflected in significantly improved glycemic control. "The injection port improved pain and/or convenience," he said.

All patients in the study used pen injection devices, which, like insulin pumps, can help alleviate needle anxiety for several reasons. "Some people just don't like to see the needle, or they're not sure how far they should inject," Dr. Korytkowski explained. "Sometimes with pen devices you don't really see the needle. And it's all a contained system [which controls insertion depth] so patients don't have to manipulate much." Jet injectors, which use air to drive an insulin dose through the skin without a needle, also are worth considering.

Devices such as pens and pumps also improve the discreetness of injecting, which is helpful for people whose needle anxiety is rooted in embarrassment, Dr. Korytkowski said. "Individuals with diabetes may be particularly conscious of self-injection in public places, as they fear the judgment of others and stigmatization as a 'sick person,' a 'dependent,' or even a 'drug user,' " she wrote in a review on addressing issues of confidence and convenience in insulin delivery (Clin. Ther. 2005;27[suppl. B]:S89-S100).

Although she has never referred a patient for psychological counseling because of needle anxiety per se, she has referred patients because they have a certain "disconnect" with their condition. "That's a different group. They'll do what has to be done, but they're not happy and they don't connect to it somehow. That takes a while to work through," she said.

Although some patients who are transitioning to insulin may be extremely vocal

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DR. CHASE

about their fear of self-injection, patients' needle anxiety may not always be obvious. Physicians should consider this possibility in patients who are not achieving good glycemic control, Dr. Korytkowski said. "If you have just one visit with a person, you may not find much out, but as you get to know these people—and diabetes is a chronic disease, so you usually get to know them—they will eventually tell you."

This can be facilitated with some pointed questions, she added. "You can ask if they have ever missed a shot, and why. Many people miss a shot occasionally, but if they're under poor control, that might make me pursue it further."

For patients with type 2 disease who are used to oral medications but are no longer in good glycemic control, the idea of injections may at first seem daunting. "They'll just say flat out, 'I'm not taking insulin.' They are terrified of giving themselves an injection." However, this is often remedied with a simple practice session in the office, where they self-inject either with insulin (if indicated) or saline, Dr. Korytkowski said.

"For the majority of people, once they've given [themselves] that first injection and seen what's involved, they see it's not as bad as they had thought, and they realize they can do it."

Both Dr. Korytkowski and Dr. Chase believe there are many layers to needle anxiety—pain and fear sometimes being separate issues, and sometimes occurring with more general phobic or depressive symptoms.

Although addressing this is usually time consuming, and may require additional help from specialists or nurse educators, it can result in improved glycemic control and frequently improves patients' quality of life. ■

Other events reported by 1% or more of patients with early Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's Disease: In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets and concomitant levodopa were postural (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.

Approximately 12% of 260 patients with advanced Parkinson's disease who received Mirapex® (pramipexole dihydrochloride) tablets and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX tablets vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX tablets vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX tablets vs 1.5% on placebo]; confusion [1.2% on MIRAPEX tablets vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX tablets vs 1.1% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, MIRAPEX tablets or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=260) vs placebo (N=264), respectively. ***Body as a whole:*** accidental injury (17% vs 15%), asthenia (10% vs 8%), general edema (4% vs 3%), chest pain (3% vs 2%), malaise (3% vs 2%). ***Cardiovascular system:*** postural hypotension (53% vs 48%). ***Digestive system:*** constipation (10% vs 9%), dry mouth (7% vs 3%). ***Metabolic and nutritional system:*** peripheral edema (2% vs 1%), increased creatine PK (1% vs 0%). ***Musculoskeletal system:*** arthritis (3% vs 1%), twitching (2% vs 0%), bursitis (2% vs 0%), myasthenia (1% vs 0%). ***Nervous system:*** dyskinesia (47% vs 31%), extrapyramidal syndrome (28% vs 26%), insomnia (27% vs 22%), dizziness (26% vs 25%), hallucinations (17% vs 4%), dream abnormalities (11% vs 10%), confusion (10% vs 7%), somnolence (9% vs 6%), dystonia (8% vs 7%), gait abnormalities (7% vs 5%), hypertonia (7% vs 6%), amnesia (6% vs 4%), akathisia (3% vs 2%), thinking abnormalities (3% vs 2%), paranoid reaction (2% vs 0%), delusions (1% vs 0%), sleep disorders (1% vs 0%). ***Respiratory system:*** dyspnea (4% vs 3%), rhinitis (3% vs 1%), pneumonia (2% vs 0%). ***Skin and appendages:*** skin disorders (2% vs 1%). ***Special senses:*** accommodation abnormalities (4% vs 2%), vision abnormalities (3% vs 1%), diplopia (1% vs 0%). ***Urogenital system:*** urinary frequency (6% vs 3%), urinary tract infection (4% vs 3%), urinary incontinence (2% vs 1%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Restless Legs Syndrome: MIRAPEX tablets for treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year.

The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events with MIRAPEX tablets in the treatment of RLS (observed in >5% of pramipexole-treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

This section lists treatment-emergent events that occurred in three double-blind, placebo-controlled studies in RLS patients that were reported by 2% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=575) vs placebo (N=223), respectively. ***Gastrointestinal disorders:*** nausea (16% vs 5%), constipation (4% vs 1%), diarrhea (3% vs 1%), dry mouth (3% vs 1%). ***General disorders and administration site conditions:*** fatigue (9% vs 7%). ***Infections and infestations:*** influenza (3% vs 1%). ***Nervous system disorders:*** headache (16% vs 15%), somnolence (6% vs 3%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

This section summarizes data for adverse events that appeared to be dose related in the 12-week fixed dose study. Dose related adverse events in a 12-week, double-blind, placebo-controlled, fixed dose study in Restless Legs Syndrome (occurring in 5% or more of all patients in the treatment phase) are listed by body system in order of decreasing incidence for MIRAPEX (0.25 mg [N=88]; 0.5 mg [N=80]; 0.75 mg [N=90]) vs placebo (n=86), respectively. ***Gastrointestinal disorders:*** nausea (11%; 19%; 27% vs 5%), diarrhea (3%; 1%; 7% vs 0%), dyspepsia (3%; 1%; 4% vs 7%). ***Infections and infestations:*** influenza (1%; 4%; 7% vs 1%). ***General disorders and administration site conditions:*** fatigue (3%; 5%; 7% vs 5%). ***Psychiatric disorders:*** insomnia (9%; 9%; 13% vs 9%), abnormal dreams (2%; 1%; 8% vs 2%). ***Respiratory, thoracic and mediastinal disorders:*** nasal congestion (0%; 3%; 6% vs 1%). ***Musculoskeletal and connective tissue disorders:*** pain in extremity (3%; 3%; 7% vs 1%).

Other events reported by 2% or more of RLS patients treated with Mirapex® (pramipexole dihydrochloride) tablets but equally or more frequently in the placebo group, were: vomiting, nasopharyngitis, back pain, pain in extremity, dizziness, and insomnia.

General

Adverse Events; Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX tablets, hallucination appeared to exhibit a positive relationship to age in patients with Parkinson's disease. Although no gender-related differences were observed in Parkinson's disease patients, nausea and fatigue, both generally transient, were more frequently reported by female than male RLS patients. Less than 4% of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During Phase 2 and 3 Clinical Trials: MIRAPEX tablets have been administered to 1620 Parkinson's disease patients and to 889 RLS patients in Phase 2 and 3 clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing; similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. Adverse events which are not listed above but occurred on at least two occasions (one occasion if the event was serious) in the 2509 individuals exposed to MIRAPEX tablets are listed below. The reported events below are included without regard to determination of a causal relationship to MIRAPEX tablets.

Blood and lymphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy, thrombocythaemia, thrombocytopenia. *Cardiac disorders:* angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomegaly, coronary artery occlusion, cyanosis, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy. *Congenital, familial and genetic disorders:* atrial septal defect, congenital foot malformation, spine malformation. *Ear and labyrinth disorders:* deafness, ear pain, hearing impaired, hypoacusis, motion sickness, vestibular ataxia. *Endocrine disorders:* goiter, hyperthyroidism, hypothyroidism. *Eye disorders:* amaurosis fugax, blepharitis, blepharospasm, cataract, dacryostenosis acquired, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, retinal vascular disorder, scotoma, vision blurred, visual acuity reduced, vitreous floaters. *Gastrointestinal disorders:* abdominal discomfort, abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis ulcerative, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia. *General disorders:* chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling hot, feeling jittery, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, pitting edema, thirst. *Hepatobiliary disorders:* biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis. *Immune system disorders:* drug hypersensitivity. *Infections and infestations:* abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex, herpes zoster, hordeolum, intervertebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection. *Injury, poisoning and procedural complications:* accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture. *Metabolism and nutrition disorders:* cachexia, decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, metabolic alkalosis. *Musculoskeletal and connective tissue disorders:* bone pain, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, polymyalgia, rheumatoid arthritis, shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis. *Neoplasms benign, malignant and unspecified:* abdominal neoplasm, adenocarcinoma, adenoma benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma. *Nervous system disorders:* ageusia, akinesia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthria, dysgraphia, facial palsy, grand mal convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, sleep talking, stupor, syncope vasovagal, tension headache. *Psychiatric disorders:* affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation. *Renal and urinary disorders:* chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis, neurogenic bladder, nocturia, oliguria, pollakiuria, proteinuria, renal artery stenosis, renal colic, renal cyst, renal failure, renal impairment, urinary retention. *Reproductive system and breast disorders:* amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, menopausal symptoms, menorrhagia, metrorrhagia, ovarian cyst, priapism, prostatitis, sexual dysfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage. *Respiratory, thoracic and mediastinal disorders:* apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospasm, nasal dryness, nasal polyps, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumonia aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing. *Skin and subcutaneous tissue disorders:* acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria. *Vascular disorders:* aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein.

Falling Asleep During Activities of Daily Living: Patients treated with Mirapex® (pramipexole dihydrochloride) tablets have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see bolded **WARNING**).

Post-Marketing Experience: In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA dictionary: abnormal behavior, abnormal dreams, accidents (including fall), blackouts, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, syncope, and weight increase.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days in a clinical trial to evaluate the effect of pramipexole in schizophrenic patients. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg TID). In a similar study of pigmented rats with 2 years' exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice: An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

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