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Ropinirole (Requip®) and Pramipexole (Mirapex®) for the Treatment of Primary Restless Legs Syndrome

Learning Objectives:

1. Describe the epidemiology, pathophysiology and diagnostic criteria for restless legs syndrome (RLS).
2. Explain the roles and limitations of levodopa, opioids, anticonvulsants, benzodiazepines and non-pharmacological therapy in RLS treatment.
3. Discuss the dosing, mechanism of action and benefits of ropinirole and pramipexole in treating RLS.
4. Characterize the evidence of the pivotal studies from the FDA drug approvals for ropinirole and pramipexole in the treatment of RLS.
5. List the adverse events, rebound and augmentation associated with drug therapy in RLS treatment.

Introduction

In recent years, restless legs syndrome (RLS) has gained an increased amount of public awareness leading to more frequent diagnosis and treatment, but it was first described in the 17th century by Thomas Willis.[1] RLS is estimated to affect 4%-10% of the adult population, including approximately 10 million adults and 1.5 million children in the United States.[2] Some studies have shown that women are 50% more likely than men to have RLS symptoms.[3] RLS prevalence and disease severity increase with age.[4]

RLS, also known as Ekbom syndrome,[5] is a common sensorimotor disorder characterized by a distressing irresistible urge to move the leg(s), but it may advance to include the arms or other body parts.[6] The urge is usually accompanied by a sensation of discomfort and sometimes pain deep inside the legs or other limbs. The RLS symptoms typically begin or worsen during periods of rest or inactivity and are temporarily relieved by movement. RLS symptoms follow a circadian pattern and are more intense in the evening and nighttime.[7] Many RLS patients also experience periodic limb movements during sleep (PLMS).[7] Patients with RLS have a disruption in their daily lives due to their difficulty getting to sleep and staying asleep. Sleep deprivation can lead to daytime fatigue, lack of concentration or depressed mood. The sleep issues can cause significant daytime difficulties which can lead to safety, social and economic issues for the patient. Many RLS patients are uncomfortable riding in a car or airplane for a prolonged time or participating in sedentary activity in the late evening or nighttime.[6] This article will discuss current non-pharmacological and pharmacological treatment of RLS, but will focus on the dopaminergic agents ropinirole (Requip®, GlaxoSmithKline) and pramipexole (Mirapex®, Boehringer Ingelheim) which have become first line agents in the treatment of daily primary RLS.

Evaluation and Classification

The International Restless Legs Syndrome Study group published criteria for the clinical diagnosis of RLS and revised the criteria in 2003.[4] The diagnosis of RLS is based on the 4 primary features. The first criterion is the urge to move the legs and often is associated with paresthesias/dysethesias. Patients describe the sensation as uncomfortable and deep within the leg occurring while awake.[6] The uncomfortable sensations vary, but phrases used to characterize it include "creepy-crawly sensations", "electric currents" and "jumpy legs."[7] When the disorder is more severe it may affect other parts of the body, but the legs are usually affected first and most severely. The second criterion is sensory symptoms that worsen during rest or inactivity such as sitting or lying down.[6] The third criterion is the partial or temporary alleviation of motor restlessness by movement such as walking or stretching with relief as long as the activity continues. The last criterion is the circadian pattern of RLS symptoms. RLS symptoms occur or are worse during evening and nighttime hours.[6] Patients with severe RLS may have the symptoms throughout the day.[1] A pneumonic to remember these 4 criteria is URGE:[6]

- **U**rge to move
- **R**est induced
- **G**ets better with activity
- **E**vening and night accentuation

The differential diagnosis starts with a patient interview to determine if the 4 established criteria are met. During a differential diagnosis other diseases that mimic RLS must be ruled out. Other conditions that cause motor restlessness and need to be excluded for accurate diagnosis include: nocturnal leg cramps, peripheral neuropathy, varicose veins, intermittent claudication, positional discomfort, neuroleptic-induced akathisia, leg pain due to arthritis, nervous fidgets or leg shaking.[8] No laboratory findings are specific for RLS, but low iron stores are a significant risk factor for exacerbation of RLS symptoms.

As part of the patient evaluation for RLS it is important to measure the serum ferritin concentration, red blood cell count, hemoglobin and hematocrit. Serum ferritin levels below 45-50 micrograms/L are related to an increased severity of RLS and are indicative of an iron deficiency.[6] Clinicians see improvements in RLS symptoms by treating the iron deficiency anemia and it is recommended that patients receive 50-65 mg elemental iron 1-3 times a day.[7] Serum ferritin levels and the percentage of transferritin saturation should be checked every 3 months for follow-up with the goal of reaching a serum ferritin levels of <50-60 micrograms/L.[7]

There are 2 distinct types of RLS: primary (idiopathic) and secondary. Secondary RLS is associated with disorders that result in iron deficiency anemia, most commonly seen in pregnancy, and end stage renal disease.[6] This article will focus on primary RLS. The pathophysiology of primary RLS is still unknown, although many causes have been proposed. Symptoms of RLS are exacerbated with dopamine antagonists and show improvement with a dopaminergic agonist.[9] Also the role of iron deficiency in the exacerbation of RLS symptoms and the fact that iron is a cofactor for tyrosine hydroxylase, the rate limiting enzyme for dopamine synthesis, lead many to see the key role iron and dopamine have in the pathophysiology of RLS.[9]

The RLS Foundation makes a distinction for therapy purposes to divide patients into 3 groups: (1) those with intermittent RLS symptoms that require treatment, but do not necessitate daily therapy (2) those with daily RLS symptoms and (3) those with RLS symptoms refractory to standard treatment.[7] The goals of RLS therapy are to reduce the number of nights with RLS symptoms, reduce nighttime awakenings and improve the patient's quality of life by decreasing RLS symptoms, daytime drowsiness and other interferences in daily activities due to poor sleep quality.

Non-pharmacological Therapies

Currently, there are no well controlled trials that have assessed the benefits of non-pharmacological therapies for RLS, but there have been benefits noted in anecdotal reports and case series. Patients with intermittent or mild RLS symptoms should attempt non-pharmacological therapies prior to initiating drug treatment. The pharmacist can play a critical part in RLS patient care by being aware of drugs that aggravate RLS symptoms. These drugs include dopamine-blocking agents (neuroleptics, antinausea medications, metoclopramide), antidepressants (SSRIs and tricyclics with the exception of bupropion) and antihistamines.[10]

The main non-pharmacological recommendation is the development of healthy sleep habits which include sleep attempted at the same time every night after a period of reduced activity and avoidance of voluntary sleep restrictions. Other recommendations include healthy diet, moderate exercise in the evening, mild physical activity involving the limbs before bedtime (e.g., stretching exercises), hot baths or massage before bed and mental activities prior to bedtime (e.g., crossword puzzles, video games, reading, and card games) all have shown improvements in some patients.[8] It appears caffeine, nicotine and alcohol consumed in the evening can worsen RLS symptoms.[7] Patients may also want to consider participating in sedentary activities such as going to the movies or long air plane flights during morning hours and performing activities that involve walking or exer-

cise later in the day.[7] The RLS Foundation (www.rls.org) has a list of local support groups that provide education for patients to learn more about RLS, how to minimize possible aggravators, and to keep up-to-date on the advantages of new treatment options. Although editorially independent, the RLS foundation is supported by grants from GlaxoSmithKline and Boehringer Ingelheim.

Therapy Monitoring Scales

Currently, studies to evaluate the efficacy of drug therapy use the International Restless Legs Scale (IRLS) and Clinician Global Impression-Improvement scale (CGI-I) to assess the primary efficacy endpoints during pharmacological therapy. The IRLS score is based on a 10 item scale with scores ranging from 0 (best) to 40 (worst). Items assess the intensity and frequency of the primary features of RLS, associated sleep problems, and the impact of RLS on mood and daily functioning. Patients with RLS are classified as mild (1-10), moderate (11-20), severe (21-30), or very severe (31-40).[11] The Clinician Global Impression-Improvement scale (CGI-I) is a rating system in which the clinician assigns a score from 1 (very much improved) to 7 (very much worse). It is not specific to RLS.[11] Another scale to measure RLS drug therapy efficacy is the Medical Outcome Study Sleep Scale. This scale has been validated in the general population, but is not specific to RLS. It assesses the patient's self report of sleep disturbance, sleep adequacy, daytime somnolence, sleep quality, respiratory impairments, and snoring.[12] Also the RLS quality of life questionnaire is used to calculate an overall life impact score.[13]

Current Treatment Options for RLS

The 4 drug classes that have been studied for the treatment of RLS are the dopaminergics, opioids, anticonvulsants and benzodiazepines. The dopaminergic drug first studied for RLS is oral levodopa combined with carbidopa or benserazide. Levodopa was the standard first-line therapy in the 2004 American Academy of Sleep Medicine evidence-based guidelines[14] for the treatment of RLS, but it is no longer first line therapy since the introduction of the nonergoline dopaminergic agonists. Levodopa is still recommended for intermittent RLS and has shown relief of symptoms 20 minutes after dose administration, but due to its short half-life (1-2 hours)[7] it does not provide a sustained effect. Typical dosage is 25/100 to 100/400 mg of carbidopa/levodopa taken 1 hour before symptom onset.[10] Some of the common side effects related to levodopa include nausea, vomiting, insomnia, hallucinations, nasal congestion, fluid retention and daytime drowsiness.[7] Levodopa has fallen out of use in daily primary RLS due to drug tolerance, rebound and augmentation.[7] Rebound is defined as the worsening of symptoms of RLS as the medication wears off resulting in late-night or morning recurrence of symptoms, and periodic limb movements of sleep, necessitating additional doses to overcome this effect.[1] Rebound is seen in 20-35% of patients taking levodopa.[15] Augmentation is defined as a change in RLS symptoms after beginning therapy. This change includes symptoms developing earlier in the day, earlier symptom onset when at rest, increased severity of symptoms, or shorter relief of symptoms following the medication dose.[1] Some studies have shown 50-85% of patients on levodopa develop augmentation.[1]

Pergolide is a semisynthetic ergot alkaloid dopamine agonist that acts at the dopamine 1 and dopamine 2 receptors. Pergolide showed promising efficacy in a few studies, but it fell out of use due its association with serious cases of pulmonary fibrosis and cardiac dysfunction.[16] In March 2007 pergolide was withdrawn from the United States market due to association with development of heart valve defects.[17]

Opioids were the first drugs used for the treatment of RLS, but they are now reserved for patients with very severe RLS symptoms who have failed other treatments, or for short-term use.[10] The lack of evidence of opioid efficacy[18] and significant concerns for their use based on their potential for addiction during long term therapy requires physicians to carefully monitor patients for development of dependency and respiratory problems.[8]

The oral anticonvulsants also have been used to treat RLS. Gabapentin, carbamazepine and valproic acid have been tested in controlled trials, but the studies have been small and have shown mixed efficacy results to support their use.[8] Gabapentin has shown good efficacy in short term trials[19] and some consider it the most promising second line agent. It is generally well tolerated, but it can cause significant daytime sedation. It may be a possible treatment option for patients with co-morbid RLS and peripheral neuropathy or patients with RLS and continued sleep disturbances.[10] Further long-term large studies will be needed to determine its role in the treatment algorithm.[10]

Clonazepam has been used in RLS due to its ability to induce sleep, but it does not address the RLS symptoms. After the introduction of the dopamine agonists, the benzodiazepines have become a second- or third-line option.[8]

Nonergoline Dopamine Agonists

Dopamine agonists are the first-line agents for the treatment of RLS. Ropinirole (Requip®, GlaxoSmithKline) and pramipexole (Mirapex®, Boehringer Ingelheim) are nonergoline derivatives which act by stimulating the dopamine 2 and dopamine 3 receptors.

Table 1. Pivotal studies for ropinirole and pramipexole in the treatment of restless legs syndrome.

Author, Year, N	Treatment Groups	Mean Change from Baseline IRLS Total Score	% Responders on CGI-I Scale	RLS Symptoms Relapse Rates on IRLS Scale
Bogan, 2006[22] n = 380	R (n =187) PL (n =193)	-13.5 -9.8 P<0.001	73.3 % 56.5% P<0.001	
Trenkwalder[23], 2004 n = 284	R (n = 146) PL (n = 138)	-11.04 -8.03 P=0.0036	53.4% 40.9% P=0.0416	
Walters, 2004[24] n = 267	R (n = 131) PL (n = 136)	-11.02 -8.7 P=0.0197	59.5% 39.6% P=0.001	
Montplaisir, 2006[25] n = 92	R (n = 45) PL (n = 47)			32.6% 57.8% P=0.0156
Winkelman, 2006 [26] n = 339	PPX 0.025 mg (n =88) PPX 0.50 mg (n= 79) PPX 0.75 mg (n = 87) PL (n =85)	-12.8 P<0.01 -13.8 P <0.01 -14.0 P<0.01 -9.3	74.7% P<0.01 67.9% P<0.05 72.9% P<0.01 51.2%	
Trenkwalder,2006 [27] n = 147	PPX (n =78) PL (n = 69)			20.5%*** 85% *** P<0.0001
Oretel, 2007 [28] n=338	PPX (n=224) PL (n=114)	-12.3 -5.7 P<0.0001	62.9% 32.5% P<0.0001	
Partinen, 2006 [29] N=107	PPX 0.125 mg (n=21) PPX 0.25 mg (n=22) PPX 0.50 mg (n=22) PPX 0.75 mg (n=21) PL (n=21)	-11.87 P=0.0274 -15.18 P<0.0001 -17.01 P<0.0001 -15.86 P<0.0001 -6.08	61.9% 68.2% P<0.05 86.4% P<0.05 85.7% P<0.05 42.9%	

*** treatment failure; R=ropinirole, PL=placebo, PPX=pramipexole

Pramipexole has a greater affinity for the dopamine 3 receptor and also acts at the dopamine 4 receptor.[1] Both drugs were approved in 1997 for treatment of Parkinson Disease.[1] The dopamine agonists have the advantage of alleviating the symptoms of RLS and have a longer elimination half-life (ropinirole = 6 hours, pramipexole = 8 hours)[20,21] compared to levodopa. This leads to a longer duration of effect during the sleeping period and less chance for rebound or augmentation. Based on current studies they also have a lower rate of side effects in the doses given for RLS, and a lower rate of complications such as rebound and augmentation.[10] Ropinirole and pramipexole have been approved by the FDA for the treatment of moderate to severe RLS and are currently used as first-line therapy for primary RLS.

Ropinirole

Ropinirole was the first drug approved by the FDA in May 2005 for the indication of treatment of RLS. Dosing is typically 0.25 mg orally once daily 1-3 hours before bedtime.[20] The dose may be titrated every 2-3 days until reaching optimum clinical response and tolerability. The dosing titration helps to lessen the side effects of nausea and orthostatic hypertension, which typically improve after 7-10 days.[20] Most patients respond to a total dosage between 1-3 mg/ day and the maximum dose is 4 mg/day.[20] Ropinirole can be given with food to decrease the potential for nausea. Although food does not change the extent of absorption, it does increase the time to peak concentration by 2.5 hours, and the peak concentration is decreased by approximately 25% when the ropinirole is taken with a high fat meal.[20] The most common side effects associated with ropinirole include nausea, somno-

lence, vomiting dizziness and fatigue.[20] Since ropinirole is not renally excreted it may be used in patients with kidney failure.[10]

Ropinirole Pivotal Studies

The FDA clinical review for approval for ropinirole for RLS identified 4 pivotal studies (Table 1).[20, 21] Three of the studies were 12-week, randomized, double blind, placebo-controlled trials in patients 18-80 years old with moderate to severe primary RLS. Moderate to severe RLS was defined as a baseline total score of at least 15 points on the International Restless Legs Scale (IRLS), a history of at least 15 nights of RLS symptoms during the previous month and documented RLS symptoms for at least 4 of the 7 nights during the screening/wash-out phase. Patients were excluded if they had secondary RLS, other movement or primary sleep disorders, required treatment for daytime RLS, had experienced augmentation or rebound with previous therapy or were taking medications known to affect RLS or sleep. The primary efficacy assessments were the mean change from baseline in the IRLS total score and the Clinician Global Impression-Improvement scale (CGI-I) at week 12.

Bogan and colleagues[22] compared the efficacy of ropinirole to placebo in a flexible-dose trial in patients with primary RLS. Patients randomized to treatment were assigned initially to 0.25 mg/day oral ropinirole given 1-3 hours before bedtime. The dose was titrated as needed and as tolerated to 0.5 mg at day 3. After the first week the dose could be increased by 0.5 mg/day in weekly increments up to a maximum dose of 4.0 mg/day. The final mean dose was 2.1 mg/day. The mean change from baseline in IRLS score with the last observation carried forward (LOCF) at 12 weeks was significantly greater for the ropinirole group (-13.5) compared with placebo (-9.8); adjusted mean treatment difference, -3.7 (95% confidence interval [CI]-5.4 to -2.0; P<0.001). Also, in a key secondary efficacy assessment measure, significantly more patients in the ropinirole group (73.3%) vs. placebo (56.5%) were rated as responders on the CGI-I scale at 12 weeks (adjusted odds ratio, 2.1; 95% CI 1.4-3.3; P<0.001). Improvements in sleep and quality of life were also reported.

During treatment 82.9% in the ropinirole and 66.8% in the placebo group reported at least one adverse event (AE), but most were mild or moderate. The severe AEs reported in more than 2% of patients were nausea (ropinirole 8.0%; placebo 0.5%) and vomiting (ropinirole 2.1%; placebo 0.5%). No serious AEs were deemed by the investigator to be related to the study drug. The withdrawal rate due to AEs during therapy was low and similar between the groups (ropinirole 2.7%; placebo 4.1%).

Trenkwalder and associates[23] compared the safety and efficacy of ropinirole versus placebo in a randomized trial in patients with primary RLS. Patients were randomized initially to 0.25 mg/day oral ropinirole or placebo given 1-3 hours before bedtime. The dose was titrated as needed during weeks 1 to 7 until subjects reached the optimal dose in the investigators' opinion or a maximum dose of 4 mg/day. The mean daily dose at 12 weeks was 1.9 mg/day. The adjusted mean improvement in the IRLS total score at 12 weeks was significantly greater for ropinirole (-11.04) compared to placebo (-8.03); treatment difference -3.01 (95% CI -5.03 to -0.99, P=0.0036). In a key secondary endpoint, significantly more patients in the ropinirole group (53.4%) compared to placebo (40.9%) demonstrated a "much improved" or "very much improved" score on the CGI-I scale at 12 weeks (P=0.0416). Subjects began to respond after the first week of treatment and showed improvement in sleep and quality of life. No augmentation was seen during the study.

Nausea, vomiting, dizziness and somnolence were reported more frequently with ropinirole compared to placebo. The most commonly reported AEs were mild to moderate in intensity and their frequency declined over time in both groups. Serious AEs were unusual and none led to withdrawal or were judged by the investigator to be related to the study drug. The withdrawals were due to nausea (ropinirole 6 vs. 0 with placebo) and worsening RLS symptoms (3 with placebo and 0 with ropinirole).

Walters and co-workers[24] also evaluated the efficacy of ropinirole compared to placebo in primary RLS. They used the same dosing titration method as the Trenkwalder and Bogan studies. At 12 weeks the mean dose was 1.5 mg/day. They also found after 12 weeks that patients in the ropinirole group showed a significantly greater mean adjusted change in IRLS, using LOCF, with ropinirole compared to placebo (-11.2 vs.- 8.7, respectively, P=0.0197). The CGI-I score for patients on ropinirole also improved compared to placebo (59.5% vs. 39.6%, respectively, P=0.001). The other secondary assessment endpoints showed improvement in sleep and quality of life.

Adverse events were more common in the ropinirole group compared to placebo, but mostly mild to moderate in intensity and resulted in discontinuation of treatment in less than 10% of the patients in each treatment group. The most common AEs with ropinirole were nausea (39.7%), headache (22.1%), fatigue (15.3%), dizziness (15.3%), upper respiratory tract infection (13.7%) and vomiting (12.2%), no augmentation was reported.

Montplaisir and coworkers[25] conducted the final pivotal study, which assessed the efficacy of ropinirole for long-term maintenance of RLS and assessed the

potential for relapse after discontinuing active treatment. The study was a 36-week randomized, placebo-controlled trial including the same patient inclusion and exclusion criteria as the other 3 pivotal studies. All patients randomized to oral ropinirole were given 0.25 mg/day at 1-3 hours before bedtime and titrated between weeks 1-20 up to a maximum dose of 4 mg/day. In patients who were responders at 24 weeks the mean dose ropinirole was 2 mg/day. After the 24 week single-blind phase, 92 patients who were responders (defined as a decrease of greater than 6 points on the IRLS scale total score relative to baseline) were randomized in a double blind method to placebo or continuation of ropinirole for an additional 12 weeks. The primary assessment endpoint was relapse defined as an increase of at least 6 points on the IRLS score compared with the score at the start of the double-blind phase or withdrawal of the patients from the study due to lack of efficacy. Patients on ropinirole for the 36 weeks had a statistically significant lower relapse rate compared to those in the placebo group (32.6% vs. 57.8%; P=0.0156). The withdrawal rate due to lack of efficacy was significantly higher in the placebo group (51.3%) compared to ropinirole (29.3%, P=0.0372).

Patients in the ropinirole and placebo groups reported a similar number of overall AEs (57.8% ropinirole vs. 51.1% in placebo). The most common AEs were nausea (17.8% ropinirole vs. 2.1% placebo), headache (11.1% ropinirole vs. 6.4 % placebo). In the double-blind phase only one patient in the ropinirole group withdrew due to an AE.

Pramipexole

Pramipexole became the second drug approved by the FDA for RLS in November 2006. It is typically dosed as 0.125 mg orally 2-3 hours before bedtime and is slowly titrated upward. The average effective dose based on current studies is 0.375 mg/ day.[24] The most common side effects associated with pramipexole are fatigue, drowsiness, headache, peripheral edema and insomnia, which typically lessen after 7-10 days of treatment.[10] Since pramipexole is not hepatically metabolized it has the potential for fewer drug-drug interactions, but because it is renally excreted, the dosage may need to be adjusted in patients with reduced creatinine clearance.[10]

Pramipexole Pivotal Studies

The FDA approved pramipexole for treatment of primary moderate to severe RLS based on 4 pivotal trials (Table 1).[21] In all pivotal trials the patients had moderate to severe RLS and were excluded if they had secondary RLS or were on any medications that exacerbated RLS symptoms or had other sleep disorders. In all the studies the patients received oral pramipexole 0.125 mg, 0.25 mg, 0.50 mg or 0.75 mg or placebo once daily 2-3 hours before bedtime. The patients in the studies were 18-81 years old. The two primary efficacy endpoints assessed were the mean change from baseline for the IRLS scale and the CGI-I assessment.

Winkelman and associates[26] evaluated the safety and efficacy of 3 fixed doses of pramipexole in a 12-week, randomized, double-blind, placebo-controlled study. Patients randomized to pramipexole all initially started on 0.125 mg oral pramipexole once daily 2-3 hours before bedtime for one week. After the first week, doses were titrated to 0.25 mg, 0.50 mg or 0.75 mg/day. The primary efficacy endpoints were mean change in IRLS from baseline to 12 weeks, with LOCF for patients who withdrew before study completion, and responders in the CGI-I scale. The mean IRLS changes from baseline to week 12 in the 0.25 mg, 0.50 mg, 0.75 mg treatment groups were -12.8, -13.8, and -14.0, respectively. These were all significantly reduced compared to baseline as well as significantly improved compared to the placebo group with a change of -9.3%. The change in IRLS scores was not significantly different between the different doses of pramipexole. The responder rate assessed by CGI-I score for patients assigned pramipexole was also greater in all pramipexole dose groups compared to placebo (74.7%, 67.9%, 72.9% and 51.2% in the 0.25 mg, 0.50 mg, 0.75mg and placebo groups, respectively). The FDA's clinical reviewer concluded that all pramipexole groups were statistically superior compared to placebo for both primary efficacy endpoints. The reviewer also saw no clear evidence of a dose-response relationship between the 3 randomized dose groups.

The overall frequency of adverse events (AE) was similar in all groups. The most common side effects were nausea, headache, insomnia, somnolence, dizziness, nasopharyngitis and fatigue. The most common adverse event in the pramipexole groups compared to placebo were nausea (19.0% vs. 4.7%) and somnolence (10.1% vs. 4.7%), but these were mild and transient. The overall rate of study withdrawal because of an AE was 11.0%. The AEs that led to withdrawal were more common in the pramipexole group (12.4%) compared to placebo (7.0%).

Trenkwalder and co-workers[27] performed a randomized-withdrawal study to assess the sustained efficacy of pramipexole for RLS after a 6 month period. In phase 1 of the study RLS patients all initially received 0.125 mg oral pramipexole daily 2-3 hours before bedtime which was titrated up to individually optimized dosages of 0.125 mg, 0.25 mg, 0.50 mg or 0.75 mg once daily. Patients who responded to pramipexole in the 6 previous months were randomized to continue active treatment or placebo for 12 weeks. Responders to pramipexole were defined as having a IRLS score of ≤ 15 and a CGI-I rating of "very

much improved or "much improved" compared to baseline. The primary endpoint was the time to treatment failure defined as an IRLS Scale total score >15 or a worsening of the CGI-I score. All patients on active treatment with pramipexole were pooled for the analysis of the efficacy endpoints. The FDA's clinical reviewer[21] noted that at study completion 85% of patients treated with placebo had treatment failure compared to 20.5 % in pramipexole groups (P<0.0001). Also the clinical reviewer noted that the majority of treatment failures occurred within 10 days of randomization.

During phase 2 of the study, 32.0% of patients experienced AEs, and the incidence was lower with placebo (23.6%) compared to pramipexole (39.7%). The AEs with an overall frequency greater than 2% were worsening of RLS, nasopharyngitis, diarrhea, vomiting and upper abdominal pain. AEs showed no dose dependency and the majority were mild or moderate. Five patients had AEs classified as severe: 3 in the placebo group (worsening of RLS) and 2 in the pramipexole group (1 forearm fracture, 1 worsening of RLS). The investigators did not rate any of the patients who completed the study as having augmentation.

Oretel and co-investigators[28] performed a 6-week double-blind, randomized trial comparing the efficacy of flexible doses of pramipexole to placebo. Patients were randomly assigned in a 1:2 ratio to placebo or pramipexole. The initial pramipexole dose was 0.125 mg/ day 2-3 hours before bedtime. The dose could be increased in weekly intervals according to the Patient Global Impression scale (PGI) rating and overall tolerability of the drug. The primary endpoints were mean improvement from baseline on the IRLS score and CGI-I scale. At week 6 the median dose of pramipexole was 0.35 mg/day. At week 6 in all the pramipexole groups the adjusted mean change from baseline in the IRLS was -12.3 compared to -5.7 for placebo (P<0.0001). More than 85% of those subjects who responded did so at a dose of ≤ 0.5mg. At week 6 on the CGI-I scale 32.5% on placebo and 62.9% of those on pramipexole were assessed as either "much improved" or "very much improved" compared to baseline (P<0.0001).

A similar number of AEs were experienced with placebo (21.7%) and pramipexole (36.5%). The most frequent AEs were nausea (5.2% vs. 9.6%), fatigue (4.3% vs. 9.1%), headache (6.1% vs. 7.0%), and dizziness (3.5% vs. 3.5%) in the placebo and pramipexole groups, respectively. In the study 11 patients withdrew due to AEs (5 (4.3%) in the placebo group, 6 (2.6%) in the pramipexole group).

Partinen and colleagues[29] in a 3-week double-blind, placebo-controlled, fixed dose trial, compared the efficacy of 0.125 mg, 0.25 mg, 0.50 mg and 0.75 mg to placebo. For the primary efficacy endpoint of IRLS score, the mean adjusted changes from baseline were -11.87, -15.18, -17.01, -15.86 and -6.08 for the 0.125 mg, 0.25 mg, 0.50 mg, and 0.75 mg treatment groups compared to placebo, respectively. The adjusted mean changes were statistically significant for all pramipexole groups compared to placebo (P=0.0274 for the 0.125 mg group and P<0.0001 for the 0.25 mg, 0.50 mg and 0.75 mg groups). The percentage of responders in the pramipexole group for CGI –I was 61.9%, 68.2%, 86.4%, 85.7% in the 0.125 mg, 0.25 mg, 0.50 mg, and 0.75 mg groups, respectively compared to 42.9% in the placebo group. With the exception of the 0.125 mg group the percentage of responders based on CGI-I was significantly greater with pramipexole compared to placebo.

A similar number of patients in all groups experienced study drug related AEs (placebo 50.0% vs. pramipexole groups ranging from 31.8%-61.9%). The most frequent drug-related AEs were fatigue (overall 16.5%), nausea (overall 12.8%), and headache (overall 5.5%). The majority of AEs were mild to moderate. Two patients in the pramipexole groups and no patients in the placebo group required a dosage reduction or withdrew from the study.

Conclusion

Several significant advances in the diagnosis and treatment of RLS have been made in the last few years, and RLS has gained an increased amount of public awareness. Further research is necessary to understand the pathophysiology of RLS and the specific roles that iron and dopamine play in its development. Patients should be encouraged, when possible, to avoid drugs or daily habits that aggravate RLS symptoms. It would be advantageous to have comparative trials to assess the efficacy and safety of ropinirole and pramipexole compared to other medications in other drug classes previously beneficial in treating RLS patients. Although ropinirole and pramipexole have shown statistically significant efficacy in treatment of RLS, more studies are necessary to assess the long-term benefits and limitations of these drugs. No augmentation or severe side effects related to the study drugs were seen in the pivotal trials for ropinirole or pramipexole. However the size, patient selection restrictions, and duration of these studies are not sufficient to ensure these drugs do not have serious side effects, augmentation or rebound with long term use in clinical practice. Both ropinirole and pramipexole were statistically superior to placebo using both the IRLS and CGI-I scales. In the pivotal trials the placebo response on the CGI-I scale showing "much improved" or "very much improved" ranged from 30-56.5% improvement. Although the CGI-I scale is not specific to RLS, this larger response of improvement with placebo may cause some investigators to reconsider its role as a key efficacy endpoint monitor.

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(continued on page 12)

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The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 107-999-08-040-H01-P. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

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ASSESSMENT QUESTIONS

CE REGISTRATION
ACPE# 107-999-08-040-H01-P (0.1 CEU/1 Hr.)
Volume: 19 Issue: 1 MARCH 2008
Title of Educational Activity

Ropinirole (Requip®) and Pramipexole (Mirapex®) for the Treatment of Primary Restless Legs Syndrome

Name _____

Address _____

City _____ State _____ Zip _____

Social Security Number (optional)_____

Pharmacy License Number(s) _____

I hereby certify that I have taken this test:

_____
Signature/Date

(circle the correct answer)

1. Secondary RLS is associated with which of the following diseases?
   a. temporal lobe epilepsy
   b. end stage renal disease
   c. aplastic anemia
   d. hyperlipidemia

2. Which of the following drug classes aggravates the symptoms of RLS?
   a. neuroleptics
   b. calcium channel blockers
   c. anticonvulsants
   d. bronchodilators

3. Which of the following is true about current therapy options for treatment of RLS?
   a. Rebound is seen in 60-80% of patients taking levodopa.
   b. Levodopa is still recommended for intermittent RLS and has shown relief of symptoms 20 minutes after dose administration, but due to its short half-life (1-2 hours) does not provide a sustained effect.
   c. Pergolide is a semisynthetic ergot alkaloid dopamine agonist that acts at the dopamine 4 receptor.
   d. Clonazepam has shown augmentation in most efficacy studies.

4. Which of the following is **NOT** a criterion for the diagnosis of RLS?
   a. temporary alleviation of motor restlessness by movement
   b. urge to move the legs associated with paresthesias/dysthesias
   c. sensory symptoms worsen during periods of activity late in the morning
   d. symptoms follow a circadian pattern

5. The recommended dosing for pramipexole is_____.
   a. 0.125 mg orally 2-3 hours before bedtime then slowly titrated up
   b. 0.25 mg orally 2-3 hours before bedtime then slowly titrated up
   c. 0.50 mg orally 2-3 hours before bedtime then slowly titrated up
   d. 0.75 mg orally 2-3 hours before bedtime then slowly titrated up

6. Ropinirole acts by stimulating which of the following receptors?
   a. dopamine 1 and dopamine 4 receptors
   b. dopamine 3 and dopamine 4 receptors
   c. dopamine 1 and dopamine 2 receptors
   d. dopamine 2 and dopamine 3 receptors

7. Which of the following is true?
   a. Pramipexole is not renally excreted and it may be used in patients with kidney failure.
   b. Pramipexole was the first drug approved by the FDA for the indication of treatment of RLS.
   c. Since ropinirole is not hepatically metabolized it has the potential for fewer drug-drug interactions.
   d. Ropinirole can be given with food to decrease the potential for nausea and does not change the extent of absorption.

8. According to the International Restless Legs Scale (IRLS) a patient with a score of 21-30 is classified as having what severity of RLS?
   a. mild
   b. moderate
   c. severe
   d. very severe

9. In the fixed dose pramipexole study by Winkelman and associates, the FDA's clinical reviewer concluded that _____.
   a. none of the pramipexole groups were statistically superior compared to placebo for both primary efficacy endpoints. The reviewer also saw no clear evidence of a dose-response relationship between the 3 randomized dose groups.
   b. none of the pramipexole groups were statistically superior compared to placebo for both primary efficacy endpoints. The reviewer also saw clear evidence of a dose-response relationship between the 3 randomized dose groups.
   c. all pramipexole groups were statistically superior compared to placebo for both primary efficacy endpoints. The reviewer also saw statistically significant evidence of a dose-response relationship between the 3 randomized dose groups.
   d. all pramipexole groups were statistically superior compared to placebo for both primary efficacy endpoints. The reviewer also saw no clear evidence of a dose-response relationship between the 3 randomized dose groups.

10. Which of the following is NOT a common side effect associated with ropinirole?
    a. diarrhea
    b. somnolence
    c. nausea
    d. fatigue

Please Note: The CE processing fee is $7.50 USD.
Forms should be mailed to:

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Phone 515-270-0713
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PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				**Disagree**
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Molecular Entities & Biologicals

FDA Approvals
November 2007 – January 2008

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (Review Classification)	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)	Indication/Use Dosage Form	Valid IDIS Disease Term Modified ICD-9-CM Number
Etravirine *Intelence* (S)	Tibotec (Jan. 18, 2008)	ETRAVIRINE 8180872 (4 citations)	HIV Infection. Oral Tablet	Infection, HIV, Asymptomatic V08. Syn-Acq Immune Deficiency 042.
Nebivolol *Bystolic* (S)	Mylan Bertek (Dec. 17, 2007)	NEBIVOLOL 12160183 (33 citation)	Hypertension. Oral Tablet	Hypertension 401.
Sapropterin *Kuvan* (P)	Biomarin (Dec. 13, 2007)	SAPROPTERIN 92000146 (15 citations)	Phenylketonuria (PKU). Oral Tablet	Disorder, Amino Acid Metab 270.

Review Classification:
S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs
AA = Accelerated Approval
FT = Fast Track
P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease
BIO = Biological
O = Orphan drug

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American Association of Colleges of Pharmacy (ACCP)
2008 Annual Meeting
Sheraton Chicago Hotel and Towers
Chicago, Illinois
July 19-23, 2008

Selected Bibliography

Etravirine

Madruga JV, Cahn P, Grinsztejn B, Haubrich R, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2007; 370:29-38. (*IDIS* Article Number 578503)

This Phase III randomized controlled trial included 612 HIV patients who had failed on stable antiviral therapy with evidence of non-nucleoside reverse transcriptase inhibitor resistance and a viral load of more than 5000 copies/ml, plus three or more mutations of primary protease inhibitor. Three hundred and four patients received etravirine 200 mg twice daily, and 308 patients received placebo. All patients received darunavir low dose ritonavir and nucleoside reverse transcriptase inhibitors selected by the investigators. Results showed that at week 24, 170 (56%) patients in the etravirine group and 119 (39%) of patients in the placebo group had viral loads of less than 50 copies/ml, with a difference in response rates of 17% (95% CI 9-25; p=0.005). Adverse effects of etravirine were mild and included rash and diarrhea. Investigators found etravirine to be safe and effective in this group of patients.

Nebivolol

Tzemos N, Lim PO, MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: a randomised, double-blind, crossover study. *Circulation*. 2001; 104:511-514. (*IDIS* Article Number 468693)

Twelve hypertensive patients were randomized to 8-week periods of either nebivolol 5 mg/day plus bendrofluazide 2.5 mg/day or atenolol 50 mg/day plus bendrofluazide 2.5 mg/day. Blood pressure was lowered in both groups to the same degree; however, there was a significant increase in the vasodilatory response to acetylcholine only in the study drug group, which showed maximum percentage change in forearm blood flow (mean +/- SEM), 435 +/- 27%, (p<0.001). There was also significant improvement of the endothelium-dependent vasoconstrictive response to NG-monomethyl-L-arginine only in the nebivolol/bendrofluazide group, with the percentage change in forearm blood flow, -54 +/- 5% (p<0.001).

Saproterin Dihydrochloride

Levy HL, Milanowski A, Chakrapani A, Cleary M, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a Phase III randomized placebo-controlled study. *Lancet*. 2007; 370:504-510. (*IDIS* Article Number 580025)

Efficacy of sapropterin dihydrochloride was assessed in this trial which randomized a total of 89 patients with phenylketonuria to once daily doses of sapropterin 10 mg/kg (42 patients), or placebo (47 patients)for 6 weeks. At 6 weeks, the group taking sapropterin showed a decrease in mean blood phenylalanine of 236 (257) micromol/L and a 3 (240) micromol/L increase in the placebo group (p<0.0001). The percentage of patients taking the study drug compared with the placebo group who experienced a reduction in blood phenylalanine was 18/41 (44%) (95% CI 28-60) and 4/47 (9%) respectively (95% CI 2-20). Adverse events were similar in both groups.

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IDIS Journal Activity

JOURNAL ADDITIONS:

National Institute for Health and Clinical Excellence (NICE): Clinical Guideline (journal code 341; abbreviation: NICE CLIN GUIDEL)

National Institute for Health and Clinical Excellence (NICE): Technology Appraisal Guidance (journal code 342; abbreviation: NICE TECHNOL APPRAISAL GUID)

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