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BYETTA®: A NEW PHARMACOLOGICAL OPTION FOR PATIENTS WITH DIABETES MELLITUS

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The prevalence of diabetes is increasing globally. In 2002, the number of Americans affected by diabetes reached 18.2 million. Diabetes is responsible for substantial morbidity and mortality. Complications of diabetes include heart disease, amputation, blindness, stroke, neuropathy, and nephropathy. Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2000.[1]

Maintaining tight control of blood glucose slows the progress of microvascular complications of diabetes, allowing the patient to live a healthier, more active lifestyle. The United Kingdom Prospective Diabetes Study (UKPDS) confirmed the value of tight control in type 2 diabetes mellitus (T2DM).[2] However, unresponsiveness to oral antihyperglycemic agents is high. Primary sulfonylurea failure affects 20% to 25% of patients.[3] After five to seven years of therapy with sulfonylureas, 50% of these patients will require insulin therapy.[4]

Exenatide (βyetta®) is the first drug in a new class of antidiabetic medication called incretin mimetics. Exenatide was approved on April 29, 2005 and is marketed by Amylin Pharmaceuticals, Inc., and Eli Lilly and Co. It is indicated as adjunctive therapy to improve glycemic control in patients with T2DM who have not achieved adequate control with metformin and/or a sulfonylurea. It is expected that the Food and Drug Administration will also consider approval of exenatide as monotherapy for patients with T2DM. Incretin hormones are peptides released from cells in the gastrointestinal tract in response to nutrient stimuli. These peptides lead to glucose-dependent insulin release from the pancreas. Glucagon-like peptide 1 (GLP-1) is a naturally occurring incretin hormone found in humans. Release of GLP-1 potentiates glucose-dependent insulin secretion by stimulating β-cell growth and differentiation, promoting insulin gene expression, and inhibiting β-cell death in human islets cultured *in vitro*.[5] Exenatide is a synthetic form of the 39-amino acid GLP-1 agonist exendin-4, which was originally isolated from the salivary secretions of the Gila monster.[6] This article will review the pharmacokinetics and pharmacodynamics, clinical trials, dosing and administration, toxicity and safety, and cost of the first available incretin mimetic.

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Table 1. Summary of Clinical Trials with Exenatide.

Reference	Sample	Study Type	Dose	Clinical Response
Buse JB, et al. (2004)[9]	Type 2 diabetics treated with sulfonylureas (n = 377)	RCT, DB, PC, Parallel group	5 and 10 μg twice daily or placebo	Improved overall HbA1c ($p < 0.001$)
Fineman MS, et al. (2004)[10]	Type 2 diabetics (n = 123)	RCT, DB, PC	Titrated to 0.24 μg/kg TID	Gradual dose-escalation of exenatide reduced N/V incidence ($p < 0.001$)
Fineman MS, et al. (2003)[11]	Type 2 diabetics (n = 116)	RCT, DB, PC, Parallel group	0.08 μg/kg BID	Decreased fructosamine ($p < 0.004$), HbA_{1c} ($p < 0.006$), PPPG ($p < 0.004$), increased β-cell function
Heine RJ, et al. (2005)[13]	Type 2 diabetics (n = 551)	RCT, OL	Exenatide 10 μg BID versus insulin glargine	Both exenatide and insulin reduced HbA_{1c} by 1.11%; postprandial glucose excursions and weight gain were less profound with exenatide

RCT = randomized controlled trial; DB = double blind; PC = placebo controlled; N/V = nausea and vomiting; PPPG = postprandial plasma glucose; OL = open-label BID= twice daily; TID= three times daily.

Mechanism of Action

Exenatide, a synthetic incretin mimetic, is a GLP-1 analog.[6] GLP-1 is rapidly secreted by the L cells of the intestine in response to food ingestion. Release of GLP-1 potentiates glucose-dependent insulin secretion by stimulating β-cell growth and differentiation and insulin gene expression. GLP-1 inhibits β-cell death in human islets cultured *in vitro*.[5] The mechanism of action involves GLP-1-induced expression of a transcription factor called islet duodenum homeobox-1 (IDX-1), which is a master regulator of pancreatic development and β-cell function. IDX-1 stimulates progenitor cells in the pancreatic ducts to develop into β-cells. These pancreatic progenitor cells have been isolated in humans. This suggests GLP-1 may improve β-cell differentiation, increase d β-cell mass, and increased β-cell lifespan. GLP-1 also inhibits glucagon secretion, delays gastric emptying, and acts through the central nervous system to decrease appetite, increase sensation of satiety, and promote weight loss.[8,12]

Pharmacokinetics and Pharmacodynamics

Kolterman, et al. reported that subcutaneous (SC) doses of exenatide increased plasma concentrations of the drug in a dose-dependent manner. Peak concentrations were reached within 2-3 hours.[7] Similar exposure was achieved with SC administration of exenatide in the abdomen, thigh, or arm. Subcutaneous injections of exenatide yield a fairly predictable plasma concentration and lower BG rapidly. The volume of distribution of exenatide following SC administration is 28.3 L, which means that this drug is highly tissue bound.

Exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.[12] Mean half-life values ranged 3.3 to 4 hours. The dose must be reduced in chronic kidney disease to prevent accumulation and hypoglycemia.[8]

In two studies by Kolterman, et al., all doses of exenatide effectively blunted the initial rise in postprandial plasma glucose.[4] Baseline plasma insulin concentrations were similar for the placebo and exenatide groups. Within 1.5 to 2 hours following drug administration, plasma glucose concentrations in all exenatide groups decreased. In contrast, 5 hours passed before postprandial plasma glucose concentrations decreased in the placebo group. Postprandial plasma insulin concentrations peaked by 2 hours in all treatment groups. Baseline plasma glucagon concentrations were similar across treatment groups. There was a dose-dependent slowing of gastric emptying.[8]

Clinical Trials

Several clinical trials have been conducted to assess the role of exenatide in the care of diabetic patients. Table 1 includes a summary of clinical trials with exenatide. Four randomized controlled trials have helped to establish the safety and efficacy of exenatide.[9-11, 13]

One trial studied the effects of exenatide on glycemic control and body weight over a 30-week pe-

Table 2. Incidence of Adverse Effects with Exenatide.[12]

Adverse effect	Placebo BID (%)	Exenatide BID (%)*
Nausea	18	44
Vomiting	4	13
Diarrhea	6	13
Feeling Jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6

* This column includes exenatide at both 5 mcg BID and 10 mcg BID.

riod in patients with T2DM treated with sulfonylureas.[9] The trial enrolled 377 adults at 101 sites in the U.S. with sulfonylurea-treated T2DM. This randomized, double-blind, placebo-controlled, parallel group clinical study was designed to evaluate glycemic control, as assessed by HbA1c and safety. The study commenced with a 4-week, single-blind, lead-in period with SC injection of placebo twice daily (BID). Thereafter, subjects were randomized to one of four treatment arms. Secondary objectives of the study included examining the effects of exenatide on fasting plasma glucose concentrations, body weight, and fasting concentrations of circulating insulin, proinsulin, and lipids. Long-term use of exenatide at fixed doses of 5 and 10 mcg BID improved HbA1c in patients failing sulfonylurea therapy. Long-term use of exenatide at fixed SC doses of 5 and 10 mcg BID appears to have potential for the treatment of patients with T2DM not adequately controlled with sulfonylurea agents, with 41% able to reach and maintain an HbA1c less than 7% in the 10 mcg BID arm at the end of 30 weeks.

Another trial studied the effectiveness of progressive dose escalation of exenatide in reducing dose-limiting side effects, such as nausea and vomiting, in type 2 diabetics. A total of 123 patients with T2DM were recruited at 31 sites in the United States. This randomized, placebo-controlled, double-blind, multicenter study was designed to compare the proportion of subjects experiencing nausea and vomiting after receiving a target dose of exenatide that was known to cause nausea and vomiting (0.24 μg/kg), delivered either in a dose-escalation regimen (exenatide-primed arm) or as a first-time exposure (exenatide-naive arm). The exenatide-primed arm experienced a lower incidence of nausea and vomiting compared with the treatment naïve group (27% vs 56%, $p < 0.001$). Gradual dose-escalation of exenatide did not compromise glucoregulatory activity, thus demonstrating the value of gradual dose-escalation in mitigating the gastrointestinal side effects of exenatide.[10]

Exenatide added to metformin and/or sulfonylureas in type 2 diabetic patients was evaluated to determining the effect on glycemic control. A total of 116 patients with T2DM were recruited from 24 sites throughout the U.S. This randomized, double-blind, parallel-group, placebo controlled study was designed to assess glucose control and evaluate safety in patients receiving subcutaneously injected exenatide (0.08 μg/kg injection) or placebo for 28 days. After a two-week, single-blind, placebo lead-in, patients were randomly assigned to one of three exenatide treatment groups: BID (breakfast and dinner); BID (breakfast and bedtime); thrice daily (TID); or placebo TID. All exenatide groups had reductions in HbA1c ranging from 0.7% to 1.1%. An end-of-study HbA1c less than 7% was achieved by 15% of exenatide patients versus 4% of placebo patients ($p < 0.006$), confirming the effects of exenatide on overall glycemia. An analytical method used to measure insulin secretion, β-cell index homeostasis model assessment (HOMA), was utilized. On days 14 and 28, the β-cell index HOMA for patients treated with exenatide was 50% to 100% higher than baseline. The β-cell index HOMA was unchanged in the placebo arm.[11] This indicates an increase in β-cell function when exenatide is administered.

Most recently, exenatide was compared with insulin glargine in T2DM patients who were suboptimally controlled with metformin and a sulfonylurea. A total of 551 patients were recruited from 82 outpatient study centers in 13 countries. This open-label, randomized, noninferiority trial was designed to compare the effects of exenatide and insulin glargine on HbA1c over 26 weeks in patients with T2DM. The exenatide arm received 5 μg BID for 4 weeks followed by 10 μg BID for the remainder of the study. The insulin glargine arm received an initial dosage of 10 units/day; then, using a fixed dose algorithm to adjust the dose, the patients self-titrated their dose in 2 unit increments every 3 days to achieve fasting blood glucose of less than 100 mg/dL on daily glucose monitoring. HbA1c was reduced by 1.11% in both arms. The difference in HbA1c between arms was 0.017 % (CI, -0.123 to -0.157 %).

Table 3. Average Retail Cost of Frequently Used Agents for the Treatment of Diabetes.*

Drug	Dose	One month of therapy ($)
Exenatide (Byetta™)	5 mcg	$194.49
	10 mcg	$220.19
Metformin	850 mg	$28.09 (generic)
Glipizide	10 mg	$28.19 (generic)
Insulin Glargine (Lantus™)	1 vial	$73.79

*Prices reflect the average retail cost from 3 community pharmacies in Gainesville, FL 32601.

Both arms reduced fasting plasma glucose levels, although the reduction was significantly greater ($p < 0.001$) in the insulin glargine arm.[13] However, this was an open-label trial, the long-term impact of exenatide on HbA1c was not assessed, and the attrition rates were high in the exenatide arm due to adverse effects.

Dosing and Administration

The initial dose of exenatide is 5 mcg SC BID within an hour of morning and evening meals. After one month of therapy, the dose can be increased to 10 mcg SC BID. Exenatide should be injected into the abdomen, arm, or thigh; these sites should be rotated to prevent lipodystrophy. Exenatide should not be administered after a meal due to increased risk of gastroparesis. Exenatide is not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or with severe gastrointestinal disease due to increased gastroparesis. No dosage adjustments are needed based on age, race, gender, or body mass index. No data are available on the safety or efficacy of intravenous or intramuscular injection of exenatide.[12]

Toxicity and Safety

Contraindications to exenatide include known hypersensitivity to exenatide or any of its components, usage in type 1 diabetes, or for the treatment of diabetic ketoacidosis. Caution is warranted with the concurrent usage of insulin, thiazolidinediones, D-phenylalanine derivatives, meglitinides, and alpha-glucosidase inhibitors due to a lack of data when exenatide is used with these drug classes and the potential for increased hypoglycemia. Other precautions include severe renal impairment, gastrointestinal disease (due to the potential for gastroparesis), and an increased risk of hypoglycemia when used with a sulfonylurea. Exenatide is not a substitute for insulin in insulin-requiring patients.[12]

Adverse effects associated with exenatide include hypoglycemia, diarrhea, nausea/vomiting, gastroparesis, and postural hypotension. Table 2 includes the incidence of various side effects. Fineman, et al. noted that there were no changes in body weight, lipids, vital signs, hematological parameters, or cortisol concentrations in type 2 diabetic patients. Approximately 20% of patients treated with exenatide develop low-titer antibodies to the drug with no effect on therapeutic results. Mild to moderate nausea develops in 31% of exenatide-treated patients; most cases occur in the initial days of therapy. Only 13% of patients had persistent nausea. Fifteen percent of patients experienced hypoglycemia. Those taking concurrent sulfonylureas were at highest risk.[11,12]

Cost/How Supplied

Exenatide is available as a 60-dose prefilled pen in either 5 mcg per dose or 10 mcg per dose. Table 3 depicts the cost of exenatide and other frequently used antidiabetic medications.[12]

Summary

Exenatide, a new therapeutic modality for use in type 2 diabetics, has a limited role in the care of diabetic patients at this point in time. This medication has a role as an adjuvant for patients who have failed metformin and/or sulfonylureas. Since no long term trials have been conducted to date, more studies are required to assess the long term efficacy and safety. It remains unclear whether exenatide provides greater blood glucose control than combinations of

oral treatments. Until further studies are conducted, exenatide's place in therapy is for short term use in patients who remain uncontrolled despite sulfonylureas and/or metformin but do not require insulin. Whether exenatide will delay the time to insulin use, and the accompanying metabolic consequences, remains to be seen.

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ROPINIROLE: THE FIRST FDA-APPROVED DRUG FOR RESTLESS LEGS SYNDROME

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Restless legs syndrome (RLS) is a debilitating disorder that continually disrupts sleep and diminishes quality of life. It is a neurological condition characterized by unpleasant sensations in the legs with an uncontrollable urge to move when at rest. These symptoms become worse during rest, particularly at night, and are usually relieved by activity. Patients frequently describe the feelings in their legs as burning, creeping, tugging, or like insects crawling inside the legs. The abnormal sensations, or paresthesias, can range in severity from uncomfortable to irritating but can deteriorate in some patients and cause pain.[1]

The leg discomfort associated with RLS is worse at night. The symptoms demonstrate a circadian rhythm becoming worse in the late evening and are usually less severe or absent during the day.[2] Relaxing or lying down can activate or worsen the symptoms. Most people with RLS have difficulty falling

asleep and trouble staying asleep during the night. This results in daytime fatigue and exhaustion, which in turn can affect patients' quality of life. Even normal activities of daily living can be adversely affected since many people are unable to concentrate, have impaired memory, or fail to complete daily tasks.[1]

RLS is underdiagnosed and sometimes even misdiagnosed. The exact prevalence is unknown and may be higher than currently reported. Some researchers have estimated that RLS affects as many as 12 million Americans, and others have reported a prevalence of 10% in the general population.[1,2] Reasons contributing to an under reporting include patients not seeking medical attention since they do not believe their condition is treatable or the symptoms are too mild, or physicians may wrongly attribute their symptoms to be associated with other conditions such as nervousness, insomnia, stress, or arthritis. RLS occurs in both genders, however the incidence is slightly higher in women. The syndrome can begin at any age; however it is more common and more severe in patients middle-aged or older.[1]

Periodic limb movement disorder (PLMD) is a common condition that usually accompanies RLS. It is characterized by involuntary leg twitching or jerking movements during sleep. These movements typically occur every ten to sixty seconds and sometimes persist throughout the night. In PLMD, the leg movements are involuntary and the patient has no control over them, unlike the movements associated with RLS, which are usually initiated by the patient in order to relieve the discomfort. More than 80% of patients with RLS also develop PLMD, however most people who have PLMD will not necessarily experience RLS.[1]

RLS is in most cases considered to be idiopathic; no causes have been identified. Family history is present in approximately 50% of cases. Other predisposing conditions that are associated with RLS include: low iron levels or anemia; chronic diseases such as kidney failure, diabetes, Parkinson's disease, and peripheral neuropathy; and pregnancy, particularly in the last trimester. In addition, certain medications such as antiemetics, antipsychotics, anticonvulsants, and cold and allergy drugs can aggravate symptoms. Dietary factors for aggravation of RLS include: caffeine, alcohol, and tobacco. Usually elimination of the underlying disorder or discontinuing the medication or substance involved can relieve symptoms.[1]

Table 1: Dose Titration Schedule of Ropinirole for RLS.

Day/Week	Dosage to be taken once daily, 1-3 hours before bedtime
Days 1 and 2	0.25 mg
Days 3-7	0.5 mg
Week 2	1 mg
Week 3	1.5 mg
Week 4	2 mg
Week 5	2.5 mg
Week 6	3 mg
Week 7	4 mg

Other than treating the underlying disorders causing RLS, or eliminating potential substances that aggravate symptoms, there are very few treatment options currently available. Some studies have shown that maintaining a regular sleep pattern, or a regular moderate exercise program may help to reduce symptoms. Other non-pharmacologic treatment options include taking hot baths, massaging the legs, or using heating pads or ice packs. Pharmacologic options include: dopaminergics, benzodiazepines, opioids, and anticonvulsants. Dopaminergic agents, commonly used to treat Parkinson's disease, reduce RLS symptoms and are considered the treatment of choice. Short-term treatment with levodopa/carbidopa may cause disease augmentation in which symptoms eventually become more severe. Another treatment option includes dopamine agonists such as pergolide mesylate, pramipexole, and ropinirole hydrochloride. These agents are effective in treating the symptoms of RLS and are less likely to cause augmentation.[1]

Ropinirole hydrochloride (Requip®) is the first FDA-approved drug for the treatment of moderate-to-severe primary RLS. Ropinirole is indicated for patients who experience fifteen or more episodes of RLS per month.[3] The purpose of this article is to review available data on the pharmacokinetics and pharmacodynamics, clinical trials, dosing and administration, toxicity and safety, and cost of ropinirole.

Mechanism of Action

Ropinirole is a non-ergoline dopamine agonist with high relative in vitro specificity and full intrin-

Table 2: Results of TREAT RLS 1 and TREAT RLS 2. [2,4]

	TREAT RLS 1		TREAT RLS 2	
END POINTS	**Ropinirole (n=146)**	**Placebo (n=137)**	**Ropinirole (n=131)**	**Placebo (n=134)**
Mean adjusted change in IRLS score	-11.04 points	-8.03 points	-11.2 points	-8.7 points
CGI-I Scale Response (%)	78 (53.4)	56 (40.9)	78 (59.5%)	53 (39.6%)

sic activity at the D_2 and D_3 dopamine receptor subtypes. It binds with higher affinity to D_3 than to D_2 or D_4 receptor subtypes. Ropinirole has moderate in vitro affinity for opioid receptors. The exact mechanism of action for RLS is unclear since the pathophysiology of RLS is also largely unknown. However, evidence suggests primary dopaminergic system involvement in RLS. Some studies show a mild striatal presynaptic dopaminergic dysfunction that may be involved in the pathogenesis of RLS.[3]

Pharmacokinetics and Pharmacodynamics

Ropinirole is rapidly absorbed after oral administration and reaches peak concentration in 1-2 hours. Absolute bioavailability is 55%, and the drug undergoes a first-pass effect. Ropinirole is extensively metabolized by the liver to inactive metabolites. The major metabolic pathways include N-despropylation and hydroxylation through the CYP1A2 isoenzyme. This enzyme is stimulated by smoking; therefore tobacco use can decrease the concentration of ropinirole. In addition, CYP1A2 inhibitors, such as fluvoxamine, mexiletine, ciprofloxacin, and norfloxacin, can increase the serum concentration of ropinirole. Steady-state concentrations are usually achieved within two days of dosing. Since the dose of ropinirole is individually titrated to a clinical response, a dosage adjustment is not necessary in the elderly even though their oral clearance is reduced by 30% compared to younger patients. Furthermore, no dosage adjustment is necessary in renal dysfunction since no difference in clearance was found in patients with moderate renal impairment. Ropinirole should be titrated with caution in patients with hepatic impairment since it is metabolized by the liver.[3]

Clinical Trials

Two major clinical studies assessed the role of ropinirole in the treatment of RLS. These trials, TREAT RLS 1 and TREAT RLS 2, were 12-week , randomized, double-blind, placebo-controlled studies. TREAT RLS 1 was conducted in 10 European countries, and TREAT RLS 2 enrolled patients in the United States, Europe, and Australia.

Both studies used similar methods of measurement for the primary outcome. The primary endpoint in both trials was the change in the International Restless Legs Scale (IRLS) score at week 12, compared to baseline. The IRLS is a disease-specific, 10-item scale that reflects the frequency and intensity of sensorimotor features, associated sleep problems, and the impact on mood and daily activities. The maximum severity score is 40, and patients were required to have a score of at least 15 to enroll in the studies. Another scale used for measurement was the Clinical Global Impression (CGI) scale. CGI is a seven-point scale ranging from 1, which is equivalent to "very much improved", to 7 or "very much worse". A response on this scale was defined as a score of 1 (very much improved) or 2 (much improved).[2]

TREAT RLS 1 was conducted in 43 hospitals, sleep centers, and neurology clinics in 10 European countries. Patients were randomly assigned to receive ropinirole or placebo for twelve weeks. Patients were initiated on ropinirole 0.25 mg once daily between one and three hours before bedtime. The dose was titrated upwards during weeks 1 to 7 until patients received a maximum of 4 mg/day or until they reached their optimal dose (Table 1). This study included 146 patients in the ropinirole arm, and 137 patients taking placebo.[4]

The primary end point was the mean IRLS score at week 12 compared to baseline. The mean IRLS score at week 12 was lower in the ropinirole group (13.5 points) than with the placebo group (17.1 points). The adjusted mean improvement in the IRLS total score at week 12 was also significantly greater for the ropinirole group (-11.04 points) than for placebo (-8.03 points), p value = 0.0036. Significantly more patients showed a "much improved" or "very much improved" score on the CGI-I scale at week 12

Table 3: Incidence of Adverse Effects with Ropinirole.[2-4]

Adverse Events	TREAT RLS 1 Study		TREAT RLS 2 Study	
	Ropinirole (n=146)	Placebo (n=138)	Ropinirole (n=131)	Placebo (n=136)
Nausea (n, %)	55 (37.7)	9 (6.5)	52 (39.7)	11 (8.1)
Vomiting (n, %)	19 (13.0)	2 (1.4)	16 (12.2)	3 (2.2)
Headache (n, %)	29 (19.9)	23 (16.7)	29 (22.1)	35 (25.7)
Fatigue/Somnolence (n, %)	18 (12.3)	12 (8.7)	20 (15.3)	9 (6.6)
Upper Respiratory Infection (n, %)	14 (9.6)	15 (10.9)	18 (13.7)	11 (8.1)
Dizziness (n, %)	Not Reported	Not Reported	20 (15.3)	6 (4.4)
Abdominal Pain (n, %)	18 (12.3)	12 (8.7)	Not Reported	Not Reported

in the ropinirole group than in the placebo group (p value = 0.0416). This study also observed several secondary endpoints including effects on sleep disturbance, sleep quantity, somnolence, mental-health, and social functioning. Overall, TREAT RLS 1 found that ropinirole was significantly more effective than placebo in alleviating symptoms of RLS, improving sleep quantity and adequacy, reducing sleep disturbance and daytime somnolence, and improving health related quality of life.[4]

TREAT RLS 2 was conducted in 46 centers in Australia, Europe, and North America. Patients were randomly assigned to placebo or ropinirole with an initial dose of 0.25 mg/day taken one to three hours before bedtime. The titration schedule was the same as the one used in TREAT RLS 1. (Table 1) The study included a total of 265 patients with 131 assigned to the ropinirole group and 134 to placebo.[2]

The primary and secondary end points were the same as in TREAT RLS 1. The mean adjusted change in IRLS score between baseline and week 12 was significantly greater for ropinirole (-11.2 points) than placebo (-8.7 points), p value = 0.0197. More patients in the ropinirole group (59.5%) were classified as "much improved" or "very much improved" on the CGI-I scale compared with the placebo group (39.6%), p value = 0.001. The results of TREAT RLS 2 demonstrated that ropinirole effectively treats the symptoms of moderate-to-severe RLS.[2] The results of these two trials are summarized in Table 2.

Dosage and Administration

The initial dose of ropinirole is 0.25 mg once daily to be taken 1-3 hours before bedtime. After two days, the dose can be increased to 0.5 mg daily and to 1 mg once daily at the end of the first week. Table 1 illustrates the titration schedule approved for the treatment of RLS. Ropinirole can be taken with or without food; however food may reduce the occurrence of nausea. In the treatment of RLS, the safety and effectiveness of doses greater than 4 mg once daily have not been established.[3]

Toxicity and Safety

The only contraindication to ropinirole is a known hypersensitivity to the agent. Ropinirole may increase the risk of patients falling asleep while engaged in daily activities, including driving vehicles, which reportedly has resulted in automobile accidents. Many patients reported somnolence before they fell asleep, while a few patients claimed they had no warning signs. Somnolence is common in Parkinson's disease patients where it is more frequent than in RLS. Other adverse effects, which were more frequent in Parkinson's patients, include syncope, symptomatic hypotension, hallucinations, dyskinesia, and melanoma. In RLS, augmentation, defined as an earlier onset of symptoms, increase in symptoms, and spread of symptoms to involve other extremities, has been reported with dopaminergic agents. Rebound, a worsening of symptoms in the early morning hours, has also been reported among patients receiving dopaminergic drugs. These phenomena have not been evaluated in controlled clinical trials with ropinirole for patients with RLS.[3]

The most common adverse events were nausea and headache. Other adverse events reported were vomiting, fatigue, somnolence drowsiness, and upper respiratory tract infection. Table 3 displays the most frequent adverse events experienced in the two major clinical trials on ropinirole in RLS.

Table 4: Cost of a One Month Supply of Ropinirole.*

Requip®	Price of one month of therapy
0.25mg	$65.11
0.5mg	$65.11
1mg	$63.94
2mg	$67.81
3mg	$83.91
4mg	$88.61
5mg	$88.61

*Prices reflect the average retail cost from 3 community pharmacies in Gainesville, FL 32601.

Cost

Ropinirole is a pentagonal film-coated tablet and is available in several different strengths including 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg. Table 4 includes prices for ropinirole in each of the dosage strengths available[3]. A dose greater than 4 mg/day is not indicated for the treatment of RLS; however patients taking 2.5 mg/day could take half of a 5 mg tablet instead of taking two different strength tablets.

Summary

Ropinirole is an effective and well tolerated therapy for RLS. The results from two major clinical trials support its first-line use in the treatment of RLS. Ropinirole is particularly indicated for the treatment of moderate-to-severe RLS in patients who experience fifteen or more episodes per month. Clinical studies of ropinirole did not find an association with worsening of RLS symptoms. Further studies are required to confirm that the efficacy and the lack of augmentation are maintained with long-term use. Additional studies should investigate earlier dosing schedules, especially for patients who experience symptoms before bedtime. Ropinirole is an effective option for patients who suffer from moderate-to-severe RLS. Ropinirole alleviates symptoms of RLS, improves sleep quantity and adequacy, reduces sleep disturbance and daytime somnolence, and improves overall health related quality of life.

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