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REVIEW

Review of the Treatment of Restless Legs Syndrome: Focus on Gabapentin Enacarbil

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Abstract: The FDA approved gabapentin enacarbil in 2011 as the first non-dopaminergic agent for the treatment of restless legs syndrome (RLS) symptoms. Although gabapentin enacarbil is a pro-drug of gabapentin, its pharmacokinetics differ. Absorption of gabapentin enacarbil is more predictable, and inter-patient variability in bioavailability is lower than that of gabapentin. Studies have demonstrated superiority of gabapentin enacarbil compared to placebo. Comparisons to currently available RLS treatments are lacking, but clinical trials demonstrate comparable improvement in RLS symptoms to the dopamine agonists ropinirole and pramipexole, which are usually considered first-line therapy for daily RLS symptoms. Gabapentin enacarbil was well tolerated in clinical trials. The role of the drug in RLS treatment remains undefined, although it will likely be used as an alternative for refractory RLS when other treatments have failed. Additionally, gabapentin enacarbil may be recommended for patients with daily RLS symptoms that are less intense or are associated with pain as an alternative to dopamine agonists.

Keywords: restless legs syndrome, RLS, gabapentin enacarbil, Horizant, dopamine agonists

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Introduction

Restless legs syndrome (RLS) is a common neurological disorder among adult patients that often disrupts sleep and can impact activities of daily living. The diagnosis of RLS is based on diagnostic criteria identified by the International RLS Study Group.[1] Criteria include an urge to move the legs or other body parts that begins or worsens during rest or inactivity. The urge to move is typically worse in the evening or nighttime hours and is relieved by movement. The sensations felt by patients with RLS evoke a sense of movement within the affected limb that is difficult for patients to describe. The symptoms, which are usually felt deep within the affected limb, may be described as burning, creeping, crawling, or itching. RLS is usually associated with involuntary contractions of the legs during sleep, known as periodic limb movements.[2,3]

Despite clear diagnostic criteria and available treatment options, RLS remains under diagnosed, and many patients are not treated appropriately.[4,5] Incidence of RLS increases with age and levels off in approximately the 6th or 7th decade of life.[6] RLS is more common in women compared to men,[7] and an estimated 2%–3% of the general population has RLS that requires treatment with pharmacotherapy.[4] RLS should be treated when a patient's symptoms affect quality of life, functioning, or sleep.[8] Intermittent symptoms noted by patients may be adequately treated by sporadic therapy, whereas daily symptoms are considered frequent and troublesome, and usually require continuous therapy. Patients with refractory symptoms exhibit poor treatment response to drug therapy, intolerable adverse effects, or possibly augmentation that is not controlled with additional treatment doses.

The purpose of this article is to review available pharmacologic treatment for RLS with a focus on gabapentin enacarbil. The results of clinical trials of gabapentin enacarbil will be discussed in order to identify the potential place in therapy of gabapentin enacarbil in RLS treatment.

Pathophysiology of RLS

Theories as to the underlying mechanism(s) of RLS abound, but more likely than not, multiple factors influence the development of symptoms across the diagnostic spectrum. Younger individuals (those under 40 years of age) are more likely to develop RLS that stems from a genetic predisposition.[9] This type of RLS typically receives the designation "primary RLS." The genetic theory of RLS has been borne out by the results of studies in twin siblings which have demonstrated an approximate 80% incidence of shared symptoms in monozygotic twins, and less concordance in dizygotic twins.[10,11] Up to 60% of persons with RLS claim a positive history within the family. Several genes have now been linked to RLS, but it remains to be seen if a genetic predisposition needs to be catalyzed by environmental or lifestyle factors in order for the syndrome to manifest.[12]

Imaging studies in persons with RLS have demonstrated that in some cases, binding at dopamine receptors is abnormal.[1] Dopamine agonists have long been first-line therapy for treatment. The nigrostriatal region of the brain is linked to voluntary movement, and alterations of dopamine in this area are likely to be involved in RLS. Further evidence of the role of dopamine is found in the fact that dopamine antagonists that work at the level of the central nervous system are frequently implicated in the worsening of RLS symptoms as compared to antagonists that remain in the periphery.[13] This is particularly true of medications that work at the level of dopamine D_2 receptors. With that in mind, it makes sense that a thorough examination of current medication therapy should be completed to determine if a drug could be linked to the emergence of RLS symptoms. Drugs that have been implicated include SSRI antidepressants and antidepressants from other classes (escitalopram, fluoxetine, mirtazapine), atypical antipsychotics (olanzapine, aripiprazole, clozapine, risperidone), tramadol, lithium and levothyroxine.[14–18]

Secondary causes of RLS include several other diseases and underlying conditions. A physiologic deficiency of iron has been implicated in both primary and secondary RLS, and is likely to be linked with syndrome development in pregnant women and those with renal disease.[19] RLS patients often display serum ferritin levels that are low or within the normal range, but near the lower end of the range threshold.[20] Derangements of iron and dopamine may be dually responsible for symptoms, as iron is a cofactor for an enzyme involved in the synthesis of dopamine in the body.[9,21]

Gamma aminobutyric acid (GABA) has also been studied as potentially playing a part in the pathogenesis of RLS, but its role remains theoretical and not well defined. The primary role of GABA in the CNS is as an inhibitory neurotransmitter. Possibly, GABA has a role in decreasing RLS symptoms by inhibiting the transmission of nerve impulses in the CNS. Benzodiazepines, which work at the level of GABA receptors, have been purported to provide relief to some RLS patients. Similarly, the endogenous opiate system has been linked RLS diagnosis.[22] Opioid levels in RLS patients have been found to be decreased in some cases, suggesting opioid system alteration.[23]

RLS Treatment

Patients with frequent and bothersome symptoms of RLS will likely require a daily treatment approach. For most of these patients, nonergot dopamine agonists such as pramipexole and ropinirole are considered the drugs of choice. These agents have consistently demonstrated superiority over placebo in decreasing RLS symptom severity in clinical trials, and pramipexole has also shown superiority over dopamine supplementation using levodopa.[24] Rotigotine, a transdermal formulation, is another nonergot dopamine agonist that has been shown to be efficacious in the treatment of RLS.[25] The role of ergot dopamine agonists such as pergolide and cabergoline is much less robust, and their use is typically limited because of frequent adverse effects.[26]

Limitations of dopamine agonists include augmentation and tolerance, which may deter the long-term use of these agents.[27] Augmentation is characterized by onset of RLS symptoms earlier in the day with increasing severity. Additionally, dopamine agonists have been associated with impulse control disorders such as pathologic gambling, compulsive shopping, and hypersexuality.[28–30] Dopamine agonists have been shown to improve subjective measures of sleep, although they have not consistently been shown to normalize sleep architecture (the structure of sleep defined by different sleep stages) or improve objective sleep parameters, according to polysomnography.[31–33]

Levodopa is a dopaminergic agent that is administered in combination with carbidopa and has consistently shown superiority over placebo in the treatment of RLS symptoms.[34] Use of this combination is appropriate for the treatment of RLS when symptoms are intermittent. The intermittent use of levodopa/carbidopa may decrease the incidence of RLS symptom augmentation, which can occur in up to 70% of patients taking this medication.[35] Rebound symptoms in the early morning can occur with levodopa treatment in 20%–35% of patients.[35,36]

Gabapentin has been used as an alternative agent for the treatment of RLS that occurs daily. Stronger consideration may be given to gabapentin for patients with less intense RLS or with RLS that occurs in combination with painful peripheral neuropathy.[37] Patients with sensory discomfort of RLS described as painful, but not considered to be due to peripheral neuropathy, may also benefit from gabapentin.[26] Trials involving gabapentin for the treatment of RLS are few in number and are limited to small numbers of subjects. In two separate studies, each lasting 4 weeks, gabapentin was shown to be similar in efficacy compared to ropinirole (n = 16)[38] and more efficacious than levodopa (n = 15).[39] Gabapentin significantly improves RLS symptoms and sleep architecture compared to placebo as determined by polysomnography.[40]

The mechanism of action for gabapentin in RLS is unknown. Despite a structural similarity to GABA, gabapentin does not interact directly with GABA receptors. Instead, it binds with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels.[41] It is unclear how this binding of gabapentin is linked to its therapeutic effects. However, it is believed that this binding results in the inhibition of calcium entry through high voltage calcium channels, which in turn leads to normalization of the release of neurotransmitters, including the excitatory neurotransmitter glutamate.[42] Gabapentin is absorbed by low-capacity solute transporters that are localized to one area of the small intestine.[43] Consequently, absorption of gabapentin can become saturated at higher doses, potentially causing unpredictable or subtherapeutic levels of the drug.[44] Due to the variability in the pharmacokinetics of gabapentin, there can be pronounced differences in serum levels among individuals.

Opioid analgesics such as tramadol, methadone, and oxycodone may be considered for RLS treatment, although trials reviewing long-term efficacy are lacking. The potential for abuse and adverse effects including dizziness, nausea, and constipation limit the usefulness of these medications. In addition, tramadol has been rarely associated with RLS

symptom augmentation.[45] Benzodiazepines have also been used to treat RLS, and clonazepam is the most widely studied. Adverse effects of benzodiazepines include sedation, dizziness, and daytime drowsiness. Perceived benefits of benzodiazepines for RLS are likely due to the effects of sleep promotion only.[46]

Mineral and electrolyte deficiencies have been associated with RLS. The administration of iron for the treatment of RLS symptoms has been explored in research studies. The concept that iron deficiency is a risk factor for RLS supports this treatment approach. Oral iron supplementation may be effective for certain patients, and should be considered for treatment of RLS in patients with low serum ferritin (<45–50 mcg/mL).[26] Two other investigational treatment options that have been considered are supplementation with magnesium and folate. However, there are no well-designed trials to support such supplementation.

Gabapentin Enacarbil

Gabapentin enacarbil is the first non-dopaminergic agent approved to treat symptoms of RLS, although as mentioned previously, gabapentin has been used off-label for this purpose. However, the pharmacokinetic properties of gabapentin enacarbil differ from that of gabapentin.

Mechanism of Action and Pharmacokinetics

Gabapentin enacarbil is a pro-drug that is converted to gabapentin and demonstrates superior pharmacokinetics as compared to gabapentin. Gabapentin enacarbil is absorbed by high capacity nutrient transporters that are located throughout the intestinal tract, and this absorption is not saturated by administration of high doses.[44,47] Absorption of gabapentin enacarbil is more predictable, and inter-patient variability in bioavailability has been shown to be lower for gabapentin enacarbil than gabapentin.[48] Bioavailability of gabapentin enacarbil ranges from 42%–65% in the fasting state and increases to 75% when consumed with a high-fat meal.[49] This is in contrast to the dose dependent bioavailability of gabapentin, which is 60% with a 900 mg dose versus only 33% with a 3600 mg dose. Once absorbed, gabapentin enacarbil is converted to gabapentin by extensive first-pass hydrolysis. Gabapentin is then excreted unchanged by the kidney. Plasma protein binding of gabapentin enacarbil is low (<3%), and steady state is reached within approximately two days of administration.

Gabapentin enacarbil provides dose-proportional systemic gabapentin exposure, a characteristic not consistently seen with gabapentin.[50] It is designed as an extended-release formulation, which further prolongs gabapentin exposure and allows for reduced dosing frequency. Gabapentin enacarbil does not affect major cytochrome P450 enzymes and is neither an inducer nor an inhibitor of P-glycoprotein. Therefore, the incidence of pharmacokinetic drug-drug interactions with gabapentin enacarbil is low.[44]

Clinical Efficacy Trials

The efficacy of gabapentin enacarbil has been assessed in several studies using a dose of 600–1800 mg daily. The approved dose of gabapentin enacarbil is 600 mg daily. (See Table 1 for a summary of studies assessing gabapentin enacarbil in the treatment of RLS).

Kushida and colleagues[51] conducted a phase 2, randomized, double-blind crossover comparison of gabapentin enacarbil 1800 mg daily (600 mg at 5 pm, 1200 mg at bedtime) versus placebo. Subjects were naïve to RLS treatment, and there was a 7-day washout period between each of the 14-day phases. The primary endpoint of the study was change in baseline International RLS (IRLS) rating scale total score at day 14, which proved to be greater with gabapentin enacarbil compared to placebo (−12.1 versus −1.9; $P < 0.0001$). The IRLS scale is a series of questions posed to a patient about their symptoms and answered in Likert scale format. Scoring ranges from very severe (31–40 points) to mild (1–10 points). Significantly more subjects treated with gabapentin enacarbil were considered "much improved" or "very much improved" according to the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale (79.5% versus 14.7%, $P < 0.006$) and the subject-rated CGI-I (85.3% versus 14.7%, $P < 0.0059$). The CGI-I scale is used by an investigator or patient to assess change in response to treatment on a scale ranging from 1 (very much improved) to 7 (very much worse).

According to a post-sleep questionnaire (PSQ), gabapentin enacarbil also significantly improved the subjective measures of sleep quality, number of nights with RLS symptoms, number of awakenings due to RLS symptoms, and number of hours awake per

Table 1. Summary of studies assessing gabapentin enacarbil in the treatment of RLS.

Study	Method	Participants	Interventions	Results of primary endpoints
Kushida et al[51]	Double-blind, randomized, placebo-controlled crossover study	n = 38	GEn 1800 mg/day or placebo; 14 days each treatment arm	Greater reduction in IRLS total score with GEn ($P < 0.0001$)
Walters et al[52]	Double-blind, randomized, placebo-controlled study	n = 95	GEn 1200 mg/day, GEn 600 mg/day, or placebo for 14 days	Greater reduction in IRLS total score with GEn 1200 mg/day ($P < 0.0001$) GEn 600 mg/day: efficacy outcomes were similar to placebo
Kushida et al[53]	Double-blind, randomized, placebo-controlled study	n = 221	GEn 1200 mg/day or placebo for 12 weeks	Greater reduction in IRLS total score ($P = 0.0003$) and more treatment responders according to investigator-rated CGI-I ($P < 0.0001$) with GEn
Bogan et al[54]	Single-blind active treatment phase and double-blind, randomized, placebo-controlled phase	n = 327 (SB phase) n = 194 (DB phase)	GEn 1200 mg/day for 24 weeks (SB phase) GEn 1200 mg/day or placebo for 12 weeks (DB phase)	Less relapse in RLS symptoms in the DB phase with GEn ($P = 0.02$)
Lee et al[55]	Double-blind, randomized, placebo-controlled study	n = 325	GEn 1200 mg/day, GEn 600 mg/day, or placebo for 12 weeks	Greater reduction in IRLS total score ($P = 0.0015$) and more treatment responders according to investigator-rated CGI-I ($P < 0.0001$) with GEn 1200 mg/day Greater reduction in IRLS total score ($P < 0.0001$) and more treatment responders according to investigator-rated CGI-I ($P < 0.0001$) with GEn 600 mg/day
Ellenbogen et al[56]	Open-label extension study	n = 573 (subjects received GEn or placebo in one of four parent studies)	GEn 1200 mg/day for 52 weeks	IRLS total score decreased from 23.3 to 8.0 Number of treatment responders according to investigator-rated CGI-I increased from 67.0% to 84.8%
Winkelman et al[57]	Double-blind, randomized, placebo-controlled crossover study	n = 136	GEn 1200 mg/day or placebo; 4 weeks each treatment arm	Greater reduction in wake time during sleep as assessed by polysomnography with GEn ($P < 0.0001$)

Abbreviations: RLS, restless legs syndrome; GEn, gabapentin enacarbil; IRLS, International RLS Rating Scale; CGI-I, Clinical Global Impression-Improvement; SB, single-blind; DB, double-blind.

night due to RLS symptoms ($P < 0.0001$ for all), but not next day functioning. Polysomnography was completed to gather objective data on sleep architecture. Results showed that treatment with gabapentin enacarbil significantly decreased amount of time spent awake after falling asleep (also known as wake time after sleep onset, or WASO, ($P = 0.0328$)), wake time during sleep (as noted via polysomnography, ($P = 0.0440$)), and number of awakenings ($P < 0.005$) at day 14. This short-term study was not powered to detect significant differences among the secondary endpoints, but does demonstrate short-term efficacy of gabapentin enacarbil at a high dose of 1800 mg daily.

Another phase 2 study, conducted by Walters and colleagues,[52] assessed the efficacy and safety of two doses of gabapentin enacarbil (600 or 1200 mg daily) compared with placebo in a randomized, double-blind, parallel group design. Only subjects that were naïve to RLS treatment were included, and 95 patients were randomized in a 1:1:1 fashion. The primary endpoint was change in IRLS total score at day 14 of treatment for gabapentin enacarbil 1200 mg versus placebo, which was significant (−16.1 versus −8.9, $P < 0.001$). Subjects treated with gabapentin enacarbil 1200 mg daily were more likely to be considered treatment responders compared to placebo according to CGI-I as rated by investigators ($P < 0.0001$) and subjects ($P < 0.001$). Gabapentin enacarbil also significantly improved overall sleep quality and resulted in fewer nights with RLS symptoms, fewer awakenings, and fewer hours awake per night according to PSQ. Improved next day functioning was seen in all groups, but was not significant between groups. The secondary outcome was the efficacy of gabapentin enacarbil at a dose of 600 mg daily. This lower dose resulted in a non-significant reduction in IRLS score (−9.1 versus −8.9) and CGI-I (58.6% versus 48.5%) compared to placebo at week 2. Changes in sleep quality, ability to function, number of nights with RLS symptoms, awakenings, hours awake, and mood assessment were also similar between gabapentin enacarbil 600 mg daily and placebo in this study.

In a second study by Kushida and colleagues (Patient Improvements in Vital Outcomes following Treatment for RLS-I (PIVOT RLS-I),[53] 222 patients were randomized to receive gabapentin enacarbil 1200 mg daily or placebo. The 12-week, double-blind study included patients who may have been treated for RLS previously (though not in the last two weeks), although the majority of patients (68.3%) were treatment naïve. Patients were excluded if they had secondary RLS, history of RLS symptom augmentation, or end-of-dose rebound with previous dopaminergic therapy. At the conclusion of the study, participants were given a 7-day taper or entered into an extension treatment phase. Gabapentin enacarbil achieved significance for the co-primary endpoints, which included change from baseline IRLS total score at week 12 (−13.2 versus −8.8, adjusted mean treatment difference [AMTD] −4.0, $P = 0.0003$) and number of treatment responders according to investigator-rated CGI-I (76.1% versus 38.9%, $P < 0.0001$). Secondary measures that showed significance at week 12 included results of several validated patient rating scales such as the subject-rated CGI-I, an RLS quality of life (RLSQoL) questionnaire, the Medical Outcomes Study (MOS) sleep scale which assesses sleep disturbance, and PSQ measures. The Pittsburgh Sleep Diary (PghSD) assessed total sleep time (TST), WASO, and RLS pain. At week 12, mean reduction in RLS pain and WASO were greater with gabapentin enacarbil, although TST was not significantly different between groups.

The PIVOT RLS Maintenance study was a long-term study that assessed the efficacy and tolerability of gabapentin enacarbil in patients with moderate to severe primary RLS for up to 9 months.[54] The design of the study was an initial 24-week, single-blind, active treatment phase with gabapentin enacarbil 1200 mg. Patients that were considered treatment responders in this phase were those with an IRLS score < 15 (moderate symptom severity) that had decreased by at least 6 points and also had an assessment of "much improved" or "very much improved" on the investigator-rated CGI-I at the end of 24 weeks. After the single-blind phase, 194 subjects (59.3%) were rated as responders and entered the 12-week double-blind phase where they were randomized to receive gabapentin enacarbil 1200 mg daily or placebo. The primary endpoint was the proportion of subjects experiencing relapse during the double-blind phase, defined as worsening of symptoms according to IRLS score or CGI-I scale. Relapse was experienced by significantly fewer patients taking gabapentin enacarbil compared to placebo (9% versus 23%, $P = 0.02$). Additionally, subjects treated

with gabapentin enacarbil experienced a longer time to relapse compared with placebo ($P = 0.03$). According to PSQ, patients treated with gabapentin enacarbil experienced fewer nights with RLS symptoms and fewer nighttime awakenings compared with placebo, although the differences in quality of sleep and daytime functioning were not significant.

Lee and colleagues[55] conducted a randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of gabapentin enacarbil 600 mg and 1200 mg daily over 12 weeks. Patients with history of RLS symptom augmentation or end-of-dose rebound with previous dopamine agonist treatment were excluded. Endpoints included mean change in IRLS total score and proportion of responders on the investigator-rated CGI-I at the end of the study. Patients taking gabapentin enacarbil experienced greater improvements in IRLS total score for both gabapentin enacarbil 1200 mg daily (−13.0 versus −9.8, $P = 0.0015$) and 600 mg daily (−13.8 versus −9.8, $P < 0.0001$). Additionally, significantly more patients were rated as responders according to CGI-I for gabapentin enacarbil 1200 mg daily and 600 mg daily compared to placebo ($P < 0.0001$ for both). Subject-rated scales were also used to measure changes in sleep outcomes from baseline to week 12. According to the PghSD, both doses of gabapentin enacarbil decreased WASO, but neither increased average daily TST.

A longer-term 52-week study, which included 573 patients that were previously treated with gabapentin enacarbil or placebo for up to 12 weeks in one of four parent studies, was conducted by Ellenbogen and colleagues.[56] All patients received gabapentin enacarbil at a dose of 1200 mg daily and were stratified into two groups (gabapentin enacarbil naïve, n = 197, or non-naïve, n = 376) based on previous exposure to gabapentin enacarbil in a parent study. Efficacy evaluations included changes in IRLS score and CGI-I. IRLS scores decreased from 23.3 at baseline to 8.0 at week 52. Number of treatment responders according to CGI-I increased from 67.0% at baseline to 84.8% at week 52. Estimated median time to onset of the first RLS symptom was also assessed using 24-hour RLS diaries and both gabapentin enacarbil naïve and non-naïve subjects had a similar delay-to-onset of the first RLS symptom. Although the study was not designed to assess RLS symptom augmentation, there were no suspected cases reported.

A study by Winkelman and colleagues[57] was performed to assess the efficacy and tolerability of gabapentin enacarbil in subjects with primary RLS and associated sleep disturbance. Patients (n = 136) were randomized 1:1 in a double-blind cross-over manner (4 weeks of each treatment arm) comparing gabapentin enacarbil 1200 mg and placebo. Gabapentin enacarbil significantly reduced the primary endpoint of wake time during sleep as assessed by polysomnography (AMTD −26.0 minutes, $P < 0.0001$). The secondary endpoint of number of periodic limb movements during sleep associated with arousal per hour of sleep decreased with treatment (AMTD −3.07, $P = 0.002$). Subjects experienced improvement in CGI-I, as 75% of subjects treated with gabapentin enacarbil were considered responders compared to 36% of subjects receiving placebo. Gabapentin enacarbil also improved objective sleep measures, including awakenings, stage N3 (slow-wave) sleep time, and TST. Improvements in subjective measures were also apparent. At baseline, 53% of subjects reported 2 or more nighttime awakenings, which decreased to 12% with gabapentin enacarbil and 26% with placebo. Subjects reported significantly improved sleep quality and restfulness upon awakening with gabapentin enacarbil compared to placebo ($P < 0.0001$ for both).

Safety

Gabapentin enacarbil was well tolerated in clinical trials, and the overall safety profile is similar to that seen with gabapentin. Somnolence and dizziness were consistently identified as the most common adverse effects in studies.[51–57] At the approved dose of gabapentin 600 mg daily, somnolence and dizziness occurred at a rate of 14%–21.7% and 10.4%–14%, respectively. At the higher dose of 1200 mg daily, somnolence was reported by up to 36% of patients, and dizziness was reported by up to 25% of patients. Placebo rates of somnolence and dizziness were up to 15% and 5%, respectively. Consequently, patients should use extra caution if they are taking other medications that can cause similar adverse effects, or if they engage in activities that require alertness.

Despite the reported incidence of somnolence by subjects, studies that specifically measured daytime sleepiness using the Epworth Sleepiness Scale (ESS) did not uncover a higher likelihood of doz-

ing during the day in subjects taking gabapentin enacarbil.[56] According to ESS, some studies actually showed a reduced likelihood of dozing during the day.[53,55] A possible explanation for this apparent discrepancy is that although patients did experience more somnolence, it was later in the day and did not affect daytime activities.

The sudden onset of sleep (SOS) questionnaire was used in some studies to record possible sleep attacks. Sudden onset of sleep was reported by one patient taking placebo[52] and three patients taking gabapentin enacarbil.[55,56] One patient withdrew from the Ellenbogen study due to mental status change.[56]

Of note, gabapentin is an antiepileptic medication, and suicidal thoughts and behaviors have been associated with this drug class.[58] Caution is probably warranted with gabapentin enacarbil as well, since it is a pro-drug of gabapentin. Other adverse effects occurring more commonly than placebo were mild and included headache, nausea, and fatigue. Gabapentin enacarbil did not significantly alter blood pressure or any laboratory measures that were assessed, including hematologic, chemistry, or urinalysis. Electrocardiogram abnormalities have not been reported with gabapentin enacarbil.

Place in Therapy

The studies using the 1200 mg daily dose of gabapentin enacarbil demonstrated improvement in RLS symptoms according to total IRLS score and the CGI-I scale as compared with placebo.[52–57] In some studies assessing 1200 mg daily dosing, efficacy with gabapentin enacarbil was demonstrated as early as week 1 according to changes in IRLS total score[52,53] and investigator-rated CGI-I.[53] However, studies investigating gabapentin enacarbil 600 mg daily are not consistent. Walters and colleagues[52] conducted a 2-week study that did not demonstrate an improvement in RLS symptoms with gabapentin enacarbil 600 mg daily compared with placebo. However, despite having a similar design to the Walters trial, the trial conducted by Lee and colleagues[55] did show improvement in IRLS total score ($P < 0.001$) and investigator-rated CGI-I ($P < 0.0001$) with gabapentin enacarbil 600 mg daily versus placebo. Despite inconsistencies in clinical trials, the 600 mg dose remains the only dose of gabapentin enacarbil approved by the FDA for the treatment of RLS.

The magnitude of the improvement in RLS symptoms demonstrated by gabapentin enacarbil in clinical trials is likely to be comparable to long-term randomized, placebo-controlled studies with ropinirole and pramipexole.[59–61] At week 52 of the Ellenbogen study, the mean change from baseline in IRLS total score was −16.8. Ropinirole and pramipexole demonstrated similar improvements in the change in IRLS total score from baseline of −12.0 and −16.9 after 52 weeks and 26 weeks, respectively.[31,62] The dopamine agonists have also demonstrated improvements in sleep parameters according to polysomnography such as periodic limb movements of sleep, although improvements in sleep efficiency and sleep latency are inconsistent.[33,63,64]

The place in therapy for gabapentin enacarbil among the other therapies currently available to treat RLS remains undefined. Its role will likely be similar to that of gabapentin, although the higher cost of gabapentin enacarbil will likely deter its use in some patients. Similar to gabapentin, gabapentin enacarbil may be recommended for daily RLS as an alternative to dopamine agonists that is less intense or is associated with pain.[37] Gabapentin enacarbil may also be considered for patients with refractory RLS when other treatments have failed.

Subjects with a history of augmentation or rebound with previous RLS treatment were excluded from the majority of gabapentin enacarbil studies. Therefore, the clinical trials provide inadequate evidence to support success in patients experiencing these phenomena. Nonetheless, as gabapentin enacarbil has not been associated with augmentation and rebound, it may be considered in patients who failed dopaminergic therapy for these reasons. Gabapentin enacarbil has not been studied in head-to-head trials with other RLS treatment options; therefore, comparative efficacy cannot be established.

Gabapentin enacarbil has theoretical pharmacokinetic advantages over gabapentin, and as such, could also be considered if a patient fails gabapentin RLS therapy. The dose of gabapentin for the treatment of RLS is 300–1800 mg daily, typically administered in two to three doses throughout the day. Gabapentin enacarbil may be preferred by patients, as the dose is 600 mg

once a day, which may improve adherence. Long-term data with gabapentin enacarbil is limited. However, to date, no reports of tachyphylaxis have emerged.

Conclusion

Gabapentin enacarbil is the first non-dopaminergic medication approved for RLS in the United States. The medication was well tolerated in clinical trials, with dizziness and somnolence experienced most frequently by subjects. Rare sleep attacks were reported, however this is also a concern associated with dopaminergic agents. The efficacy of gabapentin enacarbil compared to placebo has been demonstrated in several well-designed trials, although no trials comparing gabapentin enacarbil to currently available therapy have been completed. Primary efficacy endpoints achieved by gabapentin enacarbil in clinical trials were generally comparable to those noted in trials of dopamine agonists.

Author Contributions

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