

Role of gabapentin enacarbil XR in restless legs syndrome

Sheila Sivam^{1,2}

Brendon J Yee^{1,2}

¹NHMRC Centre for Sleep Health, Woolcock Institute of Medical Research, University of Sydney, Sydney, ²Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

Abstract: Gabapentin enacarbil XR is a new extended-release formulation which attempts to overcome the reduced efficacy of shorter-acting gabapentin, with sustained delivery over a 24-hour period. It is a gabapentin prodrug which is efficiently and rapidly converted to gabapentin during active transport throughout the length of the intestine via high-capacity monocarboxylate type 1 nutrient transporters unlike its predecessor, which is absorbed via low-capacity transporters largely confined to the upper intestinal region. Its lack of saturable absorption allows for dose-proportional absorption and hence increased bioavailability. Several clinical trials addressing its efficacy in moderate to severe restless legs syndrome (RLS) demonstrate improvements in the International RLS Rating Scale after a 2-week to 3-month period. Open-label studies of 52 weeks' duration showed maintenance of symptom reduction with once-daily administration of the extended-release formulation. The most commonly reported treatment-emergent adverse effects were somnolence and dizziness. Although the incidence of emergent adverse effects is high, it is comparable with that of gabapentin. No studies thus far have documented augmentation as an issue, unlike that observed with most dopaminergic agents. In addition, both dopamine precursors and agonists have not been shown to increase slow wave sleep or improve overall sleep architecture consistently despite improvement in the periodic leg movement index, in contrast with gabapentin enacarbil. Presently, gabapentin enacarbil has not been approved by the Therapeutic Goods Administration or Medsafe for use in RLS. The cost of this medication may also be a potential barrier for many patients. Future comparative efficacy studies with gabapentin, first-line dopaminergic agents, rotigotine, being the other once daily RLS medication, and pregabalin, the structural analog of gabapentin, will be necessary.

Keywords: extended-release gabapentin, restless legs syndrome

Introduction

Restless legs syndrome (RLS) affects 4%–14% of the adult population, depending on the rigorousness of the definition applied.¹ It is twice as common in women, and has a prevalence of 2% in the pediatric population.^{2,3} RLS is a sensorimotor disorder, in which there is an irresistible urge to move the leg, although it can progress to involve other parts of the body, including the arms, trunk, and head.⁴ Often it is described as unpleasant, creeping, and crawling sensations or paraesthesias deep in the legs. These are particularly problematic during periods of rest, classically relieved by movement and worse in the evenings. The prior three features are also part of the essential diagnostic criteria of RLS alongside the urge to move the legs.^{5,6} Other non-essential but supportive features of RLS include a positive family history, response to dopaminergic agents, and periodic leg movements.⁶ Several aspects of a patient's life can be influenced by RLS,

Correspondence: Sheila Sivam
NHMRC Centre for Sleep Health,
Woolcock Institute of Medical Research,
University of Sydney, Sydney, New South
Wales, Australia
Tel +61 2 9114 0000
Fax +61 2 9114 0010
Email sheila.sivam@sydney.edu.au

including difficulty with sleep initiation and maintenance, mood, cognitive function, and quality of life.^{7–9} While primary (idiopathic) RLS affects the majority of patients with this disorder, secondary RLS can also occur in patients with predisposing conditions, including iron deficiency, chronic renal failure, and pregnancy.^{10–12}

A decision to treat RLS is based mostly on symptom severity, frequency, and impact on quality of life.¹³ An estimated 3% of patients with RLS are started on treatment at a general practitioner's office for moderate to severe symptoms.¹⁴ Sleep diaries and validated symptom rating scales can be utilized to assess the benefits of an intervention compared with baseline.^{15,16} Both non-pharmacologic and pharmacologic treatment options are employed for the management of RLS. Although there is limited published evidence for the former, there are several non-pharmacological approaches that are utilized for milder RLS. These include partaking in mentally stimulating activities, improving sleep hygiene, lower body resistance training, aerobic exercise, weight loss, and pneumatic compression stockings.^{17–20} A reduction in alcohol, tobacco, and caffeine is also advised.²¹

With respect to vitamin and mineral supplementation, iron replacement to a goal ferritin of 50 µg/L for patients with iron deficiency (with or without anemia) and treatment of folate deficiency during pregnancy may help alleviate symptoms of RLS.^{15,22–24} Magnesium is currently being investigated as a potential treatment for RLS, with one small open-label study showing an improvement in symptoms and sleep efficiency. However, a randomized controlled trial in pregnant patients with RLS did not demonstrate relief of symptoms with 360 mg of magnesium daily.^{25,26}

The first-line pharmacotherapy for RLS is the dopaminergic agents. These include levodopa carbidopa or levodopa benserazide, which are dopamine precursors, as well as several dopamine agonists, such as pramipexole, ropinirole, and rotigotine. While dopamine agonists have a longer duration of action and an estimated 50% decrease in incidence of augmentation in comparison with dopamine precursors, one third of patients will continue to develop progressive worsening of symptoms on therapy.^{27,28} With augmentation, symptoms start to occur earlier in the day, become more severe in intensity and may affect other parts of the body, including the arms and trunk.²⁹ The pathophysiology of augmentation remains unclear and treatment is challenging, being largely based on clinical consensus and expert opinion.²⁹ Impulse control disorders, including gambling and compulsive shopping, can also occur in up to 17% of patients, much like in Parkinson's, which can result in serious social consequences.³⁰

Rotigotine is a long-acting transdermal agent with good 5-year efficacy and tolerability and may be particularly useful for patients with both daytime and night-time symptoms.³¹ However, in a recent 5-year, open-label extension study, 13% of patients developed clinically significant augmentation and 58% developed mostly mild to moderate skin reactions at the application site.³¹ In addition, it is currently more expensive than other dopamine agonists.

Second-line agents include low potency opioids, benzodiazepines, and gabapentin. With no controlled trials on opioids and limited randomized controlled trials on benzodiazepines, these agents presently remain off-label therapeutic options.^{32,33} Early morning sedation, tolerance, and dependence are potential challenges with these medications. Anticonvulsants like gabapentin are particularly useful for painful RLS.³⁴ A double-blind, randomized, placebo-controlled crossover study in 24 RLS subjects showed a significant reduction in RLS severity with gabapentin when dosed twice a day.³⁴ In addition, small clinical trials have also demonstrated better RLS symptom relief with gabapentin than with levodopa in hemodialysis patients and comparable improvements with ropinirole.^{35,36} The side effects are generally mild to moderate in nature, and include dizziness, somnolence, and peripheral edema. However, its efficacy is limited by its short half-life.³⁴ Another anticonvulsant being investigated for RLS is pregabalin, a gabapentin analog which acts on the $\alpha 2\delta$ subunit of the voltage-dependent Ca^{2+} channel like gabapentin. There are currently two published, double-blind, randomized, controlled studies lasting 6–12 weeks, showing a reduction in RLS symptoms over placebo, but future comparative efficacy and longer-term studies are necessary.^{37,38}

In April 2011, the US Food and Drug Administration approved a new long-acting gabapentin (gabapentin enacarbil XR, Horizant™) which attempts to overcome the reduced efficacy of shorter-acting gabapentin, with sustained delivery over a 24-hour period. Presently, medications listed for the management of RLS by the Therapeutic Goods Administration in Australia are pramipexole, ropinirole, and rotigotine. New Zealand's Medsafe has approved pramipexole for RLS. This article reviews the current literature on the pharmacology, pharmacokinetics, and clinical trials on gabapentin enacarbil and discusses its practical implications in the management of RLS.

Pharmacology and pharmacokinetics

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the human central nervous system.³⁹

Gabapentin is a GABA analog but is not believed to act on the same receptors. Instead, it acts on the $\alpha 2\delta$ subunit of the voltage-dependent Ca^{2+} channel.⁴⁰ This interaction reduces calcium influx into the presynaptic nerve terminals and results in inhibition of excitatory neurotransmitter release.⁴⁰ The drug is absorbed via low-capacity transporters in the upper intestinal region. These transporters become saturated at the recommended doses, and increasing doses beyond the suggested dose range results in decreased bioavailability.⁴¹ A 600 mg dose had an average bioavailability of 50%, whereas daily 3600 mg doses resulted in a reduced bioavailability of 40%.^{42,43} Wide variation in interpatient bioavailability may also be observed.⁴³ Gabapentin has a half-life of 5–7 hours and is excreted by the kidney without appreciable metabolism.

Gabapentin enacarbil XR is a gabapentin prodrug which is efficiently and rapidly converted to gabapentin during active transport throughout the length of the intestine via high-capacity monocarboxylate type 1 nutrient transporters.⁴⁴ An open-label, single-center Phase I study of 14 healthy male volunteers demonstrated up to 85% recovery of a radioactive dose in urine within 24 hours of ^{14}C -labeled gabapentin enacarbil dosing.⁴⁵ Levels of intact prodrug were low and transient.⁴⁴ Unlike gabapentin, its lack of saturable absorption allows for dose-proportional absorption.⁴⁶ In a study performed in healthy volunteers, extended-release gabapentin had a bioavailability of 83% and 72%, respectively, at doses of 350 mg and 2100 mg, whereas bioavailability was reduced at 65% and 27%, respectively, with doses of 200 mg and 1400 mg of gabapentin.⁴⁶ Consuming the drug with meals, regardless of fat or caloric content, further increased its bioavailability in a small randomized, cross-over, open-label study and several Phase I trials.^{46,47} In patients with renal impairment, dosage adjustment is necessary because its elimination is proportional to creatinine clearance.⁴⁸ No dose adjustments were needed when coadministered with either 500 mg naproxen twice daily or 400 mg cimetidine four times a day.⁴⁹ Like gabapentin enacarbil, naproxen is also a substrate for the high-capacity monocarboxylate type 1 nutrient transporter in the intestine and cimetidine is a substrate for the organic cation transporter in the kidney, by which elimination of extended-release gabapentin occurs. Hence no clinically relevant pharmacokinetic interactions are expected between gabapentin enacarbil and other substrates of these transporters.⁴⁹ Overall, the improved pharmacokinetics of this extended-release formulation compared with gabapentin thus allows for its once-daily administration.

Clinical trials

Efficacy

There are currently seven published clinical trials which address the efficacy of gabapentin enacarbil. The study characteristics, primary endpoints, and results of these trials are summarized in Table 1. Five of these are double-blind, placebo-controlled randomized trials with study sizes of 38–327 participants.^{50–54} All subjects experienced moderate to severe RLS and were either treatment-naïve or discontinued treatment at least 2 weeks prior to the study. The duration of the interventions were 14 days,^{50–52} 12,^{51,54} and 24 weeks.⁵³ Participants were advised to take the study drug at 5 pm with food in all but one study due to its previously published improved bioavailability. Kushida et al⁵² split the drug dosing (5 pm and one hour before bedtime), testing a higher dose of 1800 mg daily, whereas other studies used either 600 mg or 1200 mg daily. The primary endpoints for both 14-day studies were the change in baseline International RLS Rating Scale (IRLS) at day 14.^{50,52} The rating scale is a validated 10 question rating scale to be filled out by patients, published by the International RLS study group; this helps grade subjective RLS symptoms and may be particularly useful when assessing treatment effects.¹⁶ The other three studies also included investigator rated Clinical Global Impression-Improvement (CGI-I) in addition to the IRLS.^{51,53,54}

Four studies showed a significant improvement in their primary outcome measures, but the study by Walters et al only showed a difference with the 1200 mg/day dose and not with 600 mg/day.^{50–52,54} In contrast, the larger ($n = 95$ versus 325) and longer (14 days versus 12 weeks) study by Lee et al did show a significant difference with 600 mg/day dosing. Interestingly, improvement in the coprimary endpoints were observed even at 2 weeks into the study.⁵⁴ The fifth study was undertaken in two parts. The single-blind phase identified the responders to the drug, who then subsequently entered the double-blind phase of the study. Fewer relapses (9% versus 23%) were observed in patients taking the active study drug in comparison with placebo.⁵³ It is unclear if the proportion of relapses in the placebo arm would have increased further beyond the 12-week duration of this double-blind phase.

The last two studies are both 52-week open-label studies using gabapentin enacarbil 1200 mg/day. The first is an extension study undertaken by Ellenbogen et al.⁵⁵ Participants ($n = 573$) were enrolled from several prior gabapentin enacarbil studies.^{52–54} They consumed the study drug at 5 pm with food. The study had similar coprimary outcomes to those mentioned above and showed maintenance of symptom

Table 1 Efficacy and tolerability clinical trials

Study	Participants	Intervention	Primary endpoints	Results and adverse effects
Walters et al ⁵⁰	n = 95 Treatment-naïve patients Moderate to severe RLS	Double-blind RCT GEn 600 or 1200 mg versus placebo Taken at 5 pm daily with food Duration 14 days	Change in baseline IRLS total score at day 14	Greater reduction in IRLS with GEn 1200 mg/day (−16.1 versus −8.9, adjusted mean difference −7.2, $P < 0.0001$) No difference with GEn 600 mg/day Improvement in CGI-I responses, overall sleep quality, number of nights with RLS symptoms, hours awake per night, mood, and severity of RLS symptoms on GEn 1200 mg/day Sonnolence (36% versus 15% with placebo) and dizziness (18% versus 3% with placebo) on GEn 1200 mg/day Greater reduction in IRLS with GEn (−12.1 versus −1.9; $P < 0.0001$) Improvement in CGI-I responses, sleep quality RLS severity, and hours awake per night Documented improvement in sleep architecture by PSG with reduced stage 1 sleep and increased slow-wave sleep 85% of subjects reported “much improved” or “very much improved” symptoms versus placebo (15%) Sonnolence (30% versus 3% with placebo) and dizziness (28% versus 6% with placebo) Dose decreased or maintained at 1200 mg/day in a total of 6 subjects
Kushida et al ⁵²	n = 38 Treatment-naïve patients Moderate to severe RLS	Double-blind crossover RCT GEn 1800 mg/day versus placebo GEn 600 mg taken at 5 pm and 1200 mg taken 1 hour before bedtime GEn titrated to target dose over 4 days Duration 14 days each with 7-day washout period between arms	Change in baseline IRLS total score at day 14	Greater reduction in IRLS with GEn (−13.2 versus −8.8; mean treatment difference −4, $P = 0.0003$) and more treatment responders (76% versus 39%; $P < 0.0001$) according to CGI-I Significant treatment effects for both coprimary endpoints were observed at week 1 Sonnolence (27% versus 7% with placebo) and dizziness (20% versus 5% with placebo) Responders entered double-blind phase (n = 194 or 88%) Less relapse with GEn (9% versus 23% with placebo, odds ratio 0.35, 95% confidence interval 0.2–0.8, $P = 0.02$) Long-term tolerability for up to 9 months of treatment
Kushida et al, PIVOT RLS-I study ⁵¹	n = 222 Moderate to severe RLS Prior RLS treatment discontinued at least 2 weeks prior to baseline assessment	Double-blind multicenter RCT GEn 1200 mg/day versus placebo Taken at 5 pm daily with food Duration 12 weeks	Change in baseline IRLS total score at 12 weeks and investigator-rated CGI-I	Responders in single-blind phase (ie, improved IRLS total score and CGI-I) entered double-blind study Proportion of patients with relapse (increase > 6 points in IRLS total score and rating of “much worse” or “very much worse” on investigator-rated CGI-I)
Bogan et al, PIVOT RLS maintenance study ⁵³	n = 327 Moderate to severe RLS Treatment-naïve or prior RLS medications discontinued within the month	Multicenter RCT Single-blind phase (n = 327) GEn 1200 mg/day versus placebo Taken at 5 pm with food Duration 24 weeks Double-blind phase (n = 194) GEn 1200 mg/day versus placebo (with 2-week taper in placebo group) Taken at 5 pm with food Duration 12 weeks	Responders in single-blind phase (ie, improved IRLS total score and CGI-I) entered double-blind study Proportion of patients with relapse (increase > 6 points in IRLS total score and rating of “much worse” or “very much worse” on investigator-rated CGI-I)	

Lee et al, PIVOT RLS-II study ⁵⁴	n = 325 Moderate to severe RLS	Double-blind multicenter RCT GEn 1200 mg or 600 mg versus placebo Taken at 5 pm with food Duration 12 weeks	Change in baseline IRLS total score and proportion of responders on investigator-rated CGI-I at week 12	Greater reduction in IRLS (adjusted mean treatment difference -3.5, $P = 0.0015$ and -4.3, $P < 0.0001$) and increased treatment responders according to CGI-I (78% versus 45% with placebo; 73% versus 45% with placebo) with GEn 1200 and 600 mg/day, respectively Somnolence (18% versus 22%) and dizziness (24% versus 10%) were the most commonly reported adverse effects, percentages are for 1200 and 600 mg GEn, respectively
Ellenbogen et al ⁵⁵	n = 573 Subjects had previously participated in one of several studies ⁵²⁻⁵⁴	Open-label extension study GEn 1200 mg/day Taken at 5 pm with food Duration 52 weeks	Change in baseline IRLS total score and proportion of responders on investigator rated CGI-I	Mean IRLS reduction compared with parent study was 15.2 and 85% of subjects were CGI-I responders at week 52 GEn was safe and well tolerated for up to 64 weeks of treatment There were no changes in vital signs or electrocardiograms Mean IRLS reduction was 18% and 80% of subjects were CGI-I responders at week 52
Inoue et al ⁵⁶	n = 181 Japanese RLS patients	Multicenter open-label study GEn 1200 mg/day Taken after evening meal Duration 52 weeks	Change in baseline IRLS total score and proportion of responders on investigator rated CGI-I	Dizziness (46%) and somnolence (41%) were noted and mostly occurred in the first 4 weeks No episodes of augmentation were reported Serious adverse events (1.6%)

Abbreviations: CGI-I, Clinical Global Impression-Improvement; GEn, gabapentin enacarbil; IRLS, International RLS Rating Scale; RCT, randomized controlled trial; RLS, restless legs syndrome.

reduction even at 52 weeks. According to 24-hour RLS diaries kept by study subjects who were treatment-naïve at the start of the trial, mean time to onset of the first RLS symptoms increased from 7 to 16.5 hours at week 24. No further increase in time to symptom onset was observed beyond week 24; however, more than 50% of subjects were symptom-free at week 24. Another study by Inoue et al also showed similar improvements in IRLS and CGI-I, but was performed on Japanese subjects.⁵⁶ No comparative efficacy studies have been published at this time.

Adverse effects and tolerability

In all studies shown in Table 1, the most commonly reported treatment-emergent adverse effects were somnolence and dizziness. Despite this, daytime sleepiness based on Epworth Sleepiness Score was similar with the study drug and placebo.^{51,54} Other notable adverse effects include nasopharyngitis, nausea, fatigue, sleep attacks, headache, insomnia, decreased libido, and diarrhea.⁵⁰⁻⁵⁶ While there was a high incidence of treatment-emergent adverse effects (39%–81%), these were generally of mild to moderate intensity and of similar proportion to gabapentin (51%–82%).^{34,51-56} The majority of patients reported these effects within the first 2–4 weeks of the trial.^{53,56} A median duration of 42 days (versus 30 days with placebo) and 13 days (versus 26 days with placebo) was reported for somnolence and dizziness, respectively.⁵³ In the Inoue et al study, the prevalence of dizziness (0–4 weeks = 42% versus week 52 = 9%) and somnolence (0–4 weeks = 37% versus week 52 = 14%) gradually decreased over time. Most serious adverse effects were felt to be unrelated to the study drug; however, a limited number were felt to be related to it on the basis of a temporal relationship, including one death due to lymphoma.⁵⁶ A study investigating the effects of single doses of supratherapeutic gabapentin enacarbil of up to 6000 mg/day in healthy volunteers further supports its safety and tolerability.⁴⁴ All but four adverse effects were mild to moderate in intensity. Two subjects reported sedation (4800 mg/day) and somnolence (6000 mg/day), both of which were recorded as serious adverse events. Bogan et al reported the occurrence of seizures in one patient when switching from the study drug to placebo during the double-blind phase of their study. There have been no reported significant changes in vital signs, hematology, electrolytes, or renal function with gabapentin enacarbil. In a study of 15 patients with a creatinine clearance < 30 mL/minute, 600 mg/day dosing was well tolerated.⁴⁸

Several secondary endpoints assess additional patient-focused perspectives. In general, improvements in sleep quality, number of nights with RLS symptoms, hours awake as well as frequency of awakenings at night, mood, and patient rated CGI-I have been documented.^{50–52,54,56} Kushida et al further showed an improvement in sleep architecture by polysomnography, with reduced stage 1 sleep and increased slow wave sleep. In the same study, 85% of subjects reported feeling “much improved” or “very much improved” compared with placebo (15%). Patient symptom diaries also documented a reduction in RLS intensity or RLS symptoms altogether.⁵⁴ Overall, gabapentin enacarbil is generally safe and well tolerated without significant augmentation.

Practical implications

The improved pharmacokinetics of gabapentin enacarbil over gabapentin has been shown in several Phase 1 trials and animal studies, with its non-saturable absorption throughout the entire length of the intestine.^{44,46,57} Nevertheless, there have thus far been no comparative efficacy studies using these two medications. Hence, the practical benefit of its improved bioavailability compared with gabapentin remains a theoretical advantage at present.

Several Phase II and III studies using gabapentin enacarbil 600–1800 mg/day have shown reduced RLS severity by the IRLS and therapeutic benefit from a physician's perspective based on the CGI-I. There have also been two longer studies documenting continued benefit of the drug compared with placebo over 52 and 64 weeks. Neither of these studies documented augmentation as an issue, unlike that observed with most dopaminergic agents.^{27,28} In addition, both dopamine precursors and the agonist have not been shown to increase slow wave sleep or consistently improve overall sleep architecture despite improvement in the periodic leg movement index, in contrast with gabapentin enacarbil.^{52,58–61} Further studies with direct comparisons of gabapentin enacarbil and dopamine agonists are necessary, nonetheless.

The safety and tolerability of gabapentin enacarbil is acceptable, with mostly mild to moderate symptoms. Although the incidence of emergent adverse effects is high, it is comparable with gabapentin. It has also been tested in a small subset of patients with renal impairment. While dose adjustment will be necessary, doses of 600 mg/day were found to be well tolerated.⁴⁸

Presently, gabapentin enacarbil has not been approved by the Therapeutic Goods Administration or Medsafe for use in RLS. The cost of this medication may also be a potential barrier for many patients. It is twice the price of pramipexole and

ropinirole and five times the cost of generic gabapentin in the United States.⁶² However, it is still useful with its once-daily dosing. Patient adherence will likely improve as a result when compared with the 1–3 times daily dosing of gabapentin. As a second-line agent, it will potentially be of most benefit in patients with painful RLS or in those with augmentation. Future comparative efficacy studies with gabapentin, first-line dopaminergic agents, rotigotine, being the other once-daily RLS medication, and pregabalin, the structural analog of gabapentin, will be necessary.³⁸

Disclosure

The authors report no conflicts of interest in this work.

References

- Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res.* 2002;53(1):547–554.
- Manconi M, Ulfberg J, Berger K, et al. When gender matters: restless legs syndrome. Report of the “RLS and woman” workshop endorsed by the European RLS Study Group. *Sleep Med Rev.* 2011. Epub November 8.
- Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents – the Peds REST study. *Pediatrics.* 2007;120(2):253–266.
- Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. *Mov Disord.* 2007;22 Suppl 18:S401–S408.
- Ekbom KA. Restless legs syndrome. *Neurology.* 1960;10:868–873.
- Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med.* 2003;4(2):101–119.
- Ekbom K, Ulfberg J. Restless legs syndrome. *J Intern Med.* 2009;266(5):419–431.
- Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome (RLS). *Sleep Med.* 2006;7(1):25–30.
- Abetz L, Allen R, Follet A, et al. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther.* 2004;26(6):925–935.
- Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. *Neurology.* 2004;63(6):1065–1069.
- Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep.* 1998;21(4):371–377.
- Gigli GL, Adorati M, Dolso P, et al. Restless legs syndrome in end-stage renal disease. *Sleep Med.* 2004;5(3):309–315.
- Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc.* 2004;79(7):916–922.
- Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 2004;5(3):237–246.
- Garcia-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. *BMC Neurol.* 2011;11:28.
- Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4(2):121–132.

17. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest*. 2006;130(5):1596–1604.
18. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. *J Am Board Fam Med*. 2006;19(5):487–493.
19. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160(14):2137–2141.
20. Eliasson AH, Lettieri CJ. Sequential compression devices for treatment of restless legs syndrome. *Medicine (Baltimore)*. 2007;86(6):317–323.
21. Oertel WH, Trenkwalder C, Zucconi M, et al. State of the art in restless legs syndrome therapy: practice recommendations for treating restless legs syndrome. *Mov Disord*. 2007;22 Suppl 18:S466–S475.
22. O’Keefe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing*. 1994;23(3):200–203.
23. Botez MI, Lambert B. Folate deficiency and restless-legs syndrome in pregnancy. *N Engl J Med*. 1977;297(12):670.
24. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gend Based Med*. 2001;10(4):335–341.
25. Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. *Sleep*. 1998;21(5):501–505.
26. Nygaard IH, Valbo A, Pethick SV, Bohmer T. Does oral magnesium substitution relieve pregnancy-induced leg cramps? *Eur J Obstet Gynecol Reprod Biol*. 2008;141(1):23–26.
27. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*. 1996;19(3):205–213.
28. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Med*. 2004;5(1):9–14.
29. Garcia-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med*. 2007;8(5):520–530.
30. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med*. 2010;11(9):807–815.
31. Oertel W, Trenkwalder C, Benes H, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. *Lancet Neurol*. 2011;10(8):710–720.
32. Hening W, Allen R, Earley C, Kushida C, Picchiotti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. *Sleep*. 1999;22(7):970–999.
33. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol*. 2001;11(2):153–161.
34. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology*. 2002;59(10):1573–1579.
35. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. *Ren Fail*. 2004;26(4):393–397.
36. Happe S, Sauter C, Klosch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology*. 2003;48(2):82–86.
37. Garcia-Borreguero D, Larrosa O, Williams AM, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. *Neurology*. 2010;74(23):1897–1904.
38. Allen R, Chen C, Soaita A, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. *Sleep Med*. 2010;11(6):512–519.
39. Krnjevic K, Schwartz S. The action of gamma-aminobutyric acid on cortical neurones. *Exp Brain Res*. 1967;3(4):320–336.
40. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem*. 1996;271(10):5768–5776.
41. Stewart BH, Kugler AR, Thompson PR, Bockbrader HN. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. *Pharm Res*. 1993;10(2):276–281.
42. Gidal BE, Radulovic LL, Kruger S, Rutecki P, Pitterle M, Bockbrader HN. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. *Epilepsy Res*. 2000;40(2–3):123–127.
43. McLean MJ. Clinical pharmacokinetics of gabapentin. *Neurology*. 1994;44(6 Suppl 5):S17–S22.
44. Lal R, Sukbuntherng J, Luo W, et al. Pharmacokinetics and tolerability of single escalating doses of gabapentin enacarbil: a randomized-sequence, double-blind, placebo-controlled crossover study in healthy volunteers. *Clin Ther*. 2009;31(8):1776–1786.
45. Lal R, Sukbuntherng J, Ho J, Cundy KC. A phase I, single-dose study of the disposition of ¹⁴C-radiolabeled gabapentin enacarbil in healthy male volunteers. *Int J Clin Pharmacol Ther*. 2011;49(2):109–115.
46. Cundy KC, Sastry S, Luo W, Zou J, Moors TL, Canafax DM. Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. *J Clin Pharmacol*. 2008;48(12):1378–1388.
47. Lal R, Sukbuntherng J, Luo W, Huff FJ, Zou J, Cundy KC. The effect of food with varying fat content on the clinical pharmacokinetics of gabapentin after oral administration of gabapentin enacarbil. *Int J Clin Pharmacol Ther*. 2010;48(2):120–128.
48. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. *Clin Ther*. 2012;34(1):201–213.
49. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetic drug interaction studies of gabapentin enacarbil, a novel transported prodrug of gabapentin, with naproxen and cimetidine. *Br J Clin Pharmacol*. 2010;69(5):498–507.
50. Walters AS, Ondo WG, Kushida CA, et al. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. *Clin Neuropharmacol*. 2009;32(6):311–320.
51. Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*. 2009;72(5):439–446.
52. Kushida CA, Walters AS, Becker P, et al. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. *Sleep*. 2009;32(2):159–168.
53. Bogan RK, Bornemann MA, Kushida CA, Tran PV, Barrett RW. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. *Mayo Clin Proc*. 2010;85(6):512–521.
54. Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. *J Clin Sleep Med*. 2011;7(3):282–292.
55. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. *Clin Neuropharmacol*. 2011;34(1):8–16.
56. Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(2):251–257.

57. Cundy KC, Annamalai T, Bu L, et al. XP13512 [(+/-)-1-([(alpha-isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: II. Improved oral bioavailability, dose proportionality, and colonic absorption compared with gabapentin in rats and monkeys. *J Pharmacol Exp Ther*. 2004;311(1):324–333.
58. Saletu M, Anderer P, Saletu-Zyhlarz GM, et al. Comparative placebo-controlled polysomnographic and psychometric studies on the acute effects of gabapentin versus ropinirole in restless legs syndrome. *J Neural Transm*. 2010;117(4):463–473.
59. Saletu M, Anderer P, Saletu-Zyhlarz G, Hauer C, Saletu B. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci*. 2002;252(4):185–194.
60. Manconi M, Ferri R, Zucconi M, et al. First night efficacy of pramipexole in restless legs syndrome and periodic leg movements. *Sleep Med*. 2007;8(5):491–497.
61. Ferri R, Manconi M, Arico D, et al. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. *Sleep*. 2010;33(6):793–800.
62. Burke RA, Faulkner MA. Gabapentin enacarbil for the treatment of restless legs syndrome (RLS). *Expert Opin Pharmacother*. 2011;12(18):2905–2914.

Therapeutics and Clinical Risk Management

Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS,

Submit your manuscript here: <http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal>

EMBASE, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress