Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Treatment for Restless Legs Syndrome*

Draft review available for public comment from May 1, 2012 to May 30, 2012.

Research Review Citation: Wilt TJ, MacDonald R, Ouellette J, Tacklind J, Khawaja I, Rutks I, Butler M, Fink HA. Treatment for Restless Legs Syndrome. Comparative Effectiveness Review No. 86. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No. 12(13)-EHC147-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	There is no discussion of gabapentin enacarbil other than its listing in Table 1 (page 35) where it is incorrectly spelled.	We have more carefully discussed gabapentin enacarbil and have corrected the spelling in Table 1.
Peer Reviewer #1	Introduction	The gabapentin- pregabalin group of drugs is called "GABA analogs". Whereas this is true, it is very unlikely that this is the mechanism by which they relieve RLS. The group is usually referred to as "calcium channel (alpha-2-delta) ligands", the name representing a more likely mechanism of action. Because of the uncertainties regarding mechanism, I do not feel strongly here, but think the authors of the report should consider this nomenclature issue.	We have replaced "GABA analogs" with alpha-2-delta ligands.
Peer Reviewer #1	Introduction	I realize that any report of this nature has to have a cut-off date for including studies. However, I bring to the authors' attention an important study of IV iron (Allen et al. Sleep Med 201112(9):906-13) published in October 2011. I must also add that it is unfortunate that the first large comparative effectiveness study in RLS (pramipexole versus pregabalin) is complete and expected to be published later this year.	We have added Allen et al. Sleep Med 201112(9):906-13 to the report. This study is published only in abstract form. We have added in our discussion that this study is expected to be published soon.
Peer Reviewer #1	Introduction	There is no discussion of impulse control disorders as long term risks of dopaminergic agents. This complication can occur in 9-17% of RLS patients using these drugs. This is addressed in a case control study (Cornelius et al Sleep 2010;33(1):81-7) and a number of other case series. A comprehensive analysis of the potential harms of these agents needs to include this topic.	We have added Cornelius 2010 to the report.
Peer Reviewer #1	Introduction	Pg 10 (line 8) and pg 33 (line 33): The extensive work on the genetic basis of primary RLS should be mentioned.	We have updated the report to include information on the genetic basis of primary RLS.
Peer Reviewer #1	Introduction	Pg 10 (line 31-33) and page 34 (lines 23-25): Gabapentin enacarbil, not gabapentin, is FDA approved for RLS. Rotigotine is also FDA approved for RLS (as of last month).	We have amended to report that gabapentin enacarbil and rotigotine are FDA approved for RLS.
Peer Reviewer #1	Introduction	There are a number of sloppy or incorrect statements. First, FDA approved drugs include rotigotine (probably approved after submission) and gabapentin enacarbil (not gabapentin). These are different compounds.	*See above*. We have differentiated between gabapentin enacarbil, gabapentin and pregabalin. We are specific about using the exact drug name for each drug and not using interchangeably. We make a specific note of their differences initially.
Peer Reviewer #2	Introduction	There is almost no data on non-pharmacologic measures from page 10. I would not include anything that does not have a study to support it. For example "sleep hygiene" actually worsens RLS and nicotine probably improves it.	We agree but have included information based on information regarding recommended or considered therapies
Peer Reviewer #2	Introduction	Severe RLS is not necessarily "chronic and progressive" In fact severe RLS often improves in later life.	We have omitted "chronic and progressive".
Peer Reviewer #3	Introduction	Yes.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	page 33 0f 187, line 32: There is a revised RLS/WED definition with one additional criterion: 5. These symptoms are not solely accounted for by another condition such as leg cramps, positional discomfort, leg swelling, or arthritis.	The fifth criteria is not firmly established nor used. We have included the reviewer's statement from this revised RLS/WED definition in the introduction.
Peer Reviewer #4	Introduction	page 34 of 187, line 5: change RLS sufferers to individuals with RLS	This has been placed in quotes with the definition by original authors.
Peer Reviewer #4	Introduction	page 34 of 187, line 22: three dopamine agonists (pramapexole, ropinirole, and rotigotine) and one anticonvulsant drug (gabapentin enacarbil)	Changed

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Peer Reviewer #5	Introduction	Very well written. My comments follow. Page 10, first sentence is not clearly written. I think the prevalence in this study at 1.5% is misleading. Can you say why this may have been this low since most of the studies say 6-10% (give or take)? I disagree with the comment on page 11 line 6 which says that PLM are not specific to RLS (i.e. please consider recent updates on genetics studies related to RLS and PLMS). The term "IRLS responders" is used frequently but I am not sure what you mean by this term. On page 20, line 38, I had to read the second to the last sentence several times to get the number of withdrawals due to lack of efficacy. I was not sure where these numbers came from - even though the author writes "respectively". I think it would read better if it said "19 out of 21 and 5 out of 9" so we don't have to figure out which number we are looking at. Again, on page 25, line 18, the authors say "IRLS responders" - are you talking about participants who responded to treatments in all the studies? Or those who used the IRLS scale? Needs clarification please. On page 27, the authors say augmentation can occur with long term treatment of drug. Augmentation can also occur when you first start taking the drug and is reason to change medications. TYPO: page 33 of 187, ".....is a neurological disorder that IS characterized by.....". TYPO: please do a search for RSL vs. RLS - I saw it once (page 155/187) but it may be more in the document. On page 33 of 187, it might be nice to add the severity of RLS may also impact quality of life (lines 40-45). Mimic conditions (page 34 of 187) require more explanation - very important as it results in over or under diagnosis of RLS. The impact of health outcomes in lack of treatment efficacy would be better identified if morbidity and mortality were discussed i.e. we know that people with RLS have increased morbidity and mortality when their disease is not treated and it impacts co-morbid health conditions (hypertension, diabetes, stroke, etc). Table 1 is leaving off the anti-hypertensives that are used to treat RLS i.e Catapress/Clonidine. Table 2: There are a variety of other instruments specific to RLS that are used in the assessment, evaluation, and diagnosis of RLS. TYPO: page 39 of 187 - under key questions - I think Key question 1 should be a, b, c, and Key question 2 should be d, e, f.	We thank the reviewer. We have provided references regarding prevalence. We agree further research is needed. We stand by our statement re; PLM are not specific. We have defined RLS responders. We have clarified the statement that was on page 20 line 38. We have altered the wording and the numbering. We have clarified RLS responders on the noted page 25 line 18. We have addressed typos. We have further described “mimic” conditions. We have changed the KQ1 to read a, b, c etc… Catapress/Clonidine was not identified as a therapy commonly used and we identified no eligible studies examining these drugs. No change.
Peer Reviewer #6	Introduction	Introduction defines the target patient population appropriately as well as other populations where further study should be done.	We thank the reviewer.
Peer Reviewer #7	Introduction	I consider the introduction to be well written and appropriate to the topic.	We thank the reviewer.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Introduction	Page ES-2,paragraph 4,lines 4-5: Rotigotine patch (Neupro) is approved.	We have noted that rotigotine is now FDA approved.
Peer Reviewer #9	Introduction	Gabapentin is not FDA approved but gabapentin enacarbil is approved.	We have noted that gabapentin enacarbil and not gabapentin are FDA approved.
Peer Reviewer #9	Introduction	Also on page 2 of Introduction and Overview (page 34 of 187 of the document), page 2,line 9: two dopamine agonists should be changed to three and rotigotine patch should be added.	We have noted that three dopamine agonists are now FDA approved.
Public Comment	Introduction	Differentiate between gabapentin enacarbil and other gabapentin products based on differences in FDA approval and strength of evidence.	We have updated the report to reflect the difference between gabapentin and gabapentin enacarbil. Our thanks to the reviewer.
Public Comment	Introduction	Table 1: Rotigotine is now approved in the US for RLS	We have noted that rotigotine is now FDA approved.
Peer Reviewer #2	Methods	Is there are specific reason some of these parameters were chosen. They eliminate a number of other studies. The main elimination factor is use of the IRLS exclusively. This eliminates a number of well done, large European studies that used the RLS-6. Since most of the report does not actually compare drugs, why can these not be included? A number of other trials include the IRLS as secondary endpoints.	We included studies if they enrolled patients with RLS diagnosed by the validated diagnostic 4-item RLS diagnostic criteria. We included studies if they reported our described outcomes of interest even if IRLS scores were not reported.
Peer Reviewer #3	Methods	Yes.	Thank you.
Peer Reviewer #4	Methods	Page 35 of 187, line 11: Neupro has been approved by the FDA for the treatment of RLS	We have noted that rotigotine is now FDA approved.
Peer Reviewer #4	Methods	Page 35 of 187, line 15: Gabapentin enacarbil (b vs p)	This has been addressed.
Peer Reviewer #4	Methods	Page 37 of 187, lines 32-35: DTC marketing observation is just YOUR opinion and not substantiated with any fact, REMOVE IT.	We have added a reference supporting our statement. We leave otherwise unchanged.
Peer Reviewer #4	Methods	page 46 of 187, line 7 anticonvulsants: Please distinguish between gabapentin (Neurontin) and gabapentin enacarbil (Horizant). You left out most of the Horizant studies--I attached the citations below	We have differentiated between gabapentin enacarbil and gabapentin and have incorporated the gabapentin enacarbil trials that met our inclusion criteria.
Peer Reviewer #5	Methods	Yes - this was all written very well and is explained very well. Can you tell us which quality of life scales were used in the report? There are others than what is mentioned in the table.....	We mainly focused on the RLS-QoL. Details of QoL instruments may be found in the Appendix.
Peer Reviewer #6	Methods	Methods, inclusion/ exclusion criteria, definitions, search criteria all correctly defined and outlined. Method of analysis of data followed criteria outlined in the introduction.	We thank the reviewer.
Peer Reviewer #7	Methods	Inclusion and exclusion criteria are justified. Searches are logical. Definitions and diagnostic criteria are appropriate. Outcome measures are valid in their limitations. Statistical methods are appropriate.	We thank the reviewer.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Methods	Appropriately addressed	We thank the reviewer.
Public Comment	Methods	Consider including additional endpoints of assessment, as many studies with dopamine agonists, as well as other treatments for RLS, evaluated change in IRLS total scores and CGI-I.	We included studies reporting on a wide range of study outcomes including change in IRLS total scores and CGI scores.
Public Comment	Methods	Consider evaluation of additional ropinirole studies – please see enclosed responses	We have reviewed and included additional eligible studies.
Public Comment	Methods	Table 3: Extra “Outcomes” bullet	Corrected.
Public Comment	Methods	Not all studies used “50% reduction in IRLS score” which was the primary outcome measure used in this report – consider changing primary outcome measure to standard measures traditionally used in the majority of studies which are change in IRLS scores and CGI-I.	Primary outcomes were determined by us, discussed with our TEP and described in our protocol. There are no validated measures indicating “clinically important differences”. A 50% reduction in IRLS scores was determined a priori as our primary outcome. This is often referred to by authors as “RLS responders”. WE also included changes in the CGI and PGI scores of “improved” or “much improved” as a measure of clinical significance as it seemed to have “face validity”. We stand by these as our primary outcomes. Other outcomes are included.
Public Comment	Methods	Across the studies, daily dosing was taken into account, but the number of times study medication was given per day may not have been (i.e., ropinirole twice daily dosing was not stated)	We have provided this information in our revised Table to include dose formulations and timing
Public Comment	Methods	Consider removing the Alder, 2004 study because it is very small (N = 22) and assessed IRLS remitters and not other traditional endpoints due to the crossover design	We have kept Alder 2004 in the review since it did meet our inclusion criteria but it is discussed separately from the other studies.
Peer Reviewer #1	Results	Pg 17 (lines 18-20) and page 51 (line 35-53): The quality of the pneumatic compression study is less good than implied in the text. Although sham compression was used for the control subjects, the authors admit in their discussion that it is very likely that blinding was broken, as it was easy for the patients to distinguish real pressure from sham pressure.	We have added a phrase from this study’s discussion to better demonstrate this point. Thank you.
Peer Reviewer #1	Results	Pg 18 and pg 53: Short-term Harms. There is no discussion of the GABA agonists in this section despite the data having been abstracted in Figure 13 (pg 78). This should to be included in the text.	We have added a section on the adverse events associated with alpha-2-delta ligands.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Pg 25 (line 55-56), pg 37 (line 29) and pg 82 (lines 9-12): It is stated that the "consensus definition of RLS is not routinely used in clinical settings to diagnose, assess severity or initiate therapy" and "thus the applicability of results in primary care or mental health settings is not established." I do not believe the first statement is supported by any data. RLS is diagnosed clinically, the 4 basic criteria have been widely disseminated, and it is likely that most (although not all) patients are correctly diagnosed.	We have revised this statement though as a primary care clinician and someone who has informally surveyed other PCP the actual RLS basic criteria, used verbatim, are not routinely used or recognized by PCP. We stand by our statement re: applicability to mental health or PCP settings as enrollees were not recruited from these settings.
Peer Reviewer #1	Results	Pg 26 (line 38), pg 82 (line 48): With respect to opioids, the text reads "No eligible studies evaluated these agents" This should read "no eligible RCT studies evaluated these agents" as there are a number of long-term opioid studies included in the review.	Corrected
Peer Reviewer #2	Results	The reason cabergoline was not used in the U.S. for RLS was cost and lack of insurance coverage, different dosing from what is available to treat hyperprolactinemia, and lack of familiarity, not, as is mentioned 5 times, the cardiac valve problems. The report is extremely repetitive in general. Most point i.e. no studies in pregnancy are mentioned more than 5 times.	We have deleted several of the mentions of this point and modified the statement.
Peer Reviewer #2	Results	It is an egregious error that gabapentin and gabapentin enacarbil are lumped together as a single drug. There are several other published trials on gabapentin enacarbil that would seem to fit the inclusion criteria.	We have differentiated between gabapentin enacarbil and gabapentin. Our updated review now includes several gabapentin enacarbil trials.
Peer Reviewer #2	Results	There clearly are trials that show a dose response for dopamine agonists, including at least one you cite as not. Henning et al showed no benefit of 0.5mg, borderline at 1.0 and more robust at 2 and 3 mg for rotigotine. All of the numerous statements about lack of dose response need to be eliminated. The authors somehow state response is not a dose response.	We have reviewed and included our data in the report. The reviewer is correct that some doses showed a statistical significance while others did not. However, confidence intervals overlapped and there was no evidence of subgroup interaction by dose effect. We stand by our statements.
Peer Reviewer #3	Results	Yes.	We thank the reviewer.
Peer Reviewer #4	Results	page 50 of 187, line 7 and ongoing: Add gabapentin enacarbil to this discussion section	Done
Peer Reviewer #4	Results	page 53 of 187, line 35-37: Question about augmentation--please read attached excellent article on augmentation variation	We have read the article and do not believe it contains primary information beyond what is included in our report
Peer Reviewer #4	Results	page 81 of 187, line 6: restless legs (not leg)	Corrected
Peer Reviewer #5	Results	Please look at page 135 of 187. This figure is called "IRLS Remitters analyses". Is this title clear to people who are not RLS experts?	Changed to clarify

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Peer Reviewer #6	Results	The detail of the results as described was certainly adequate with some repetition of results which could possibly have been streamlined to this reviewer. Overall the results were presented and reviewed in a manner which was logical. I am unaware of any studies which should have been included or excluded- the results do suggest areas for further research.	We thank the reviewer.
Peer Reviewer #7	Results	The results section is thorough. It provides sufficient detail. Figures, tables and appendices provide summarized information that supports the text.	We thank the reviewer.
Peer Reviewer #7	Results	The authors should consider a review of gabapentin enacarbil and RCTs. I believe studies have been missed and should be included based upon publication of the articles already cited in the draft manuscript.	We have included additional gabapentin enacarbil trials that have met our inclusion criteria not previously cited.
Peer Reviewer #9	Results	Addressed adequately	We thank the reviewer.
Public Comment	Results	Outline strength of evidence by specific GABA analogs FDA-approved for RLS, rather than grouping together.	We have stratified the strength of evidence according to type of alpha-2-delta ligand.
Public Comment	Results	Incorporate data from Lee et al (N=325) into the section regarding efficacy of gabapentin enacarbil, as it appears to meet inclusion criteria set forth within methods section for this report. Re-evaluate strength of evidence for gabapentin enacarbil given the additional data available.	We have added the trial by Lee and have re-evaluated strength of evidence for gabapentin enacarbil.
Public Comment	Results	Similar to sections for dopamine agonists related to RLS quality of life and patient-reported sleep quality, consider including similar sections for gabapentin enacarbil based on the following data. MOS Sleep Scale: In study XP052, improvements in the total sleep score and all domains of the MOS sleep domains (i.e., sleep adequacy, sleep quantity, sleep disturbance, and daytime somnolence) were observed at Week 12 using LOCF in both the gabpentin enacarbil (1200 mg) and placebo groups. There was a statistically significantly greater improvement in all domains of the MOS at Week 12 using LOCF in the gabpentin enacarbil group as compared with the placebo group ($P<0.05$). [Kushida CA, Becker PM, Ellenbogen AL, et al. Neurology 2009;72:439-446] In study XP053, there was a statistically significantly greater improvement in all domains of the MOS at Week 12 using LOCF in the gabpentin enacarbil treatment groups (1200 mg and 600 mg) compared with the placebo group (judged at the $p<0.05$ level), with the exception of Daytime Somnolence in the gabpentin enacarbil 600 mg group ($P=0.8926$). [Lee DO, et al. J Clin Sleep Med 2011;7(3):282-292.]	We reviewed and included outcomes from eligible studies of gabapentin enacarbil.

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Public Comment	Results	Quality of Life (QoL) In Study XP052, improved RLSQoL scores, as assessed by the Johns Hopkins QoL Questionnaire, at week 12 compared with placebo (mean [SD] change from baseline: gabapentin enacarbil, 21.4 [17.00]; placebo, 14.1 [17.32]; LS treatment difference 7.8; *P* < 0.0001). [Kushida CA, Becker PM, Ellenbogen AL, et al. Neurology 2009;72:439-446.] In Study XP053**,** baseline Overall-Life-Impact scores were similar between treatment groups. However, at Week 12 using LOCF, there was an improvement in quality of life scores for all treatment groups, but the treatment difference was statistically significant favoring the gabpentin enacarbil 1200 mg and 600 mg groups compared with placebo (*P*=0.0009 and *P*=0.0025, respectively).	We have included the published study by Kushida with the statement about the improvement in RLS QOL scores.
Public Comment	Results	On p. 19 of the document, last sentence in section titled, "Long-term tolerability and durability," it is stated that augmentation is believed not to occur with gabapentin or opioids. The data available for gabapentin enacarbil to date support that statement. It seems that statement and perhaps supporting data should also be included on p. 23 within the section titled, "Long-term harms and withdrawal from treatment", as this section seems to go into more detail around augmentation.	We have included
Public Comment	Results	Consider adding information related to early morning rebound (EMR) as it relates to short-term and long-term harms. EMR refers to the worsening of RLS symptoms in the early morning usually followed by a symptom-free period until symptoms reappear again in the afternoon or evening. EMR differs from augmentation because symptoms appear in the early morning rather than earlier onset of symptoms in the evening. EMR is considered to be an end-of-dose effect and may be related to the half-life of the medication (the effect of the medication is wearing off).	This is considered an efficacy outcome and falls outside of our scope of outcomes. We briefly mention it.
Public Comment	Results	Add information related to gabapentin enacarbil in the section outlining short-term harms. This section currently focuses only on dopamine agonists.	We have added a section on the adverse events associated with alpha-2-delta ligands, including gabapentin enacarbil.
Public Comment	Results	Please see comments in the Executive Summary section regarding request to remove information concerning indirect evidence that suggests fatigue is more common with ropinirole than other dopamine agonists; consider removing bullet in the Key Points and Comparative Harms sections on this topic	Removed
Public Comment	Results	Comparative Effectiveness – please see enclosed response regarding ropinirole vs. gabapentin for RLS for small studies that evaluated these agents (may not meet review criteria)	These studies did not meet inclusion criteria.

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Public Comment	Results	Long-Term Harms/Withdrawal from Treatment – please see enclosed response with direction on accessing ropinirole 52-week extension studies (101468/192 and 101468/243) on the GSK Clinical Study Register available at: http://www.gsk-clinicalstudyregister.com/.	We have included withdrawals and reasons for withdrawals from these unpublished studies.
Public Comment	Results	Please see enclosed responses containing additional ropinirole data (i.e., as needed and twice daily dosing, 52-week open-label studies)	See above
Public Comment	Results	Please see comments in "Tables" section regarding Table 4 in this section	Modified
Peer Reviewer #1	Discussion	Pg 28 Table D, pg 84 Table 13: "long-term durability of treatment benefits remains an unaddressed concern." While I agree more research needs to be done in this area, the wording seems to suggest that there are no studies dealing with this topic. On the contrary, refs 41-53 all provide long-term data. I suggest rewording such as "There is incomplete information regarding long-term durability of treatments"	We have modified and agree this is a future research need
Peer Reviewer #2	Discussion	I must disagree that RCT for RLS is "limited in quality" All four of the FDA approved drugs have at least two class 1 trials (level A evidence for efficacy). Length of treatments and other issues are legitimate issues but you can't say the quality is limited in these studies. The statement of recruitment sites is absolutely false, especially for rotigotine and gabapentin enacarbil. Patients were recruited from primary sleep centers. Very few "RLS clinics" were involved in these studies. I suspect the authors made this blanket statement without actually checking.	We have deleted the statement "limited quality". We expanded on eligibility and study design features that limit the applicability to broad populations and our understanding on comparative effectiveness and long-term effectiveness. Patients were recruited from sleep centers and RLS clinics per the authors' description in the manuscripts. Few studies enrolled patients from primary care clinics. A large selection bias versus primary care patients is possible.
Peer Reviewer #2	Discussion	Although there is no data either way, I suspect most RLS in the primary care setting is based on formal criteria, as they are quite simple, and have been widely disseminated by the pharmaceutical companies when they promoted RLS drugs. Unless the authors have clear evidence to the contrary, this needs to be eliminated.	We respectfully disagree and have discussed the use of these scale scores in primary care with many primary care providers.
Peer Reviewer #2	Discussion	Although there is little data correlating change in IRLS and meaningful improvement, almost all of these studies also used CGI scales, which do correlate with meaningful improvement, and essentially all of them show positive findings on CGI. This needs to be mentioned as there is a very strong correlation between CGI results and IRLS results.	We have reported CGI and "RLS responder" data where available. We stand by our statement that a minimally important change in the IRLS scale score has not been defined.

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Peer Reviewer #2	Discussion	I am not sure where the authors obtained their epidemiology numbers. The article they cite does not correlate with their numbers. The 1.5% of "RLS sufferers" the authors report is not cited. RLS epidemiology is very dependent geographic origin. Most studies, including the best study (REST) report around a 10% prevalence in Caucasian populations. A brief mention of the genes associated with RLS is warranted. This contributes to the impression that the authors are trying to minimize RLS as a medical problem.	We have added a citation to clarify our source. We have also added text to briefly describe the genes associated with RLS.
Peer Reviewer #2	Discussion	In general, one gets the impression that the Discussion was a preconceived, boilerplate design arguing that there is no good data on any aspect of RLS.	We respectfully disagree. This was not a preconceived boilerplate design. We have incorporated new evidence and peer reviewer comments into our discussion.
Peer Reviewer #3	Discussion	Yes.	Thank you.
Peer Reviewer #4	Discussion	Comments on first section Effective Health: page 9 of 187, lines 11-15: INCORRECT TITLE	We have corrected the title.
Peer Reviewer #4	Discussion	page 9 of 187, lines 36 and 37: RLS (also known as Willis-Ekbom disease); sensations in the limbs (not just legs)	We have made the requested change.
Peer Reviewer #4	Discussion	page 10 of 187, lines 31-32: add rotigitone and gabapentin enacarbil; line 46 restless LEGS (not leg)	We have added rotigotine and gabapentin enacarbil. We have searched for, and replaced all references to Restless Leg.
Peer Reviewer #5	Discussion	Yes, it was very well written and it was right on course with the current discussion in RLS.	We thank the reviewer.
Peer Reviewer #6	Discussion	The findings as presented are clearly stated as well as their limitations. Again, I am unaware of any research literature which should have been included or referenced to. As noted above, the results and subsequent discussion suggest areas for future research.	We thank the reviewer.
Peer Reviewer #7	Discussion	Discussions and conclusions provide sufficient information on major findings. I would encourage the authors to be somewhat more succinct. It was my impression that information was repeated in various sections.	We thank the reviewer.
Peer Reviewer #7	Discussion	The authors demonstrate insufficient understanding of clinical practice. For example, opiates. Attempts to obtain funding for RCT assessment of opiates in the management of RLS have proven unsuccessful, even as the most severe patients show benefit, often at less harm than dopaminergic therapy. A paragraph to summarize this discrepancy between research and clinical practice would assure that the reader of the manuscript does not take lack of evidence for lack of efficacy. The jury should remain out to lessen the chance of denial of treatment to those in need.	We agree and have stated that there is lack of evidence of benefit rather than evidence of lack of benefit.

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Peer Reviewer #7	Discussion	The authors are to be commended for their future research section that provides a clear and easily translated path to the future.	We thank the reviewer.
Peer Reviewer #9	Discussion	Implications of treatment outcome on comorbidities are not discussed	There are no data and this would be better left for future research needs.
Peer Reviewer #9	Discussion	In the future research recommendations address the deficiencies of the document as listed in the confidential comments to the editor.	
Peer Reviewer #2	General	The first major concern is calling gabapentin / pregabalin "GABA analogues." They have no affinity for GABA receptors. They have affinity for the alpha 2 delta subunit of L voltage gaited Ca channels. Call them that or "seizure meds". Presumably this has a deadline, but the best comparative trial (pregabalin vs. pramipexole) has been presented, but not yet published. It generally favored high dose pregabalin. There are several other published trials of gabapentin enacarbil.	Changed to alpha 2 delta ligands. We have made a statement about the unpublished results of the comparative trial.
Peer Reviewer #3	General	Yes. It is very helpful.	We thank the reviewer.
Peer Reviewer #5	General	Yes, the report is clinically meaningful. While it is written as a meta analysis, I think more work will need to be done to translate it for a clinical application for those health care providers who are not so familiar with RLS.	We have attempted to modify the language to better facilitate clinical applicability for those less familiar with RLS.
Peer Reviewer #5	General	Thank you for giving me the honor of reviewing this paper. It was well written and easily understood. I do have a couple of comments: 1) Please consider the implications of the dopaminergic medications on PLMS - as this evidence is increasing on how PLMS (seen in a high percentage of persons with RLS) contributes to morbidity and mortality. 2) Please look at the literature (which is not much) on magnesium. I beleive there have been some clinical trials on its effectiveness in decreasing symptoms. 3) Please consider an update on the definition for "secondary RLS i.e. iron deficiency, ESRD, and pregnancy. These are all associated with iron deficiency and were the first labeled as "secondary RLS", there are many other co-morbidities that are considered secondary RLS. As well, some believe that there is NO primary or secondary RLS - it is based on genetics and we are not really sure why some people develop symptoms and others do not.	1.) While we appreciate the suggestion, the implications of dopaminergic medications on PLMS are out of the scope of this project. 2.) We were unable to find any data to describe the impact of magnesium on symptoms. 3.) We respectfully decline-we agree there are other "secondary causes" of RLS-the role of genetics and/or other etiologies of RLS are an active area of research that are discussed in our future research needs.
Peer Reviewer #6	General	The report identifies the key questions appropriately as well as the target audience for the report. Report as outlined will be clinically useful for primary care and specialty physicians alike.	We thank the reviewer.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	The general comments are clinically meaningful and appropriate to the target audience and populations. The key questions certainly are appropriate, although data is too limited on Key Question 1: comparative efficacy.	We thank the reviewer.
Peer Reviewer #9	General	Clinically meaningful, explicitly defined, and the key questions are defined.	We thank the reviewer.
Peer Reviewer #1	Clarity and Usability	Yes, with exceptions discussed above under General Comments	We thank the reviewer.
Peer Reviewer #2	Clarity and Usability	Clarity and Usability: In general it suffers from a presumed lack of first hand expertise in RLS so that many of the references are taken out of context or are inaccurate. It is extremely redundant, makes many assertions that are not based on evidence but appear to be preconceived notions of the authors, appears to omit studies that I think would meet their criteria, and is frequently factually inaccurate.	We respectfully disagree and have incorporated other comments.
Peer Reviewer #3	Clarity and Usability	Yes.	We thank the reviewer.
Peer Reviewer #4	Clarity and Usability	page 16 of 187, lines 39 - 56: add discussion of gabapentin enacarbil with published citations	Done
Peer Reviewer #4	Clarity and Usability	page 25 of 187, line 7: restless LEGS not leg	Thank you. We have replaced all incidents of restless leg with restless legs.
Peer Reviewer #4	Clarity and Usability	page 26 of 187, lines 35-38: None of these.....(this is opinion and highly inflammatory---REMOVE)	We disagree, do not intend for it to be inflammatory and leave unchanged.
Peer Reviewer #4	Clarity and Usability	page 27 of 187, lines 49-51: Applicability....(this is opinion and highly inflammatory. No place for this in a scientific report)	We have reviewed, clarified and stand by the general context given the available data and the population of individuals with RLS.
Peer Reviewer #4	Clarity and Usability	page 34 0f 187, line 5: change RLS sufferers to individuals with RLS	We clarified that this describes the definition used by the authors of “RLS sufferers”
Peer Reviewer #4	Clarity and Usability	page 34 of 187, line 22: add rotigotine and gabapentin enacarbil	Done
Peer Reviewer #5	Clarity and Usability	Yes, using PRISMA statement is very logical and provides report with structure.	We thank the reviewer.
Peer Reviewer #6	Clarity and Usability	Overall, report appears well organized and complete in view of the available data/ research. Translating the report into practice guidelines applicable to primary care will be limited in view of the limitations/ need for further research as outlined in the report.	Thank you.
Peer Reviewer #7	Clarity and Usability	Within the limits of the data, report is appropriately structured and organized, except as noted for the discrepancy of clinical to research practice.	Thank you.
Peer Reviewer #9	Clarity and Usability	OK	We thank the reviewer.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		NEUPRO (dopamine agonist) : In clinical trials, the lowest effective dose was 1 mg/24 hours. The highest recommended does is 3 mg/24 hours. The most common adverse reactions (≥ 5% greater than placebo) for the highest recommended does (3mg) for RLS were application side reactions, nausea, somnolence and headache.	We have included dosing information and previously noted the adverse effects.
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		We request the draft be updated accordingly to state that NEUPRO is FDA approved for the treatment of moderate-to-severe RLS.	We have noted that rotigotine is now FDA approved.
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Continuous dopaminergic treatment was developed to mimic the endrogenous dopamine system; thus, though further studies are needed to confirm, continuously-delivered agents may provide stable plasma concentrations which may be important in the treatment of unpredictable onset and severity of symptoms, daytime occurrence, and symptoms occurring outside the therapeutic window of an immediate-release product. In fact, up to 60% of patients with moderate-to-severe RLS report breakthrough symptoms during the daytime (Tzonova et al. 2012)	We thank them for this information but do not believe this is necessary for inclusion in the report. No change
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		It is important to describe in the ES the differences in formulations between dopamine agonists, and state which formulations are FDA approved for the treatment of RLS.	We provide this information
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Table 1 should be modified to include a column with the product's formulations (oral, transdermal, etc) as well as the FDA approval status by formulations. Furthermore, both immediate-release and extended-release formulations are available for pramipexole and ropinirole. The current report does not clarify which type of formulations were used in which study. We ask that the authors please consider clearly defining which dopamine agonist was evaluated per study, including the formulations type.	Done

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Upon review of the draft report, it appears that the following study was omitted from the report" *Oertel WH, et al. Efficacy of rotigotine transdermal system in severe restless leg syndrome: A randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Med. 2008; 9:228-239*. It is unclear why this study was omitted as the outcomes measured meet the stated inclusion criteria for the CER. We respectfully request AHRQ to reconsider including these outcomes of SP709 as appropriately applied throughout this review for all evidence generated for rotigotine.	Now included As above we have included this information
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		We respectfully request that AHRQ reconsider the conclusion that there is no clear evidence of a dose effect for mean change in IRLS scale scores for all Das based on over-lapping confidence intervals and absolute effects. In Oertel 2008 and in Hening 2010, a dose-response relationship was found for rotigotine doses 0.5mg, 1mg, 2mg and 3mg/24 hours. Statistically speaking, while non-overlapping CIs for two different population means point to a statistically significant difference, one cannot conclude the opposite – that overlapping CIs show no difference between population means. In additional, it is unclear if the authors are proposing that a four-point change in the IRLS scale should be used as a cut-off for clinical significance. We respectfully request that AHRQ provide additional data to support this cut-off	No change. We are not proposing that a 4-point change in the IRLS scale is of clinical significance. We have stated that future research is needed to determine the minimally important difference.
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Study Duration Treatment duration of 6 to 24 months was classified as intermediate in duration. We understand the importance of conducting long-term trials of sufficient length to capture important safety signals, such as augmentation. However, given the impact of moderate-to-severe RLS on a patient's health and well-being, conducting a placebo-controlled trial longer than six months could raise questions that a relative benefit of a placebo-controlled trial may not justify the risks for subjects foregoing therapy while on placebo.	We defined short term studies a priori and continue to believe that adequately assessing the long-term efficacy of these treatments through longer duration RCTs is needed. No change
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		We respectfully request modifying the first bullet point of the Key points from "randomized controlled trials results were limited to short-term efficacy studies versus placebo or usual care" to read "the majority of randomized, controlled trials were of short duration (≤12 weeks), however, longer controlled trials up to six months duration have be conducted for some RLS treatments, including rotigotine, pramipexole and iron supplementation."	Our definition of short term was 6 months or less

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Use of Polysomnography Data We feel sleep data would make a valuable contribution to the characterization of the therapeutic effects of RLS treatments for Key Question 1. We respectfully request AHRQ to reconsider including these outcomes in this review.	These data are out of scope for this review.
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Placebo Response We agree with AHRQ that future controlled studies evaluating treatment for RLS need to be adequately blinded. However, as written and within the context of the information in the ES and Discussion, we worry that the statement might imply that the previously conducted trials were not adequately blinded. We believe that AHRQ meant to highlight the importance of considering the placebo response when designing clinical trials in this patient population.	We do not believe our writing leads to these implications. No change
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Adverse Events On page 23 of the draft report, long-term augmentation was generally categorized as common with dopaminergic treatment. However, as shown in Table 10 the range of augmentation incidence was quite variable from study to study and it appears that the rates associated with the dopamine agonists were lower than those observed with L-dopa. Further, as stated on ES-17 and pg.49 of the draft report, levodopa is no longer widely used for treatment of RLS. Thus we respectfully request AHRQ modify the statement "In general, augmentation was common across dopaminergic or dopamine agonist drugs" to read " In general, augmentation was common across dopaminergic or dopamine agonist drugs; however, rates were variable from study to study and appeared to be lower with dopamine agonists than L-dopa.	Modification made
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		UCB requests that AHRQ consider including within the discussion section an acknowledgement of other metanalyses that have been conducted. Scholz 2011 – dopamine agonists for Cochrane; Scholz 2011 – levodopa for Cochrane; Zintzaras 2010	References included
Reviewer #8 Kimberly Moran, PhD Medical Director, CNS UCB		Various technical corrections identified on page 8.	Addressed