BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"What pharmacological or non-pharmacological interventions are beneficial in managing restless leg syndrome?"

Clarification of question using *PICO* structure

Patients:	*Adults with restless leg syndrome (in mental health services).*
Intervention:	*Pharmacological interventions for restless leg syndrome.*
Comparator:	*Any other intervention/treatment as usual.*
Outcome:	*Any patient outcomes.*

Plain language summary

The research evidence presented suggests that dopamine medications are recommended as effective pharmacological treatments for Restless Leg Syndrome (RLS). However larger scale studies need to be conducted to establish which dopamine antagonist may be most effective. Further studies also need to be done specifically with adults within a mental health services population.

Clinical and research implications

There is evidence to suggest that the use of dopamine agonists can be recommended for the treatment of restless leg syndrome (RLS). This recommendation is based on three well-conducted systematic reviews (SR) that evaluated a number of good quality trials comparing dopamine agonists with placebo. No definite implications, however, can be made regarding which dopamine agonist may be most effective, given the lack of large scale head-to-head trials. The evidence was in the general population and not specific to people with mental health conditions.

For further research, the SR authors stated that; more trials evaluating iron and opioid therapy are needed; and more research into the comparative effectiveness and harms of other commonly used treatments, particularly those without FDA approval is also needed. The SR of pramipexole recommended that studies with longer-term follow-up and comparing pramipexole with other dopamine agonists, anticonvulsants and levodopa are needed. The SR of iron therapy recommended that more research is needed into the effects of iron therapy, particularly the best route of delivery, in people with RLS.

What does the evidence say?

Number of included studies/reviews (number of participants)

Four systematic reviews (SRs) met the inclusion criteria for this BEST summary. One (Hornyak et al. 2013) was an update of two previous Cochrane Reviews (Scholz et al 2011a; 2011b, see the results table).

Main Findings

Dopaminergic agents:

Three SRs evaluated dopaminergic agents for the treatment of restless leg syndrome (Hornyak et al. 2013; Wilt et al. 2013; Zhang et al. 2013). The SR by Hornyak et al. included 62 RCTs of which 38 evaluated dopamine agonists, 4 evaluated levodopa, 13 evaluated anticonvulsants, 6 evaluated iron, and one trial evaluated oxycodone. Results from 38 placebo controlled trials, showed that treatment with dopamine agonists was found to significantly reduce mean International Restless-Leg Syndrome Scale (IRLS) scores, decrease periodic limb movements, and improve self-rated quality of sleep, Clinical Global Impression (CGI) Improvement, and quality of life. Patients were however, significantly more likely to drop out and experience adverse events with treatment.

Three trials compared a dopamine agonist (cabergoline, pergolide, pramipexole) to levodopa, and showed superiority of dopamine agonists on the IRLS (cabergoline, pramipexole) and quality of life (cabergoline). The number of patients experiencing adverse events was higher during treatment with cabergoline and pergolide compared to levodopa. No significant differences between dopamine agonists and levodopa were found for PLMI, dropout rates due to adverse events, CGI, self-rated quality of sleep and daytime tiredness. One trial compared lisuride with ropinirole and found significant improvements in RLS severity and quality of life with lisuride.

The SR by Wilt et al (2013) also evaluated dopamine agonists (16 trials), cabergoline (3 trials) as well as calcium channel alpha-2-delta ligands (7 trials), iron (1 trial) and bupropion (1 trial). Dopamine agonists resulted in significantly more participants with an IRLS response, a CGI response, a significantly larger reduction in IRLS score, improved sleep quality and quality of life compared with placebo. Two small trials also found significant improvements in IRLS score, one favouring cabergoline over levodopa, and one favouring pramipexole over levodopa-benserazide. For calcium channel alpha-2-delta ligands, seven trials showed that they were superior to placebo for IRLS response, CGI response, mean reduction in IRLS score and sleep quality. There were no significant differences between bupropion and placebo.

The third SR (Zhang et al, 2013) only evaluated pramipexole and included six placebo-controlled trials, four evaluated a flexible dose and two evaluated a fixed pramipexole dose. Pramipexole significantly reduced IRLS scores, improved sleep quality, and increased the number of IRLS responders as well as CGI and PGI (Patient Global Impressions) responders. More nausea and fatigue were experienced with pramipexole compared with placebo.

Iron:

One SR evaluated the effectiveness of iron therapy and included six RCTs (Trotti et al 2012). There were no significant differences between iron and placebo using the IRLS severity scale (4 trials). However, a fifth trial did find iron therapy to be beneficial ($p = 0.01$). Quality of life was improved with iron compared with placebo in some studies but not others. No significant differences in periodic limb movements were found between groups (2 studies). Objective sleep quality, subjective sleep quality, daytime functioning and adverse events were also not significantly different between treatment groups. One study in subjects with end stage renal disease did show a benefit of iron therapy.

Two other SRs also included trials of iron therapy. Hornyak et al. 2013 included six trials comparing iron therapy with placebo and reported a significant reduction in IRLS scores and an improvement in quality of life, but no difference in CGI, PMLI or self-rated sleep quality between iron therapy and placebo. However more people experienced an adverse event with iron therapy. Wilt et al. 2013 included one small trial of iron which found a significant improvement in IRLS scores after 28 days compared with placebo.

Authors Conclusions

The most comprehensive review of dopaminergic and non-dopaminergic treatments concluded that as well as dopamine agonists showing efficacy, other treatments such as gabapentin, gabapentin enacarbil and pregabalin also showed efficacy and may be well-tolerated alternatives in the treatment of RLS (Hornyak et al. 2013). Another review of pharmacologic therapy concluded that dopamine agonists and calcium channel alpha-2-delta ligands improved RLS symptoms, sleep outcomes and quality of life (Wilt et al. 2013). However this was based on short-term evidence from trials in patients with long-term moderate, high or very severe symptoms. The third review of pramipexole concluded that pramipexole had a positive effect on RLS symptoms and sleep quality but increased fatigue and nausea compared with placebo (Zhang et al. 2013).

Trotti et al (2012) concluded that there was insufficient evidence to determine whether iron therapy is beneficial in the treatment of RLS.

Reliability of conclusions/Strength of evidence

All three of the reviews that evaluated dopaminergic agents were methodologically well conducted (Hornyak et al. 2013, Wilt et al. 2013 and Zhang et al. 2013) and the trials included in them were also The only concern was that it was unclear if all of the review methods were performed by two reviewers as some aspects were clear but others were not reported (e.g. in study selection). The results of these reviews are likely to be reliable. The review of iron therapy (Trotti et al 2012) was also well-conducted, and the authors' cautious conclusions are likely to be reliable.

What do guidelines say?

There are no UK guidelines specifically about treating restless leg syndrome, other than as symptoms experienced as a result of another diagnosis. These were not considered relevant to this review.

Date question originally received: 09/11/12
Updated searches conducted: 14/12/15
Date answer completed: 23/12/15

References

Systematic reviews

1. Hornyak, M., Scholz, H., Kohnen, R., Bengel, J., Kassubek, J., & Trenkwalder, C. (2014). What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. *Sleep medicine reviews*, 18(2), 153-164.

2. Scholz. H., Trenkwalder, C., Kohnen, R., Kriston, L., Riemann, D. and Hornyak, M. Levodopa for the treatment of restless legs syndrome. *Cochrane Database of Systematic Reviews (*2011), Issue 2.

3. Scholz, H., Trenkwalder, C., Kohnen, R., Kriston, L., Riemann, D. and Hornyak, M. Dopamine agonists for the treatment of restless legs syndrome. *Cochrane Database of Systematic Reviews (*2011), Issue 3

4. Trotti LM, Bhadriraju S, Becker LA. Iron for restless legs syndrome. *Cochrane Database of Systematic Reviews (*2012), Issue 5.

5. Wilt, T. J., MacDonald, R., Ouellette, J., Khawaja, I. S., Rutks, I., Butler, M., & Fink, H. A. (2013). Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis. *JAMA internal medicine*, 173(7), 496-505.

6. Zhang, W., Wang, Y., Cong, S. Y., Nao, J. F., Feng, J., & Bi, G. R. (2013). Efficacy and tolerability of pramipexole for the treatment of primary restless leg syndrome: a meta-analysis of randomized placebo-controlled trials. *Neuropsychiatric disease and treatment*, 9, 1035.

Guidelines

Neither NICE or SIGN guidelines comment of pharmacological treatments for restless leg syndrome.

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Hornyak et. al. (2014)	31/01/2012	***Population*:** Adults between the age of 48 – 68 years with idiopathic Restless Leg Syndrome (RLS) ***Intervention*:** - Dopamine agonists; (38 trials: cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine, sumanirole). - Levodopa (4 trials). - Anticonvulsants (13 trials: gabapentin, gabapentin enacarbil, pregabalin, levetiracetam, and topiramate) - Oxycodone (1 trial), - Iron (6 trials) ***Comparator*:** - Placebo (58 trials) - Active controls (4 trials: levodopa; lisuride) ***Outcome*:** Change of RLS severity; International Restless-Leg Syndrome Scale (IRLS) Clinical global impression improvement (CGI)	62 RCT's (15 crossover, 47 parallel group trials (N=9596))	58 placebo-controlled and 4 active-controlled trials were included. The majority of trials were considered to be at low risk of bias, and most clearly reported randomisation and blinding methods. ***Comparisons with placebo:*** Most treatments had clinically and statistically significant improvements in RLS severity, with there being similar effects for dopamine agonists, anticonvulsants and iron. Mean reductions in IRLS score ranged from -5.47% (dopamine) to -4.59 (iron). Significant improvements in overall improvement (CGI) were seen with dopamine (RR 1.43 (95% CI 1.34 to 1.52) and anticonvulsants (RR 1.72, 95% CI 1.45 to 2.04) but not iron. Most treatments also improved leg movements (PLMI) with there being larger improvements with oxycodone (-34.46/hr), levodopa (mean -26.01/hr) and	Low Most aspects of the review (inclusion criteria, searching, risk of bias assessment and synthesis) used appropriate methods. It was unclear if two reviewers performed the study selection, data extraction and bias assessment but given that they followed Cochrane Collaboration methods it was likely this was

		Periodic limb movements index (PLMI) Self-rated quality of sleep Depression and anxiety Quality of life Adverse events ***Study design*:** Randomsed controlled trials		dopamine (mean -22.5/hr). Significant improvements were also seen for most treatments in sleep quality (not iron), quality of life, and depression. ***Comparisons with active control:*** Three trials compared dopamine agonists with levodopa and found significantly greater improvements in RLS severity (mean difference [MD] -5.25, 95% CI -8.40 to -2.10); and CGI (RR 1.29, 95% CI 1.14 to 2.47) and quality of life (MD – 0.43, 95% CI -0.65 to -0.20) with cabergoline. There were no significant differences in quality of sleep. One trial compared two dopamine agonists and found significant improvements in RLS severity (MD -3.00, 95% CI -5.70 to -0.30) and quality of life (MD – 0.33, 95% CI -0.61 to -0.06), but not CGI, with lisuride compared with ropinirole.	done.
Scholz et al (2011a) (Dopamine Agonists)	18/01/2011	***Population**:* Adults with a diagnosis of primary or secondary RLS, according to diagnostic criteria IRLSSG. ***Intervention:*** Any dose or regimen of a dopamine agonist by any route (oral, intravenous or transdermal) for a minimum of seven days.	38 RCTs (32 parallel and 6 cross-over) were included in the analysis. (N= 7365)	35 placebo-controlled and 3 active controlled trials were included in the review. The trial methods were adequately reported in the majority of studies. Compared with placebo, treatment with dopamine agonists significantly reduced	Low

		Comparator: Placebo or other comparative drugs. ***Outcome:*** Primary outcomes; number of PLM (periodic leg movement) per total sleep time, sleep efficiency, number of dropouts due to adverse events, Secondary outcomes; Clinical Global Impressions-Improvement Scale (CGI-I), self-rated quality of sleep, disease-specific quality of life. ***Study Design*:** Randomised controlled trials.		mean IRLS (−5.7 points (95% confidence interval−6.7 to −4.7, 30 trials), decreased periodic limb movements in sleep per hour of sleep (PLMS-Index; PLMSI) −22.4/h (95% CI −27.8 to −16.9, 15 trials), improved self-rated quality of sleep (SMD 0.40 (95% CI 0.33 to 0.47, 22 trials), improved CGI-I (RR 1.44, 95% CI 1.34 to 1.54, 27 trials), and improved disease specific quality of life (0.34 (95% CI 0.23 to 0.44, 17 trials). Patients were more likely to drop out (OR 1.82, 95% CI 1.35 to 2.45) and experienced more adverse events under dopamine agonist treatment than with placebo (OR 1.82, 95% CI 1.59 to 2.08, 33 trials). Three trials comparing a dopamine agonist (cabergoline, pergolide, pramipexole) to levodopa showed superiority of dopamine agonists on the IRLS (cabergoline, pramipexole) (MD −5.3, 95% CI −8.4 to −2.1, 2 trials) and with regard to quality of life (cabergoline) (MD −5.5, 95% CI −8.4 to −2.7, 1 trial). The number of patients experiencing adverse events was higher during treatment with cabergoline and pergolide compared to levodopa. No treatment difference between	

				dopamine agonists and levodopa was seen on the following outcomes: PLMSI, dropout rates due to adverse events, CGI-I, self-rated quality of sleep, and daytime tiredness.	
Scholz et al (2011b) (Levodopa)	12/2008	***Population****:* Adults with a diagnosis of primary or secondary RLS, according to diagnostic criteria IRLSSG. ***Intervention:*** Levodopa treatment ***Comparator:*** Placebo or other active treatment for at least seven days. ***Outcome:*** Symptom severity, self-rated sleep parameters, quality of life and safety parameters. ***Study Design*****:** Randomised controlled trials.	9 RCTs (8 cross-over and 1 parallel) were included in the analysis. (N= 521)	6 placebo controlled trials and 3 active controlled trials were included in the review. The trials appear to have a low or unclear risk of bias. Compared with placebo, treatment with levodopa significantly reduced symptom severity (mean difference (MD) -1.34, 95% confidence interval (CI) -2.18 to -0.5, P = 0.002, 2 trials), improved periodic limb movements in sleep per hour of sleep (PLMS-Index; PLMSI) improved by -26.28/h (95% CI -30.53 to -22.02, P < 0.00001, 5 trials), changed the CGI-I more (MD -1.25, 95% CI -1.89 to -0.62, P = 0.0001, 2 trials), improved sleep quality (standardised mean difference (SMD) 0.92, 95% CI 0.52 to 1.33, P < 0.00001, 2 trials), and improved QoL (50 mm Visual Analogue Scales) improved by 3.23 (95% CI 1.64 to 4.82, P < 0.0001). Patients receiving levodopa did not significantly differ from patients receiving placebo with regard to total sleep time (4 trials). Few patients dropped out of	Low

				treatment (3 of 218 patients) but more levodopa treated patients experienced adverse events than with placebo (odds ratio 2.61, 95% CI 1.35 to 5.04, P = 0.004). Two trials showed improvement with dopamine agonists (cabergoline and pramipexole) compared with levodopa the IRLS (MD 5.25, 95% CI 2.10 to 8.40, P =0.001, 2 trials), CGI-I (MD 0.62, 95% CI 0.37 to 0.87, P < 0.00001, 1 trial), and QoL (MD 5.54, 95% CI 2.65 to 8.43, P = 0.0002, 1 trial). No significant difference between treatments was observed for change in periodic limb movements per time in bed, number of drop-outs due to adverse events, total sleep time, or self-rated quality of sleep.	
Trotti et al (2012)	04/2011	***Population:*** Adult patients who had a diagnosis of RLS according to expert clinical interview or to explicit diagnostic criteria. Including pregnant women and patients with renal disease. ***Intervention:*** Therapy with any dose or regimen or oral or parenteral iron-containing compounds. ***Comparator:*** Placebo, other drugs or no intervention. ***Outcome:*** Primary outcome; restlessness or	6 RCTs were included in the analysis. (N=192)	The authors stated that the quality of included trials was variable. There was no significant difference between iron treatment compared with placebo using the IRLS severity scale (mean difference -3.79, 95% CI: -7.68 to 0.10, p = 0.06, 4 trials). However, a 5th trial did find iron therapy to be beneficial (median decrease of 3 points in the iron group and no change in the placebo group on a 10 point scale of RLS	Low

		unpleasantness experienced subjectively, Secondary outcomes; quality of life, patient satisfaction with treatment, number of periodic limb movements per hour of sleep, sleep quality, daytime functioning, decreased occurrence augmentation. ***Study Design*****:** Randomised and non-randomised controlled trials.		symptoms, p = 0.01). Quality of life was improved in the iron group relative to placebo in some studies but not others. Changes in periodic limb movements were not different between groups (measured in two studies). Objective sleep quality, subjective sleep quality and daytime functioning were not different between treatment groups in the studies that assessed them. The single study of subjects with end stage renal disease did show a benefit of therapy. Most trials did not require subjects to have co-morbid iron deficiency and several excluded patients with severe anemia. The single study that was limited to iron deficient subjects did not show clear benefit of iron supplementation on RLS symptoms. There was no clear superiority of oral or intravenous delivery of iron. Iron therapy did not result in significantly more side effects than placebo (RR 1.39, 95% CI 0.85 to 2.27).	
Wilt et. al. (2013)	June 2012	***Population*****:** Adults with newly diagnosed with Restless Leg Syndrome, as well as those who had and had not received prior RLS treatment. ***Intervention*****:**	29 RCTs (approx. N= 6003)	Overall the evidence was considered to be low risk of bias. For dopamine agonist studies the durations were 28 weeks or less, the mean participant age was 55 years and 65% were women. The mean duration of RLS ranged from 2 to 17 years and most trials	Low Most aspects of the review (inclusion criteria, searching, risk of bias

		- Dopamine antagonists (16 trials: Pramipexole, Ropinirole and Rotigotine) - Cabergoline (3 trials: an ergot-derived dopamine agonist) - Calcium channel alpha-2-delta ligands (7 trials: including the prodrug gabapentin enacarbil,30-33 pregabalin,34,35 or gabapentin) - Intravenous iron (1 trial) - Bupropion (1 trial) ***Comparator*:** Placebo (18 trials); active controls (2 trials: levodopa, dual release levodopa-benserazide) ***Outcome*:** RLS response (≥ 50% reduction in International Restless-Leg Syndrome Scale (IRLS) score) Mean change in IRLS score Clinical global impression improvement (CGI) response (much to very much improved) Periodic limb movements index (PLMI) Self-rated quality of sleep Quality of life Adverse events ***Study design*:** Randomised controlled trials and comparative effectiveness studies		included those with “high to moderate” or “severe” symptoms at baseline (the overall mean baseline IRLS score was 25.1). More participants had an IRLS response (RR 1.60, 95% CI 1.38 to 1.86) and CGI response (RR 1.45, 95% CI 1.36 to 1.55) with dopamine agonists compared with placebo. There was no difference between pramipexole and rotigotine. Dopamine treatment significantly reduced IRLS scores compared with placebo (MD -4.56, 95% CI -5.42 to -3.70) with rotigotine having a greater improvement than pramipexole or ropinirole. Dopamine treatment also significantly improved sleep quality and quality of life more than placebo, with similar effects for the different drugs. One trial found a significant improvement in IRLS score with cabergoline compared with levodopa, and another small cross-over trial found a greater improvement with pramipexole compared with levodopa-benserazide. For calcium channel alpha-2-delta ligands, all trials lasted less than 12 weeks, mean age was 51 years and 60% of participants were	assessment and synthesis) used appropriate methods. It was unclear if two reviewers selected the studies, although data extraction and quality assessment were performed by two reviewers.

				women, the mean baseline IRLS score was 24 and mean disease duration was 12 years. Calcium channel ligands were superior to placebo for IRLS response (RR 1.66, 95% CI 1.33 to 2.09), CGI response (RR 1.60, 95% CI 1.21 to 2.10) mean change in IRLS score and sleep quality. One small trial of iron found it significantly improved IRLS scores after 28 days compared with placebo, and another small trial found no significant difference between bupropion and placebo.	
Zhang et. al. 2013	2012	***Population*****:** Adults who fulfilled the essential diagnosis criteria of International Restless Legs Syndrome Study Group (IRLSSG), with baseline scores of at least 15 on the International RLS Study Group Rating Scale (IRLS). ***Intervention*****:** Pramipexole. ***Comparator*****:** Placebo. ***Outcome*****:** - Primary outcome; change in RLS symptom severity (International Restless-Leg Syndrome Scale (IRLS))	6 RCTs (N= 1506)	The overall risk of bias of the included trials was low, although three were unclear for randomisation and allocation concealment methods. Trial durations ranged from three to 12 weeks, four used a flexible dose (0.125 to 0.75 mg/day) and two had a fixed dose of pramipexole. Mean ages ranged from 52 to 61 years, and mean baseline IRLS scores from 22.7 to 25.1. Pramipexole significantly reduced IRLS scores (MD -5.96, 95% CI -7.79 to -4.41) and increased the number of IRLS responders (OR 2.51, 95% CI 2.00 to 3.16), CGI responders (OR 3.13, 95% CI 2.48 to 3.95)	Low Most aspects of the review (inclusion criteria, searching, risk of bias assessment and synthesis) used appropriate methods. It was unclear if two reviewers selected the studies and performed the quality assessment.

		Clinical global impressions-improvement (CGI) and patient global impressions (PGI) response Self-rated sleep quality Adverse events ***Study design*:** Double-blind, randomised, placebo-controlled trials.		and PGI responders (OR 2.80, 95% CI 1.90 to 4.10) compared with placebo. It also significantly improved self-rated sleep quality more than placebo (MD -0.48, 95% CI -0.61 to -0.35; 4 trials). Due to substantial heterogeneity for IRLS and PGI outcomes subgroup analyses were performed but did not show any differences with respect to race, medication period, or dose. More nausea and fatigue were experienced by pramipexole patients.	

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Hornyak et. al. (2014)	☺	☺	?	☺	☺
Scholz et al (2011a) (Dopamine Agonists)	☺	☺	☺	☺	☺
Scholz et al (2011b) (Levodopa)	☺	☺	☺	☺	☺
Trotti et al (2012)	☺	☺	☺	☺	☺
Wilt et. al. (2013)	☺	☺	?	☺	☺
Zhang et. al. 2013	☺	☺	?	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search details

Source	Search Strategy		Number of hits	Relevant evidence identified
SRs and Guidelines				
NICE & SIGN	Restless Leg Syndrome		1	0
Embase	1 akath*.ab,ti.	2456	176	
	2 (restless adj2 leg*).ab,ti.	5661		
	3 RLS.ab,ti.	4684		
	4 (periodic adj2 (limb or leg) adj2 movement).ab,ti.	816		
	5 Ekbom*.ab,ti.	309		
	6 1 or 2 or 3 or 4 or 5	10184		
	7-36 ***Systematic Review Filter applied***	511883		
	37 6 and 36	449		
	38 limit 37 to yr="2012 -Current"	176		
Medline	1 akath*.ab,ti.	1808	301	
	2 (restless adj2 leg*).ab,ti.	3543		
	3 RLS.ab,ti.	2980		
	4 (periodic adj2 (limb or leg) adj2 movement).ab,ti.	479		
	5 Ekbom*.ab,ti.	183		

	6 1 or 2 or 3 or 4 or 5 6734 7-26 **Systematic Review Filter applied** 932491 27 6 and 26 760 28 limit 27 to yr="2012 -Current" 301		
PsycINFO	1 akath*.ab,ti. 1206 2 (restless adj2 leg*).ab,ti. 1312 3 RLS.ab,ti. 1024 4 (periodic adj2 (limb or leg) adj2 movement).ab,ti. 225 5 Ekbom*.ab,ti. 62 6 1 or 2 or 3 or 4 or 5 2785 7 (Cochrane$ or review or overview or (review adj2 literature) or (synthes$ adj3 (literature$ or research or studies or data))).ti. 108229 8 (meta analysis or literature review or systematic review).md. 112538 9 (pooled analys$ or ((data adj2 pool$) and studies) or ((hand or manual$ or database$ or computer$ or electronic$) adj2 search$) or ((electronic$ or bibliographic$) adj2 (database$ or data base$))).ab,ti. 9242 10 exp Meta Analysis/ 3492 11 7 or 8 or 9 or 10 194147 12 (comment reply or editorial or letter or review book or review media).dt. 227436 13 (electronic collection or dissertation abstract or encyclopedia).pt. 301742	98	

	14	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ab,sh,ti.	206057		
	15	12 or 13 or 14	695523		
	16	11 not 15	121780		
	17	6 and 16	276		
	18	limit 17 to yr="2012 -Current"	98		
Primary studies					
Medline	1	akath*.ab,ti.	1808	189	
	2	(restless adj2 leg*).ab,ti.	3543		
	3	RLS.ab,ti.	2980		
	4	(periodic adj2 (limb or leg) adj2 movement).ab,ti.	479		
	5	Ekbom*.ab,ti.	183		
	6	1 or 2 or 3 or 4 or 5	6734		
	7	"randomized controlled trial".pt.	418428		
	8	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	904606		
	9	(retraction of publication or retracted publication).pt.	8504		
	10	7 or 8 or 9	1001014		
	11	(animals not humans).sh.	4063091		
	12	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.	3625923		

	13 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.	57145		
	14 10 not (11 or 12 or 13)	744521		
	15 6 and 14	757		
	16 limit 15 to yr="2012 -Current"	189		
PsycINFO	1 akath*.ab,ti.	1206	130	
	2 (restless adj2 leg*).ab,ti.	1312		
	3 RLS.ab,ti.	1024		
	4 (periodic adj2 (limb or leg) adj2 movement).ab,ti.	225		
	5 Ekbom*.ab,ti.	62		
	6 1 or 2 or 3 or 4 or 5	2785		
	7 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	148697		
	8 (animals not humans).sh.	3339		
	9 exp Clinical Trials/	9204		
	10 random*.mp.	132655		
	11 9 not 10	3949		
	12 7 not (8 or 11)	148129		
	13 6 and 12	474		
	14 limit 13 to yr="2012 -Current"	130		
EMBASE	1 akath*.ab,ti.	2456	435	

	2	(restless adj2 leg*).ab,ti.	5661		
	3	RLS.ab,ti.	4684		
	4	(periodic adj2 (limb or leg) adj2 movement).ab,ti.	816		
	5	Ekbom*.ab,ti.	309		
	6	1 or 2 or 3 or 4 or 5	10184		
	7	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	1158614		
	8	RETRACTED ARTICLE/	7926		
	9	7 or 8	1166351		
	10	(animal$ not human$).sh,hw.	3977758		
	11	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/	4305271		
	12	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/	68724		
	13	9 not (10 or 11 or 12)	897436		
	14	6 and 13	1265		
	15	limit 14 to yr="2012 -Current"	435		

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