SUPPLEMENTAL MATERIALS

Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

All Literature Search Terms

("Willis-Ekbom disease"[All Fields] OR "Ekbom syndrome"[All Fields] OR (hereditary[All Fields] AND acromelalgia[All Fields]) OR "restless legs"[All Fields] OR "jimmy legs"[All Fields] OR "jitter legs"[All Fields]] OR "nocturnal myoclonus"[All Fields]] OR "restless legs syndrome"[MeSH Terms]] OR "restless legs syndrome"[All Fields]] OR "myoclonus Syndrome"[All Fields]] OR "Myoclonus Syndrome"[All Fields]] OR "Nocturnal Myoclonus Syndrome"[All Fields]] OR "Periodic Leg Movements"[All Fields]] AND English[All Fields] Filters applied: Clinical Study, Clinical Trial, Controlled Clinical Trial, Evaluation Study, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans.

Exclusion Criteria

Exclusion criteria are applied during the abstract review of all retrieved publications. Studies that meet <u>any</u> of the exclusion criteria are rejected from the systematic review.

- A. Publication type
 - a. Book and book chapters
 - b. Conference abstracts
 - c. Dissertations
 - d. Editorials
 - e. Letters to the editor
 - f. Methods papers
 - g. Review papers
 - h. Sleep fragment or sleep medicine pearls
 - i. Case reports
- B. Study type
 - a. animal research
- C. Language
 - a. non-English
- D. Patients
 - a. Did not undergo treatment for RLS or PLMD
 - b. For RCTs: # Patients less than or equal to 4 in each arm for data reported at the end of study.
 - c. For observational studies and case series: # patients less than 5

Inclusion Criteria

Inclusion criteria are applied during the full publication review of all publications that were not rejected during the abstract review. Studies that **meet all inclusion criteria will be accepted as evidence to use in the systematic review.**

- A. Outcomes of interest (must meet at least 1)
 - 1. Disease Severity

- 2. Sleep Quality
- 3. Quality of Life
- 4. Sleep Latency
- 5. Wake After Sleep Onset
- 6. Excessive Daytime Sleepiness
- 7. Fatigue
- 8. Work/School Performance/Attendance
- 9. Resolution of ADHD symptoms
- 10. PLM Frequency
- 11. Unwanted Side Effects

B. Publication type

- 1. RCTs: compares interventions vs. placebo, withdrawal studies.
- 2. Observational studies: longitudinally examines the effects of intervention, withdrawal studies.

C. Patients

- 1. Adults with RLS
- 2. Special adult populations with comorbid RLS
- 3. Adults with PLMD
- 4. Pediatric populations with RLS
- 5. Special pediatric populations with comorbid RLS
- 6. Pediatric populations with PLMD

D. Interventions (must include at least 1)

- 1. Pharmacological:
 - a. dopamine agonists
 - b. dopaminergic agents(carbidopa/levodopa)
 - c. anticonvulsants
 - d. opioids
 - e. adrenergic agonists
 - f. hypnotics (benzodiazepines and non-benzodiazepines)
 - g. iron supplements (oral and infusion)
 - h. muscarinic antagonists
 - i. cannabis derivatives or hybrids
 - beta blockers
 - k. supplementation with:
 - i. magnesium
 - ii. folate
 - iii. vitamins (C, D or E)
 - iv. melatonin
 - v. valerian root extract
 - vi. quinine
- 2. Surgical/procedural:
 - a. subthalamic nucleus and other deep brain stimulation
 - b. hemodialysis
 - c. nerve decompression surgery
 - d. endovenous laser ablation (ELA)
 - e. botox treatment

- f. physical treatment methods:
 - i. spinal cord stimulation
 - ii. transcranial direct current or magnetic stimulation
 - iii. acupuncture.
- 3. Non-pharmacological:
 - a. Sleep Hygiene
 - b. moderate-intensity exercise or yoga
 - c. avoidance of excessive exercise in the afternoon
 - d. massage
 - e. hypnosis
 - f. cognitive behavioral therapy
 - g. meditation/music/ prayer
 - h. mental activity
 - i. sexual activity
 - j. compression devices (e.g., pneumatics)
 - k. vibrating pads
 - I. direct electrical stimulation of the legs
 - m. infra-red light spectroscopy

Abbreviations:

- AASM -- American Academy of Sleep Medicine
- CST Clinical significance threshold
- CGI Clinical Global Impressions Scale
- CGI-I Clinical Global Impressions-Improvement Scale
- COI conflict of interest
- CPG Clinical practice guideline
- DBS Deep brain stimulation
- DLB Dementia with Lewy bodies
- EMG -- Electromyography
- ESS Epworth Sleepiness Scale
- FDA U.S. Food and Drug Administration
- GRADE Grading of Recommendations, Assessment, Development and Evaluation
- KESS Korean Epworth Sleepiness Scale
- MFQ Mayo Fluctuations Scale
- MMSE -- Mini-Mental State Examination
- NPI Neuropsychiatric Inventory
- PAP Positive airway pressure
- PICO Patient, intervention, comparator, outcome
- PSG Polysomnography
- PSQI Pittsburgh sleep quality index
- RCT Randomized controlled trial
- REM Rapid eye movement
- RLS Restless leg syndrome
- SD Standard deviation
- SF-36 Short form 36 health questionnaire
- SMD Standardized mean-difference
- SR Systematic review
- TF Task force

UPDRS – Unified Parkinson's Disease Rating Scale



PICO 1: Adults with RLS

Gabapentin Enacarbil

Summary of Findings (GRADE)

Table S1 Gabapentin enacarbil in adults with RLS

References: Garcia-Borreguero 2019, Innoue 2013, Kushida 2009 Neuro, Kushida 2009 SLEEP, Lee 2011, Walters 2009, Winkelman 2011, Lal 2011, Bogan 2010, Innoue 2012,

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Gabapentin Enacarbil vs Placebo or Control	
Disease severity [IRLS]	⊕⊕⊕⊕ HIGH	The mean difference in the gabapentin enacarbil group was 4.9 points lower (6.8 lower to 3 lower) compared to control	1511 (7 RCTs)
Quality of life [RLS QOL Abetz]	⊕⊕⊕⊜ MODERATE ^a	The mean difference in the gabapentin enacarbil group was 7.3 points higher (2.8 higher to 11.8 higher) compared to control	221 (1 RCT)
Sleep Quality [MOS sleep disturbance]	⊕⊕⊕⊜ MODERATE ^b	The standardized mean difference in the gabapentin enacarbil group was 0.5 SD lower (0.95 lower to 0.04 lower) compared to control	78 (1 RCT)
Sleep quality [MOS sleep adequacy]	⊕⊕⊕⊜ MODERATE ^b	The standardized mean difference in the gabapentin enacarbil group was 0.66 SD higher (0.2 higher to 1.1 higher) compared to control	78 (1 RCT)
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATE ^a	48 per 1,000 (26 to 87) in the gabapentin enacarbil group compared to 22 per 1,000 in the control group Risk Ratio = 2.2 (1.2 to 4.0)	1729 (8 RCTs)
Adverse event (somnolence)	⊕⊕⊕ ні с н	249 per 1,000 (139 to 439) in the gabapentin enacarbil group compared to 73 per 1,000 in the control group Risk Ratio = 3.4 (1.9 to 6.0)	1733 (8 RCTs)
Adverse event (dizziness)	⊕⊕⊕⊕ HIGH	191 per 1,000 (129 to 283) in the gabapentin enacarbil group compared to 42 per 1,000 in the control group Risk Ratio = 4.6 (3.1 to 6.8)	1733 (8 RCTs)

small sample size

Critical Outcomes

Figure S1. Gabapentin enacarbil vs placebo (IRLS) [CST =-3.0 pts] RCTs1

	Gabapent	in enaca	rbil	Pla	cebo)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Garcia-Borreguero 2019	12.9	6.5	39	17.7	7.8	39	12.4%	-4.80 [-7.99, -1.61]	
Innoue 2013 (CMRO)	-10.9	8	352	-9	8	116	16.4%	-1.90 [-3.58, -0.22]	
Kushida 2009 (Neurology)	-13.2	9.2	112	-8.8	8.6	108	14.6%	-4.40 [-6.75, -2.05]	
Kushida 2009 (SLEEP)	-12.1	6.5	34	-1.9	6.3	34	12.7%	-10.20 [-13.24, -7.16]	
Lee 2011	-13.4	8.6	225	-9.8	7.7	96	15.8%	-3.60 [-5.51, -1.69]	
Walters 2009	-12.8	7	61	-8.9	7.7	33	12.4%	-3.90 [-7.06, -0.74]	
Winkelman 2011	-15	8.3	131	-8.4	8.2	131	15.6%	-6.60 [-8.60, -4.60]	
Total (95% CI)			954			557	100.0%	-4.93 [-6.85, -3.02]	◆
Heterogeneity: Tau ² = 5.07; C	$hi^2 = 27.96.1$	df = 6 (P ·	< 0.000	1); l²=	79%				
Test for overall effect: Z = 5.0									-20 -10 0 10 20
		•							Favors gabapentin ena. Favors placebo

^{1.} Change scores were not reported in Garcia-Borreguero 2019 so posttreatment values were compared. Data from both drug naïve and drug-treated groups were pooled.

Figure S2. Gabapentin enacarbil pre- vs posttreatment (IRLS) [CST =-3.0 pts] Observational¹

	Postt	reatme	ent	Pretr	eatme	ent		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
Inoue 2012	6.3	6.9	132	24.4	4.6	132	55.3%	-18.10 [-19.51, -16.69]	-			
Raissi 2017	16.8	11.7	16	22.7	11.1	16	44.7%	-5.90 [-13.80, 2.00]				
Total (95% CI)			148			148	100.0%	-12.64 [-24.53, -0.76]				
Heterogeneity: Tau² = Test for overall effect:				= 1 (P =	0.003); l² = 8	9%		-20 -10 0 10 20			

^{1.} SEs reported in study were converted to SDs.

Figure S3. Gabapentin enacarbil vs placebo (CGI-I responders) [CST = +15%] RCTs

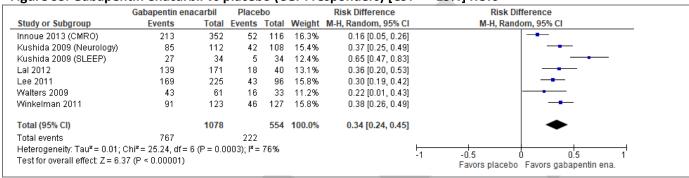


Figure S4. Gabapentin enacarbil pre- vs posttreatment (Disease severity, CGI-I responders) [CST = +15%] Observational

	Posttreat	ment	Pretreat	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bogan 2010	248	311	0	311	53.3%	0.80 [0.75, 0.84]	•
Inoue 2012	115	132	0	132	46.7%	0.87 [0.81, 0.93]	-
Total (95% CI)		443		443	100.0%	0.83 [0.76, 0.90]	•
Total events	363		0				
Heterogeneity: Tau²: Test for overall effect				0.05); I²	= 75%		-1 -0.5 0 0.5 1 pretreatment posttreatment

Figure S5. Gabapentin enacarbil vs placebo (PGI responders) [CST= +15%] RCTs

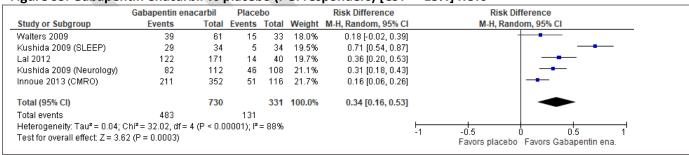


Figure S6. Gabapentin enacarbil pre- vs posttreatment (Disease severity, PGI-I responders) [CST = +15%] Observational

	Posttreat	ment	Pretreat	ment		Risk Difference		Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Bogan 2010	245	308	0	308	53.0%	0.80 [0.75, 0.84]			-
Inoue 2012	115	132	0	132	47.0%	0.87 [0.81, 0.93]			•
Total (95% CI)		440		440	100.0%	0.83 [0.76, 0.91]			•
Total events	360		0						
Heterogeneity: Tau² : Test for overall effect			•	0.04); l²	= 76%		-1	-0.5 0 C).5 1 ent

Figure S7. Gabapentin enacarbil vs placebo (Disease severity, CGI-S) [CST= -0.5 pts] RCT1

	Gabapent	tin enac	arbil	Pla	cebo)	Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	m, 95% CI		
Garcia-Borreguero 2019	3.4	1.1	39	4.6	1	39	-1.20 [-1.67, -0.73]		_			
								-4 -	.2 (2	4
								Favors gaba	pentin ena.	Favors pla	cebo	

1. Change scores were not reported in Garcia-Borreguero 2019 so posttreatment values were compared. Data from both drug naïve and drug-treated groups were pooled.

Figure S8. Gabapentin enacarbil vs placebo (Disease severity, RLS-6 pooled) [CST= 0.2 SD] RCT¹

	Gabapent	tin enac	arbil	Placebo		Placebo Std. Mean Difference		Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Rando	m, 95% CI		
Garcia-Borreguero 2019	2.8	2.3	39	3.9	2.5	39	-0.45 [-0.90, -0.00]				
								-1 -0.5	0 0.5		
								Favors gabapentin ena.	Favors placebo		

1. Change scores were not reported in Garcia-Borreguero 2019 so posttreatment values were compared. Data from both drug naïve and drug-treated groups were pooled.

Figure S9. Gabapentin enacarbil vs placebo (RLS QOL - Abetz) [CST = +5 pts] RCT

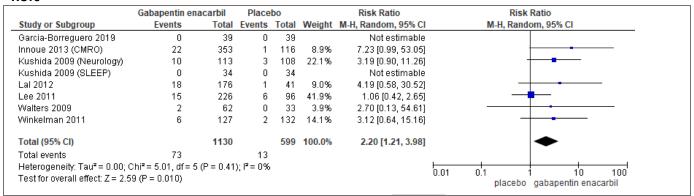
Mean SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Randor	m 05% CI	
					,		iv, italiuo	III, 95% CI	
21.4 17	113	14.1	17.3	108	7.30 [2.78, 11.82]				
						-20	-10 (1	0 20
							Favors placebo	Favors gab	apentin ena.
	21.4 17	21.4 17 113	21.4 17 113 14.1	21.4 17 113 14.1 17.3	21.4 17 113 14.1 17.3 108	21.4 17 113 14.1 17.3 108 7.30 [2.78, 11.82]	· · · - -	-20 -10 (• • • • • • • • • • • • • • • • • • • •

Figure S10, Gabapentin enacarbil vs placebo (Sleep quality, MOSS pooled) [CST = 0.2 SDs] RCT¹

	Gabaper	itin enac	arbil	Pla	cebo)	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Garcia-Borreguero 2019	0.65	1.45	39	-0.2	1.4	39	0.59 [0.14, 1.04]	
								-2 -1 0 1
								Favors placebo Favors gabapentin ei

1. Change scores were not reported in Garcia-Borreguero 2019 so posttreatment values were compared. Data from both drug naïve and drug-treated groups were pooled.

Figure S11. Gabapentin enacarbil vs placebo (Total AEs leading to study withdrawal) [CST = 50/1000 patients] RCTs¹



^{1.} Data from both drug naïve and drug-treated groups were pooled for Garcia-Borreguero 2019 study.

Figure S12. Gabapentin enacarbil pre- vs posttreatment (Total AEs leading to study withdrawal) [CST = 50/1000 patients] Observational

	Posttreat	ment	Pretreat	ment		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
Bogan 2010	42	326	0	326	64.9%	0.13 [0.09, 0.17]		_
Inoue 2012	24	182	0	182	35.1%	0.13 [0.08, 0.18]		
Total (95% CI)		508		508	100.0%	0.13 [0.10, 0.16]		•
Total events	66		0					
Heterogeneity: Tau² = Test for overall effect:			•	0.92); l²	= 0%		-0.2	-0.1 0 0.1 0.2 pretreatment posttreatment

Figure S13. Gabapentin enacarbil vs placebo (adverse event, somnolence) [CST = 50/1000 patients] RCTs¹

<u> </u>							
	Gabapentin ena	acarbil	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Garcia-Borreguero 2019	9	39	4	39	12.7%	2.25 [0.76, 6.70]	+-
nnoue 2013 (CMRO)	92	353	20	116	20.5%	1.51 [0.98, 2.34]	 • -
Kushida 2009 (Neurology)	30	113	8	108	16.9%	3.58 [1.72, 7.47]	
Kushida 2009 (SLEEP)	11	36	1	36	6.1%	11.00 [1.50, 80.82]	
Lal 2012	51	176	2	41	10.0%	5.94 [1.51, 23.41]	
Lee 2011	45	226	2	96	9.8%	9.56 [2.37, 38.61]	
Walters 2009	16	62	5	33	14.7%	1.70 [0.68, 4.24]	 • -
Winkelman 2011	16	127	2	132	9.4%	8.31 [1.95, 35.44]	
Total (95% CI)		1132		601	100.0%	3.41 [1.92, 6.05]	•
Total events	270		44				
Heterogeneity: Tau ^z = 0.37; 0	hi ² = 18.09, df= 1	7 (P = 0.0)	1); I ² = 61	%			
Test for overall effect: $Z = 4.1$		•					0.01 0.1 1 10 100 placebo gabapentin encarbil

 $^{1\ \}mathsf{Data}\ \mathsf{from}\ \mathsf{both}\ \mathsf{drug}\ \mathsf{na\"{i}ve}\ \mathsf{and}\ \mathsf{drug-treated}\ \mathsf{groups}\ \mathsf{were}\ \mathsf{pooled}\ \mathsf{for}\ \mathsf{Garcia-Borreguero}\ \mathsf{2019}\ \mathsf{study}.$

Figure S14. Gabapentin enacarbil pre- vs posttreatment (adverse event, somnolence) [CST = 5%] Observational

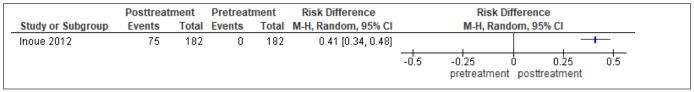


Figure S15. Gabapentin enacarbil vs placebo (adverse event, dizziness) [CST = 50/1000 patients] RCTs¹

<u> </u>						<u>-</u>	, , , ,
	Gabapentin ena	acarbil	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Garcia-Borreguero 2019	3	39	0	39	1.8%	7.00 [0.37, 131.17]	-
Innoue 2013 (CMRO)	93	353	8	116	33.2%	3.82 [1.91, 7.62]	
Kushida 2009 (Neurology)	22	113	5	108	18.1%	4.21 [1.65, 10.71]	
Kushida 2009 (SLEEP)	10	36	2	36	7.6%	5.00 [1.18, 21.23]	
Lal 2012	48	176	1	41	4.2%	11.18 [1.59, 78.66]	
Lee 2011	39	226	5	96	19.6%	3.31 [1.35, 8.15]	_ -
Walters 2009	10	62	1	33	3.9%	5.32 [0.71, 39.79]	+
Winkelman 2011	26	127	3	132	11.6%	9.01 [2.80, 29.02]	
Total (95% CI)		1132		601	100.0%	4.57 [3.07, 6.80]	•
Total events	251		25				
Heterogeneity: Tau ^z = 0.00; 0	hi²= 3.05, df= 7	(P = 0.88)); I ² = 0%				
Test for overall effect: $Z = 7.4$	8 (P < 0.00001)						0.01 0.1 1 10 100 placebo gabapentin enacarbil

^{1.} Data from both drug naïve and drug-treated groups were pooled for Garcia-Borreguero 2019 study.

Figure S16. Gabapentin enacarbil pre- vs posttreatment (adverse event, dizziness) [CST = 5%] Observational

	Posttreat	ment	Pretreat	ment	Risk Difference	Risk Difference					
Study or Subgroup	Events	Total	Events Total		M-H, Random, 95% CI	M-H, Random, 95% CI					
Inoue 2012	84	182	0	182	0.46 [0.39, 0.53]		1	+	-		
						-1	-0.5	o o.	5 1		
							pretreatment	posttreatme	ent		

Important Outcomes

Figure S17. Gabapentin enacarbil vs placebo (PLM Freq, PLMI) RCTs [No CST]

	Gabapentin enacarbil Placebo							Mean Difference	Mean Difference
Study or Subgroup	Mean	Mean SD Tota		Mean	ean SD Total		Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kushida 2009 (SLEEP)	-8.6	23.6	34	0.8	27.9	34	21.2%	-9.40 [-21.68, 2.88]	
Winkelman 2011	-12.7	26.3	131	-4.6	26.3	131	78.8%	-8.10 [-14.47, -1.73]	- -
Total (95% CI)			165			165	100.0%	-8.38 [-14.03, -2.72]	•
Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 2			(P = 0.8	5); I² = 0	1%				-50 -25 0 25 50 Favors gabapentin ena. Favors placebo

Figure S18. Gabapentin enacarbil vs placebo (Sleep latency, PSG) RCTs [CST =-10 min]

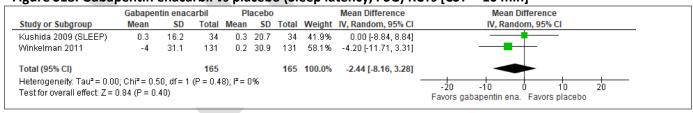


Figure S19. Gabapentin enacarbil vs placebo (WASO, PSG) RCTs [CST =-10 min]

0	•			•		•	•		<u>-</u>
	Gabapen	ntin enac	arbil	Pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kushida 2009 (SLEEP)	-21.5	50.2	34	6.7	38.2	34	29.8%	-28.20 [-49.40, -7.00]	
Winkelman 2011	-32.2	57.2	131	-3.8	56.8	131	70.2%	-28.40 [-42.20, -14.60]	
Total (95% CI)			165			165	100.0%	-28.34 [-39.91, -16.77]	•
Heterogeneity: Tau ² = 0.0			(P = 0.9)	9); I² = 0	0%				-50 -25 0 25 50
Test for overall effect: Z =	: 4.80 (P < 0.	.00001)							Favors gabapentin ena. Favors placebo

^{1.} Combined change scores were not reported in Garcia-Borreguero 2019 so posttreatment values were compared. Data from both dopamine naïve and previously dopamine treated groups were pooled.

Gabapentin

Summary of Findings (GRADE)

Table S2 Gabapentin in adults with RLS

References: Garcia-Borreguero 2002, Saletu 2010, Happe 2001, Happe 2003, Raissi 2017, Adler 1997

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Gabapentin vs Placebo or Control	
Disease severity [IRLS]	⊕⊕⊕⊜ MODERATE ^a	The mean difference in the gabapentin group was 8.4 points lower (12 lower to 4.8 lower) compared to control	44 (1 RCT)
Quality of life [QLI]	⊕○○○ VERY LOW ^{a,b}	The mean QLI pre-post difference was 1.6 points higher (0.12 lower to 3.32 higher)	9 (1 observational study)
Sleep quality [PSQI]	⊕⊕⊕⊜ MODERATEª	The mean difference in the gabapentin group was 2.9 points lower (4 lower to 1.8 lower) compared to control	44 (1 RCT)
Adverse events leading to study withdrawal	⊕⊕⊕⊕ нібн	0 per 1,000 (-40 to 40) in the gabapentin group compared to 0 per 1,000 in the control group	128 (2 RCTs)
Adverse event (somnolence)	⊕⊕⊕⊜ MODERATEª	95 per 1,000 (-30 to 221) in the gabapentin group compared to 0 per 1,000 in the control group	47 (1 RCT)
Adverse event (dizziness)	⊕○○○ VERY LOW ^a	154 per 1,000 (15 to 293) in the gabapentin group	26 (3 observational studies)
Adverse event (augmentation)	⊕⊕⊕⊜ MODERATEª	0 per 1,000 (-80 to 80) in the gabapentin group compared to 0 per 1,000 in the control group	44 (1 RCT)
a. Small sample size.			

Small sample size.

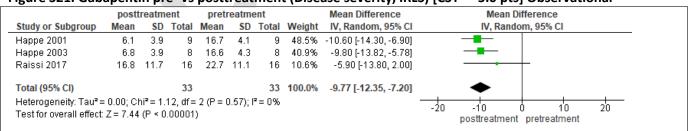
Critical Outcomes

Figure S20. Gabapentin vs placebo (Disease severity, IRLS) [CST =-3.0 pts] RCT¹

	gabapentin			placebo			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI				
Garcia-Borreguero 2002	9.5	6.1	22	17.9	6.1	22	-8.40 [-12.00, -4.80]					
								-20 -10 0 10 20				
								Favors gabapentin Favors placebo				

^{1.} SE reported in the study was converted to SD.

Figure S21. Gabapentin pre- vs posttreatment (Disease severity, IRLS) [CST = -5.0 pts] Observational



b. 95% CI crosses CST.

Figure S22. Gabapentin vs placebo (Disease severity, CGI-S) [CST = -0.5 pts] RCT¹

	gabapentin plac		ceb	0	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Garcia-Borreguero 2002	1.8	1.4	22	2.9	1.4	22	-1.10 [-1.93, -0.27]	-2 -1 0 1 2 Favors gabapentin Favors placebo

^{1.} SE reported in study was converted to SD.

Figure S23. Gabapentin pre- vs posttreatment (QOL index, QLI) [CST= +10 pts] Observational

		•	•		•				, , , , ,	· -			
Happe 2001 8.2 1.1 9 6.6 2.4 9 1.60 [-0.12, 3.32] -4 -2 0 2 4		Posttr	Posttreatment Pretreatment				ent		Mean Difference	Mean Difference			
-4 -2 0 2 4	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
	Happe 2001	8.2	1.1	9	6.6	2.4	9		1.60 [-0.12, 3.32]	-4 -2 0 2 4 pretreatment posttreatment			

Figure S24. Gabapentin vs placebo (Sleep quality, PSQI) [CST =-3.0 pts] RCT¹

	gaba	apent	in	pla	iceb)	Mean Difference	Mean Di	fference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Rando	m, 95% CI
Garcia-Borreguero 2002	6.4 1.9 22		6.4 1.9 22 9.3			1.9 22 -	-2.90 [-4.02, -1.78]		
								-4 -2 (j 2 4
								Favors gabapentin	Favors placebo

^{1.} SE reported in study was converted to SD.

Figure S25. Gabapentin pre- vs posttreatment (PSQI) [CST= -5.0 pts] Observational

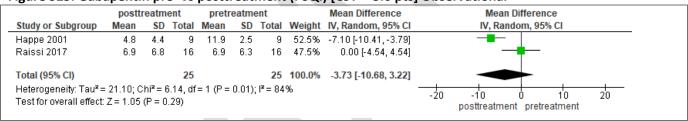


Figure S26. Gabapentin vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT

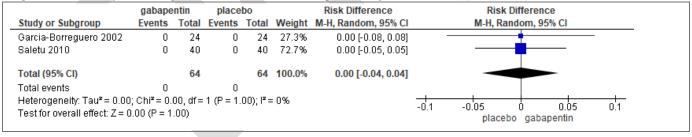


Figure S27. Gabapentin pre- vs posttreatment (Total AEs leading to study withdrawal) [CST = 10%] Observational

	posttreat		pretreati			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Adler 1997	2	8	0	8	7.5%	0.25 [-0.08, 0.58]	+
Happe 2001	0	9	0	9	22.3%	0.00 [-0.19, 0.19]	-
Happe 2003	0	8	0	8	18.2%	0.00 [-0.21, 0.21]	
Raissi 2017	2	25	0	25	52.0%	0.08 [-0.05, 0.21]	+
Total (95% CI)		50		50	100.0%	0.06 [-0.03, 0.15]	•
Total events	4		0				
Heterogeneity: Tau ² :	= 0.00; Chi ² :	= 2.25, (f=3(P=	0.52); P	²= 0%		1, <u>1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1</u>
Test for overall effect				-71			-1 -0.5 0 0.5 1 pretreatment posttreatment

Figure S28. Gabapentin vs placebo (adverse event, somnolence) RCT [CST = 5%]

	gabape	ntin	place	bo	Risk Difference		Risk Difference			
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI				
Garcia-Borreguero 2002	2	23	0	24	0.09 [-0.05, 0.22]		 -			
						-0.5	-0.25 0 0.25	0.5		
							placebo gabapentin			

Figure S29. Gabapentin pre- vs posttreatment (adverse event, somnolence) Observational [CST = 10%]

	posttreat	ment	pretreat	ment		Risk Difference	Risk Difference				
Study or Subgroup	Events	Total	Events Total		Weight	M-H, Random, 95% CI	M-H, Random, 95% CI				
Adler 1997	1	8	0	8	34.4%	0.13 [-0.16, 0.41]	- •				
Happe 2001	2	9	0	9	31.1%	0.22 [-0.08, 0.52]					
Happe 2003	1	8	0	8	34.4%	0.13 [-0.16, 0.41]	- •				
Total (95% CI)		25		25	100.0%	0.16 [-0.01, 0.32]	•				
Total events	4		0								
Heterogeneity: Tau² = Test for overall effect				0.87); 1	'= 0%		-1 -0.5 0 0.5 1 pretreatment posttreatment				

Figure S30. Gabapentin pre- vs posttreatment (adverse event, dizziness) Observational [CST = 10%]

	posttreat	ment	pretreat	ment		Risk Difference		Ris	k Differenc	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, R	andom, 95	% CI	
Adler 1997	3	8	0	8	23.7%	0.38 [0.02, 0.73]				-	
Happe 2001	1	9	0	9	33.4%	0.11 [-0.15, 0.37]			-	_	
Happe 2003	0	9	0	9	42.9%	0.00 [-0.19, 0.19]			+		
Total (95% CI)		26		26	100.0%	0.13 [-0.09, 0.34]				-	
Total events	4		0								
Heterogeneity: Tau² = Test for overall effect			•	0.13); l ^a	= 51%		-1	-0.5 pretreatm	0 nent posttr	0.5 eatment	1

Figure S31. Gabapentin vs placebo (adverse event, augmentation) RCT [CST = 5%]

<u> </u>			•		<u> </u>		
	gabape	ntin	place	bo	Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Random, 95% CI
Garcia-Borreguero 2002	0	22	0	22	0.00 [-0.08, 0.08]		+
						-1	-0.5 0 0.5 1
							placebo gabapentin

Important Outcomes

Figure S32, Gabapentin vs placebo (PLM Freq. PLMI) [No CST] RCT¹

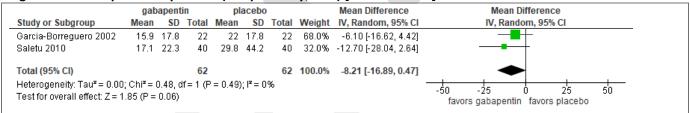
	gab	apenti	in	pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Garcia-Borreguero 2002	11.1	15.5	22	20.8	15.5	22	74.1%	-9.70 [-18.86, -0.54]	———
Saletu 2010	21.4	29.9	40	29	40	40	25.9%	-7.60 [-23.08, 7.88]	-
Total (95% CI)			62			62	100.0%	-9.16 [-17.04, -1.27]	•
Heterogeneity: Tau² = 0.00			f= 1 (P	= 0.82)	; I² = 0	%			-50 -25 0 25 50
Test for overall effect: $Z = 2$.28 (P =	0.02)							Favors gabapentin Favors placebo

^{1.} SE reported in study was converted to SD for Garcia-Borreguero RCT.

Figure S33. Gabapentin pre- vs posttreatment (PLM Freq, PLMI) Observational [No CST]

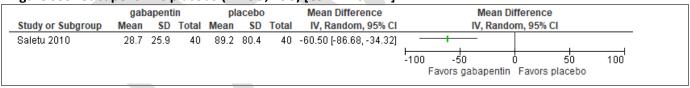
	postt	reatme	ent	pretr	eatme	ent		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Happe 2001	20.8	23.9	9	38.2	18.8	9	55.2%	-17.40 [-37.27, 2.47]	
Нарре 2003	22.6	24.9	8	39.2	19.8	8	44.8%	-16.60 [-38.64, 5.44]	
Total (95% CI)			17			17	100.0%	-17.04 [-31.80, -2.28]	-
Heterogeneity: Tau² = Test for overall effect:				1 (P = 0	0.96); I	²= 0%			-50 -25 0 25 50

Figure S34. Gabapentin vs placebo (sleep latency, PSG) [CST = -10 min] RCT¹



^{1.} SE reported in study was converted to SD for Garcia-Borreguero RCT.

Figure S35. Gabapentin vs placebo (WASO, PSG) [CST = -10 min]



13

Pregabalin

Summary of Findings (GRADE)

Table S3 Pregabalin in adults with RLS

References: Allen 2010, Allen 2014, Garcia-Borreguero 2014

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Pregabalin vs Placebo or Control	
Disease severity	$\Theta \oplus \Theta \oplus \Theta$	The mean difference in the pregabalin group was 4.8 points	486
[IRLS]	HIGH	lower (6.2 lower to 3.4 lower) compared to control	(2 RCTs)
Quality of life	$\Theta\Theta\Theta$	The mean difference in the pregabalin group was 4.6 points	349
[RLS QOL Abetz]	MODERATE	higher (2 higher to 7.2 higher) compared to control	(1 RCT)
Sleep quality	$\Theta\Theta\Theta$	The standardized mean difference in the pregabalin group was	282
[MOS pooled]	MODERATE ^a	0.41 higher (0.14 higher to 0.7 higher) compared to control	(2 RCTs)
WASO	$\Theta\Theta\Theta$	The mean difference in the pregabalin group was 27.1 minutes	145
[PSG]	MODERATE ^b	lower (38.7 lower to 15.5 lower) compared to control	(1 RCT)
Adverse events leading to study	$\Theta\Theta\Theta$	186 per 1000 (156 to 130) in the pregabalin group compared to 6	585
withdrawal	MODERATE	per 1,000 in the control group	(3 RCTs)
Adverse event (dizziness)	$\oplus \oplus \oplus \oplus$	193 per 1000 (156 to 130) in the pregabalin group compared to 7	705
	HIGH	per 1,000 in the control group	(3 RCTs)
Adverse event (somnolence)	$\Theta \oplus \Theta \oplus \Theta$	189 per 1000 (156 to 130) in the pregabalin group compared to	643
	HIGH	15 per 1,000 in the control group	(3 RCTs)

small sample size

Critical Outcomes

Figure S36. Pregabalin vs placebo (Disease severity, IRLS) [CST = -3 pts] RCTs

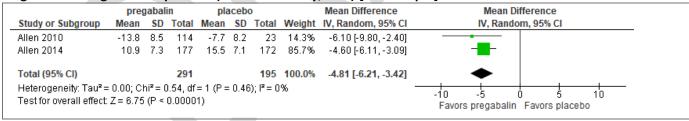
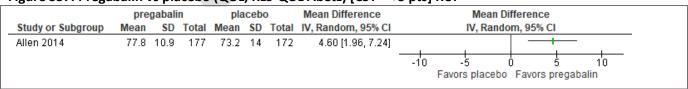


Figure S37. Pregabalin vs placebo (QOL, RLS-QOL Abetz) [CST = +5 pts] RCT



Supplemental material 14

Figure S38. Pregabalin vs placebo (Sleep quality, MOS pooled) [CST = 0.2] RCTs^{1,2}

		•							
	pre	gabali	n	pla	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allen 2010	19.5	18.9	114	12.1	17.6	23	34.8%	0.39 [-0.06, 0.84]	+
Garcia-Borreguero 2014	33.4	18.7	73	25.6	18.7	72	65.2%	0.41 [0.09, 0.74]	
Total (95% CI)			187			95	100.0%	0.41 [0.14, 0.67]	-
Heterogeneity: Tau² = 0.00; Test for overall effect: Z = 3			,	= 0.94)	; I² = 0	%		5	1 -0.5 0 0.5 1 Favors pregabalin Favors placebo

- 1. For Garcia-Borreguero 2014 study, SEM data converted to SD. Posttreatment data used for analysis.
- 2. For Allen 2010 study, SEM data converted to SD. Data pooled across 4 doses. Change scores used for analysis.

Figure S39. Pregabalin vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCTs¹

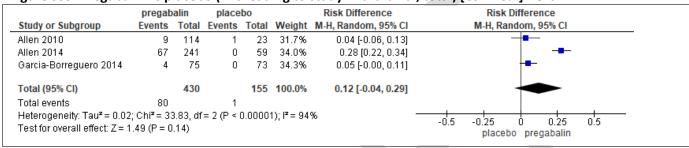


Figure S40. Pregabalin vs placebo (Adverse event, dizziness) [CST = 5%] RCT

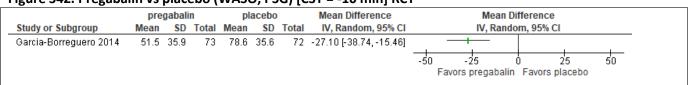
	pregab	alin	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2010	16	114	1	23	25.2%	0.10 [-0.01, 0.20]	-
Allen 2014	49	241	0	179	48.2%	0.20 [0.15, 0.25]	-
Garcia-Borreguero 2014	18	75	1	73	26.6%	0.23 [0.13, 0.33]	_ -
Total (95% CI)		430		275	100.0%	0.18 [0.12, 0.25]	•
Total events	83		2				
Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 5				15); l² =	= 48%		-0.5 -0.25 0 0.25 0.5 placebo pregabalin

Figure S41. Pregabalin vs placebo (Adverse event, somnolence) [CST = 5%] RCT

	pregab	alin	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2010	18	114	1	23	25.4%	0.11 [0.01, 0.22]	-
Allen 2014	39	182	0	179	45.9%	0.21 [0.15, 0.27]	-
Garcia-Borreguero 2014	13	75	3	73	28.7%	0.13 [0.04, 0.23]	
Гotal (95% CI)		371		275	100.0%	0.17 [0.10, 0.23]	•
Total events	70		4				
Heterogeneity: Tau² = 0.00 Fest for overall effect: Z = 4			•	16); l² =	= 45%		-0.5 -0.25 0 0.25 0.5 placebo pregabalin

Important Outcomes

Figure S42. Pregabalin vs placebo (WASO, PSG) [CST = -10 min] RCT



Intravenous (IV) Ferric Carboxymaltose

Summary of Findings (GRADE)

Table S4 IV Ferric Carboxymaltose(FCM) in adults with RLS

References: Allen 2011, Bae 2021, Cho 2018, Trenkwalder 2017

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference IV FCM vs Placebo or Control	No of Participants (studies)
Disease severity	⊕⊕⊕⊜	The mean difference in the IV FCM was 7.0 points lower (12.11 lower to 1.8 lower) compared to control	219
[IRLS]	MODERATE ^a		(4 RCTs)
Quality of Life	⊕⊕⊕⊜	The mean difference in the IV FCM group was 11.1 points higher (0.3 lower to 22.5 higher) compared to control	136
[RLS QOL – Abetz]	MODERATE ^a		(3 RCTs)
Sleep Quality	⊕○○○	The mean difference in the IV FCM group was 2.5 points lower (9.4 lower to 4.4 higher) compared to control	93
[PSQI]	VERY LOW ^{b,c}		(2 RCTs)
Adverse events leading to study withdrawal	⊕⊕⊕⊕ HIGH	7 per 1,000 (1 to 114) in the IV FCM group compared to 8 per 1,000 in the control group RR 0.86 (0.06 to 13.47)	248 (4 RCTs)

- a. 95% confidence interval crossed the clinical significance threshold.
- b. $I^2 = 85\%$ with unexplained heterogeneity.
- c. 95% confidence interval crosses both sides of clinical significance threshold and small sample size (<100).

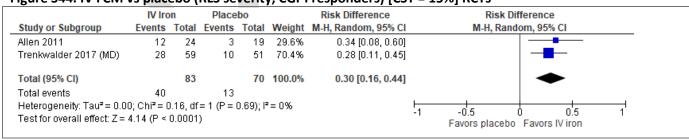
Critical Outcomes

Figure S43. IV FCM vs placebo (RLS severity, IRLS) [CST =-3.0 points] RCTs¹

	F	CM		Pla	icebo)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allen 2011	-8.9	8.5	24	-4	6.1	22	24.7%	-4.90 [-9.15, -0.65]	+
Bae 2021	-13.5	7.4	15	1.4	3.6	14	24.8%	-14.90 [-19.09, -10.71]	*
Cho 2018	-8.3	7.5	32	-4.8	8.7	32	25.3%	-3.50 [-7.48, 0.48]	<u>≠</u>
Trenkwalder 2017 (MD)	-9.6	9.4	45	-5	8.9	35	25.2%	-4.60 [-8.63, -0.57]	-
Total (95% CI)			116			103	100.0%	-6.96 [-12.11, -1.80]	•
Heterogeneity: Tau² = 23.2 Test for overall effect: Z = 3				3 (P =	0.000)3); I²=	84%		-100 -50 0 50 100 Favours FCM Favours placebo

^{1.} Bae 2021 study included patients with iron deficiency anemia.

Figure S44. IV FCM vs placebo (RLS severity, CGI-I responders) [CST = 15%] RCTs



Supplemental material 16

Figure S45. IV FCM vs placebo (RLS severity, PGI responders) [CST= 15%] RCT

	IV Iro	n	Place	bo	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2011	10	21	2	19	0.37 [0.12, 0.63]	-1 -05 0 05 1
						Favors placebo Favors IV iron

Figure S46. IV FCM vs placebo (RLS QOL – Abetz) [CST = +5 points] RCTs

	IN	/ Iron		Pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allen 2011	56.5	49.1	24	19.5	51.7	19	12.0%	37.00 [6.57, 67.43]	
Bae 2021	4.8	22.8	15	-2	9.2	14	41.4%	6.80 [-5.70, 19.30]	- ■
Cho 2018	5.5	19	32	-2.8	25.5	32	46.6%	8.30 [-2.72, 19.32]	+
Total (95% CI)			71			65	100.0%	11.11 [-0.26, 22.48]	•
Heterogeneity: Tau²: Test for overall effect				= 2 (P =	= 0.19)	; I² = 40)%		-100 -50 0 50 100 Favors placebo Favors IV iron

Figure S47. IV FCM vs placebo (Sleep quality, PSQI) [CST = -3 points] RCTs

	IV	Iron		Pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bae 2021	-5.4	3.7	15	0.4	3.8	14	53.5%	-5.80 [-8.53, -3.07]	
Cho 2018	-1.9	4.6	32	-3.2	12.4	32	46.5%	1.30 [-3.28, 5.88]	
Total (95% CI)			47			46	100.0%	-2.50 [-9.44, 4.44]	
Heterogeneity: Tau² = Test for overall effect:				df=1 (P	= 0.00	09); I²=	85%		-10 -5 0 5 10 Favors IV Iron Favors placebo

Figure S48. IV FCM vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs

	IV Iro	n	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2011	0	24	0	21	16.3%	0.00 [-0.08, 0.08]	+
Bae 2021	0	15	0	14	7.2%	0.00 [-0.12, 0.12]	+
Cho 2018	0	32	0	32	32.3%	0.00 [-0.06, 0.06]	+
Trenkwalder 2017 (MD)	1	59	1	51	44.3%	-0.00 [-0.05, 0.05]	†
Total (95% CI)		130		118	100.0%	-0.00 [-0.03, 0.03]	+
Total events	1		1				
Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			= 3 (P = 1	1.00); l ^a	°= 0%		-1 -0.5 0 0.5 placebo IV iron

Intravenous (IV) Iron Dextran

Summary of Findings (GRADE)

Table S5 IV Iron Dextran in adults with RLS

References: Cho 2013, Earley 2004, Ondo 2010											
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference IV Iron Dextran vs Placebo or Control	No of Participants (studies)								
Disease severity [IRLS]	⊕○○○ VERY LOW ^{b,c}	The mean difference in the IV dextran was 6.8 points lower (11.53 lower to 2.7 lower) compared to control	23 (1 Obs)								

Adverse events leading to study withdrawal	⊕○○○ VERY LOW ^{b,c}	3% more (4% lower to 9% higher) in the IV Dextran group compared to	59 (3 Obs)
		8 per 1,000 in the control group	

- 95% confidence interval crossed the clinical significance threshold.
- b. $I^2 = 85\%$ with unexplained heterogeneity.
- 95% confidence interval crosses both sides of clinical significance threshold and small sample size (<100).

Critical Outcomes

Figure S49. IV Dextran Pre-post (RLS severity, IRLS) [CST =-3.0 points] Observational study

	Postti	treatment Pretreatment		Mean Difference	Mean Difference							
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
Cho 2013 (SM)	16.7	9.5	23	23.5	6.6	23	-6.80 [-11.53, -2.07]			$-\top$		
								-20	-10	\dashv	10	20
								po	osttreatm	ent pre	etreatment	

Figure S50. IV Dextran Pre-post (Total AEs leading to study withdrawal) [CST = 10%] Observational study

	Posttreat	tment	Pretreat	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cho 2013 (SM)	0	23	0	23	64.3%	0.00 [-0.08, 0.08]	
Earley 2004	1	11	0	11	8.8%	0.09 [-0.13, 0.31]	
Ondo 2010	2	25	0	25	26.9%	0.08 [-0.05, 0.21]	 •
Total (95% CI)		59		59	100.0%	0.03 [-0.04, 0.09]	•
Total events	3		0				
Heterogeneity: Tau² = Test for overall effect:				0.39); l²	= 0%		-0.5 -0.25 0 0.25 0.5 pretreatment posttreatment

Oral Iron

Summary of Findings (GRADE)

Table S6 Oral iron in adults with RLS

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)		
	(GRADE)	Oral iron vs Placebo or Control			
Disease severity	$\oplus\oplus\oplus\bigcirc$	The mean difference in the oral iron group was 9.2 points lower	18		
[IRLS]	MODERATE ^a	(15.2 lower to 3.2 lower) compared to control	(1 RCT)		
Adverse events leading to study	$\oplus \oplus \oplus \bigcirc$	100 per 1,000 (-120 to 320) in the oral iron group compared to 0	46		
withdrawal	MODERATE ^a	per 1,000 in the control group	(2 RCTs)		
a. Small sample size	MODERATE	per 1,000 in the control group	(2 RCTs)		

Supplemental material 18

Figure S51. Ferrous sulfate vs placebo (RLS severity, IRLS) [CST =-3.0 points] RCT

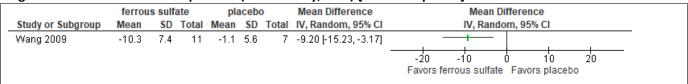


Figure S52. Ferrous sulfate vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT

ferrous si	ulfate	place	bo		Risk Difference	Risk Difference
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3	14	0	14	46.8%	0.21 [-0.02, 0.45]	-
0	11	0	7	53.2%	0.00 [-0.20, 0.20]	
	25		21	100.0%	0.10 [-0.12, 0.32]	-
3		0				
		f=1 (P=	0.14);	r = 53%		-1 -0.5 0 0.5 1 placebo ferrous sulfate
	3 0 3 0 3 : 0.01; Chi ² =	3 14 0 11 25	Section Section	Events Total Events Total 3 14 0 14 0 11 0 7 25 21 3 0 0 0.01; Chi² = 2.13, df = 1 (P = 0.14); leading 0	Events Total Events Total Weight 3 14 0 14 46.8% 0 11 0 7 53.2% 25 21 100.0% 3 0 0 0.01; Chi² = 2.13, df = 1 (P = 0.14); ² = 53%	Total Events Total Weight M-H, Random, 95% Cl



Dipyridamole

Summary of Findings (GRADE)

Table S7 Dipyridamole in adults with RLS

References: Garcia-Borreguero 2021, Garcia-Borreguero 2018

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)	
	(GRADE)	Dipyridamole vs Placebo or Control		
Disease severity	$\oplus\oplus\oplus\bigcirc$	The mean difference in the dipyridamole group was 7.6 points	28	
[IRLS]	MODERATE ^a	lower (9.1 lower to 6.1 lower) compared to control	(1 RCT)	
Sleep latency	$\oplus\oplus\oplus\bigcirc$	The mean difference in the dipyridamole group was 7.2	28	
[PSG]	MODERATE ^{a,b}	minutes fewer (12.3 fewer to 2.1 fewer) compared to control	(1 RCT)	
WASO	$\oplus \oplus \oplus \bigcirc$	The mean difference in the dipyridamole group was 14.5	28	
[PSG]	MODERATE ^a	minutes fewer (28.6 fewer to 0.4 fewer) compared to control	(1 RCT)	
Adverse events leading to study	$\oplus\oplus\oplus\bigcirc$	0 per 1000 in the dipyridamole group compared to	28	
withdrawal	MODERATE ^a	0 per 1,000 in the control group	(1 RCT)	
Adverse event (dizziness)	$\oplus \oplus \oplus \bigcirc$	107 per 1000 (19 to 593) in the dipyridamole group compared	28	
	MODERATE ^a	to 71 per 1,000 in the control group	(1 RCT)	
Adverse event (dizziness)	ФООО	133 per 1000 (-40 to 305) in the dipyridamole group	15	
	VERY LOW ^a		(1 observational study	

a. Small sample size

Critical Outcomes

Figure S53. Dipyridamole vs placebo (Disease severity, IRLS) [CST = -3 pts] RCT

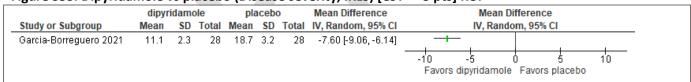


Figure S54. Dipyridamole vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT

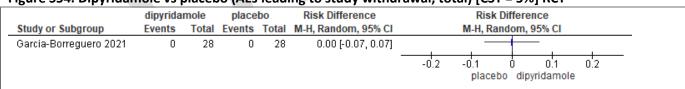
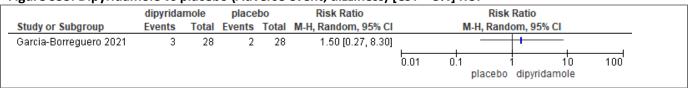


Figure S55. Dipyridamole vs placebo (Adverse event, dizziness) [CST = 5%] RCT



Supplemental material 20

b. 95% CI crosses CST

Figure S56. Dipyridamole pre- vs posttreatment (Adverse event, dizziness) [CST = 10%] Observational

	posttreatment		pretreat	ment	Risk Difference		Risk Difference				
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Random, 95% CI				
Garcia-Borrequero 2018	2	15	0	15	0.13 [-0.06, 0.33]	-0.5	-0.25 0 0.25	0.5			

Figure S57. Dipyridamole vs placebo (Sleep latency, PSG) [CST = -10 min] RCT¹

	dipyr	idam	ole	pla	acebo		Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	m, 95% CI		
Garcia-Borreguero 2021	20.3	8.1	28	27.5	11.1	28	-7.20 [-12.29, -2.11]	1				
								-20 Fa	ا -۱۰ vors dipyridamole	Favors pla	cebo	20

^{1.} Posttreatment values were entered as change scores were not reported.

Figure S58. Dipyridamole vs placebo (WASO, PSG) [CST = -10 min] RCT¹

	dipyridamole placebo				Mean Difference		Mean [Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rand	om, 95% CI		
Garcia-Borreguero 2021	59.8	22.9	28	74.3	30.3	28	-14.50 [-28.57, -0.43]			1		
								-50	-25	Ó	25	50
								Fav	ors dipyridamole	e Favors p	lacebo	

^{1.} Posttreatment values were entered as change scores were not reported.

Oxycodone

Summary of Findings (GRADE)

Table S8 Oxycodone in adults with RLS

References: Trenkwalder 2013, Walters 1993

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants		
	(GRADE)	Oxycodone vs Placebo or Control	(studies)		
Disease severity [IRLS]	⊕⊕⊕⊕ HIGH	The mean difference in the oxycodone group was 5.6 points lower (8.2 lower to 3.0 lower) compared to control	276 (1 RCT)		
Sleep quality [MOS]	⊕⊕⊕⊜ MODERATEª	The standardized mean difference in the oxycodone group was 0.14 SD lower (0.1 lower to 0.37 lower) compared to control	276 (1 RCT)		
PLM frequency [PSG]	⊕⊕⊕⊜ MODERATE ^{a,b}	The mean difference in the oxycodone group was 34.5 PLMs/hour fewer (62.7 fewer to 6.4 fewer) compared to control	22 (1 RCT)		
Sleep latency [PSG]	⊕⊕⊕○ MODERATE ^{a,b}	The mean difference in the oxycodone group was 25.5 minutes lower (68.4 lower to 17.4 higher) compared to control	22 (1 RCT)		
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATE ^c	121 per 1000 (61 to 255) in the oxycodone group compared to 61 per 1,000 in the control group	326 (2 RCTs)		
Adverse event (fatigue)	⊕⊕⊜⊝ LOWa,c	299 per 1000 (182 to 468) in the oxycodone group compared to 130 per 1,000 in the control group	304 (1 RCT)		
Adverse event (somnolence)	⊕⊕⊜⊝ LOWa,c	109 per 1000 (45 to 250) in the oxycodone group compared to 45 per 1,000 in the control group	304 (1 RCT)		
Adverse event (dizziness)	⊕⊕⊜⊝ LOW ^{a,c}	86 per 1000 (29 to 260) in the oxycodone group compared to 26 per 1,000 in the control group	304 (1 RCT)		

- a. 95% CI crosses CST.
- b. Small sample size.
- c. Cannot determine if adverse events were directly attributable to the drug. Some adverse events may be more serious than others.

Critical Outcomes

Figure S59. Oxycodone vs placebo (Disease severity, IRLS) RCT [CST =-3 pts]

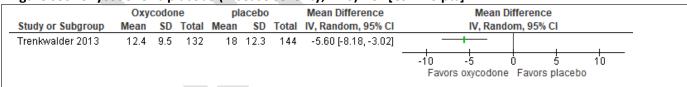


Figure S60. Oxycodone vs placebo (Sleep quality, MOS pooled) [CST = 0.2] RCT

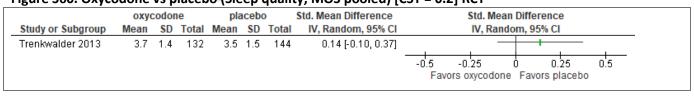


Figure S61. Oxycodone vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT

<u> </u>							
	Oxycod	lone	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Trenkwalder 2013	20	150	10	154	85.1%	0.07 [0.00, 0.14]	
Walters 1993	0	11	0	11	14.9%	0.00 [-0.16, 0.16]	
Total (95% CI)		161		165	100.0%	0.06 [-0.00, 0.12]	-
Total events	20		10				
Heterogeneity: Tau² :	= 0.00; Chi	$^{2} = 0.63$, df = 1 (F	P = 0.43	3); I² = 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect	: Z=1.85 (P = 0.00	6)				placebo oxycodone

Figure S62. Oxycodone vs placebo (adverse event. fatigue) [CST = 5%] RCT

	oxycod	one	place	bo	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Rand	om, 95% CI	
Trenkwalder 2013	44	150	20	154	2.26 [1.40, 3.64]			-	
						0.01 (0.1	1	0 10
							placebo	oxycodone	

Figure S63. Oxycodone vs placebo (adverse event, somnolence) [CST = 5%] RCT

	oxycod	one	place	bo	Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, F	Random, 95	5% CI	
Trenkwalder 2013	16	150	7	154	2.35 [0.99, 5.54]			-	—	
						0.01	0.1	1	10	100
							plac	ebo oxyco	done	

Figure S64. Oxycodone vs placebo (adverse event, dizziness) [CST = 5%] RCT

<u> </u>						_			
	oxycod	lone	place	bo	Risk Ratio		Risl	k Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Ran	dom, 95% CI	
Trenkwalder 2013	13	150	4	154	3.34 [1.11, 10.00]				
						0.01	0.1	1 10	100
							placebo	oxycodone	

Important Outcomes

Figure S65. Oxycodone vs placebo (PLM Freq, PLMI) [No CST] RCT

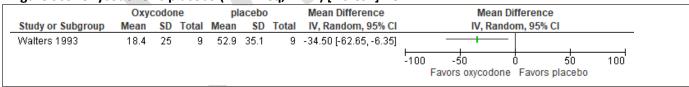
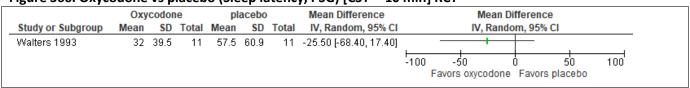


Figure S66. Oxycodone vs placebo (Sleep latency, PSG) [CST =-10 min] RCT



23

Peroneal Nerve Stimulation

Summary of Findings (GRADE)

Table S9 Peroneal Nerve Stimulation in adults with RLS

References: Buchfuhrer 2021

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference PNS vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊜⊝ LOW ^{a,b,c}	The mean difference in the PNS group was 3.4 points lower (6.0 lower to 0.8 lower) compared to control	72 (1 RCT)
Disease severity [CGI-I]	⊕⊕⊜⊝ LOWa,c	655 per 1000 (283 to 1000) in the PNS group compared to 172 per 1,000 in the control group	58 (1 RCT)

- a. Lack of adequate blinding and allocation concealment.
- b. 95% CI crosses CST.
- c. Small sample size.

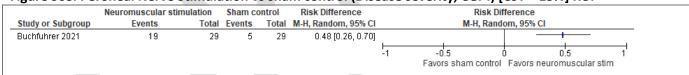
Critical Outcomes

Figure S67. Peroneal Nerve Stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT¹

Neuromusc	ular stimul	ation	Sham	cont	rol	Mean Difference		Mea	n Differen	ıce		
Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Ra	ndom, 95	% CI		
-6.8	5.6	36	-3.4	5.8	36	-3.40 [-6.03, -0.77]			-			
							-10	-5	ó	5	5 10	
	Mean	Mean SD		Mean SD Total Mean	Mean SD Total Mean SD	Mean SD Total Mean SD Total	Mean SD Total Mean SD Total IV, Random, 95% CI	Mean SD Total Mean SD Total IV, Random, 95% CI -6.8 5.6 36 -3.4 5.8 36 -3.40 [-6.03, -0.77]	Mean SD Total Mean SD Total IV, Random, 95% CI IV, Ra -6.8 5.6 36 -3.4 5.8 36 -3.40 [-6.03, -0.77] -10 -5	Mean SD Total Mean SD Total IV, Random, 95% CI IV, Random, 95% -6.8 5.6 36 -3.4 5.8 36 -3.40 [-6.03, -0.77] -10 -5 0	Mean SD Total Mean SD Total IV, Random, 95% CI IV, Random, 95% CI -6.8 5.6 36 -3.4 5.8 36 -3.40 [-6.03, -0.77] -10 -5 0 5	Mean SD Total Mean SD Total IV, Random, 95% CI IV, Random, 95% CI

1. SEMs reported in study were converted to SDs.

Figure S68. Peroneal Nerve Stimulation vs sham control (Disease severity, CGI-I) [CST = 15%] RCT¹



1. SEMs reported in study were converted to SDs.

Levodopa

Summary of Findings (GRADE)

Table S10 Levodopa in adults with RLS

References: Beneš 1999, Eisensehr 2004, Trenkwalder 1995, Allen 1996, Bassetti 2011, Earley 1996, Hogl 2010, Saletu 2003, Trenkwalder 2003, Trenkwalder 2007

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Levodopa vs Placebo or Control	
Disease severity [CGI-S]	⊕⊕⊜⊝ LOWª	The mean difference in the levodopa group was 0.2 points lower (0.8 lower to 0.4 higher) compared to control	34 (1 RCT)
Disease severity IRLS	⊕⊖⊖⊖ VERY LOW ^b	The pre-post difference was 4.7 points lower (7.0 lower to 2.4 lower)	81 (2 observational studies)
Quality of life [QLI]	⊕○○○ VERY LOW ^a	The pre-post difference was 0.1 points higher (0.7 lower to 0.9 higher)	18 (1 observational study)
Sleep quality [PSQI]	⊕○○○ VERY LOW ^a	The pre-post difference was 0.1 points higher (0.7 lower to 0.9 higher)	18 (1 observational study)
Adverse events leading to study withdrawal	LOMc'p	0 per 1000 in the levodopa group compared to 29 per 1,000 in the control group	138 (1 RCT)
Adverse events (dizziness/vertigo)	⊕○○○ VERY LOW ^c	94 per 1000 (57 to 130) in the levodopa group compared to 0 per 1,000 in the control group	246 (2 observational studies)
Adverse event (somnolence)	⊕○○○ VERY LOW ^{c,b}	150 per 1000 (-50 to 350) in the levodopa group compared to 0 per 1,000 in the control group	40 (1 RCT)
Adverse event (augmentation)	⊕⊕⊕○ MODERATE ^a	115 per 1000 (29 to 202) in the levodopa group compared to 0 per 1,000 in the control group	104 (2 RCTs)
Adverse event (augmentation)	⊕⊕⊕⊜ MODERATE	310 per 1000 (266 to 355) in the levodopa group compared to 0 per 1,000 in the control group	416 (7 observational studies)

- a. Small sample size. 95% CI crosses both sides of CST.
- b. Small sample size. 95% CI crosses CST.
- c. Cannot determine for certain whether adverse events were directly attributed to the drug.

Critical Outcomes

Figure S69. Levodopa pre- vs posttreatment (Disease severity, IRLS) [CST =-5 points] Observational¹

	Posttr	eatme	ent	Pretro	eatme	ent		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bassetti 2011	17.1	7.8	63	21.1	6.9	63	75.2%	-4.00 [-6.57, -1.43]	
Saletu 2003	14.3	7.4	18	21	6.5	18	24.8%	-6.70 [-11.25, -2.15]	
Total (95% CI)			81			81	100.0%	-4.67 [-6.96, -2.38]	•
Heterogeneity: Tau² = Test for overall effect:					.31); I	= 2%			-20 -10 0 10 20 posttreatment

1. Bassetti 2011 RCT compared levodopa to pramipexole so pre-vs posttreatment data was used for comparison.

Figure S70. Levodopa vs placebo (CGI-S) [CST = -0.5] RCT

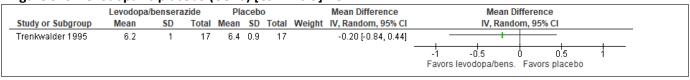


Figure S71. Levodopa pre- vs posttreatment (QOL index, RLS-QLI) [CST= +10 points] Observational

	Posttr	eatm	ent	Pretre	eatme	ent		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Saletu 2003	8.2	1.3	18	8.1	1.1	18		0.10 [-0.69, 0.89]	-1 -0.5 0 0.5 1 pretreatment posttreatment

Figure S72. Levodopa pre- vs posttreatment (PSQI) [CST= -3.0 points] Observational

Figure S73. Levodopa vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs

	Levodo	opa	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Benes 1999	0	32	2	32	33.1%	-0.06 [-0.16, 0.04]	
Eisensehr 2004	0	20	0	20	38.5%	0.00 [-0.09, 0.09]	
Trenkwalder 1995	0	17	0	17	28.4%	0.00 [-0.11, 0.11]	
Total (95% CI)		69		69	100.0%	-0.02 [-0.08, 0.04]	-
Total events	0		2				
Heterogeneity: Tau² : Test for overall effect			,	P = 0.5	8); I² = 09	6	-0.2 -0.1 0 0.1 0.2 placebo levodopa

Figure S74. Levodopa vs placebo (adverse event, augmentation) [CST = 5%] RCT

gare of the Level						, , ,	25. 5/0] N.C.
	Levode	opa	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Benes 1999	2	32	0	32	65.0%	0.06 [-0.04, 0.16]	
Eisensehr 2004	4	20	0	20	35.0%	0.20 [0.01, 0.39]	
Total (95% CI)		52		52	100.0%	0.11 [-0.03, 0.25]	-
Total events	6		0				
Heterogeneity: Tau ² =	0.01; Chi	$i^2 = 1.8^\circ$	7, df = 1 (P = 0.1	7); l ² = 47	% -	-0.5 -0.25 0 0.25 0.5
Test for overall effect:	Z = 1.57	(P = 0.1)	2)				-0.5 -0.25 0 0.25 0.5 placebo levodopa

Figure S75. Levodopa pre- vs posttreatment (adverse event, augmentation) [CST = 5%] Observational¹⁻³

	Posttreat	ment	Pretreatr	ment		Risk Difference	Risk	Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	ndom, 95% CI
Allen 1996	22	30	0	30	13.9%	0.73 [0.57, 0.90]		-
Bassetti 2011	7	63	0	63	14.8%	0.11 [0.03, 0.19]		-
Earley 1996	29	36	0	36	14.3%	0.81 [0.67, 0.94]		_ -
Hogl 2010 (JN)	36	60	0	60	14.4%	0.60 [0.47, 0.73]		
Saletu 2003	1	21	0	21	14.4%	0.05 [-0.07, 0.17]		 -
Trenkwalder 2003	8	23	0	23	13.4%	0.35 [0.15, 0.55]		_ -
Trenkwalder 2007	26	183	0	183	14.9%	0.14 [0.09, 0.19]		-
Total (95% CI)		416		416	100.0%	0.39 [0.17, 0.61]		-
Total events	129		0					
Heterogeneity: Tau ² =	0.08; Chi ² =	= 180.22	2, df = 6 (P	< 0.000	$(01); I^2 = 9$	97%	I	
Test for overall effect:							-1 -0.5 pretreatme	0 0.5 1 ent posttreatment

- 1. Bassetti 2011 RCT compared levodopa to pramipexole so pre-vs posttreatment data used for comparison.
- 2. Earley 1996 RCT compared levodopa to pergolide so pre- vs posttreatment data used for comparison.
- 3. Trenkwalder 2007 RCT compared levodopa to cabergoline so pre-vs posttreatment data used for comparison.

Figure S76. Levodopa pre- vs posttreatment (adverse event, dizziness/vertigo) [CST = 5%] Observational^{1,2}

	Posttreat	ment	Pretreat	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bassetti 2011	11	63	0	63	42.4%	0.17 [0.08, 0.27]	
Trenkwalder 2007	12	183	0	183	57.6%	0.07 [0.03, 0.10]	-
Total (95% CI)		246		246	100.0%	0.11 [-0.00, 0.22]	•
Total events	23		0				
Heterogeneity: Tau² = Test for overall effect				0.03); l²	= 80%		-0.5 -0.25 0 0.25 0.5 pretreatment posttreatment

- 1. Bassetti 2011 RCT compared levodopa with pramipexole so pre-vs posttreatment data used for comparison.
- 2. Trenkwalder 2007 RCT compared levodopa to cabergoline so pre-vs posttreatment data used for comparison.

Figure S77. Levodopa vs placebo (adverse event, somnolence) [CST = 5%] RCT

	Levode	opa	Placebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Eisensehr 2004	4	20	3	20	0.05 [-0.18, 0.28]	
						-1 -U.5 U U.5 1 placebo levodopa



Pramipexole

Summary of Findings (GRADE)

Table S11 Pramipexole in adults with RLS

References: Allen 2014, Basetti 2011, Ferini-Strambi 2008, Garcia-Borreguero 2014, Hogl 2011, Inoue 2010, Jama 2009, Lipford 2012, Ma 2012, Manconi 2008, Manconi 2011, Manconi 2011 (N), Manconi 2011(SM), Montagna 2011, Montplaisir 1999, Oertel 2007, Partinen 2006, Silber 2003, Takahashi 2017, Winkelman 2004, Winkelman 2006, Zhang 2015

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Pramipexole vs Placebo or Control	
Disease severity	$\oplus \oplus \oplus \oplus$	The mean difference in the pramipexole group was 4.9 points	2917
[IRLS]	HIGH	lower (6.2 lower to 3.5 lower) compared to control	(1 RCT)
Quality of life	$\Theta\Theta\Theta$	The mean difference in the pramipexole group was 5.4 points	1634
[RLS QOL Abetz]	MODERATE	higher (2 higher to 8.7 higher) compared to control	(4 RCTs)
Sleep quality	$\oplus\oplus\oplus\bigcirc$	The mean difference in the pramipexole group was 0.69 SD	397
[PSQI/MOS pooled]	MODERATE ^a	higher (0.1 lower to 1.5 higher) compared to control	(2 RCTs)
Adverse events leading to study	$\oplus \oplus \oplus \bigcirc$	82 per 1000 (61 to 107) in the pramipexole group compared	3548
withdrawal	MODERATE ^a	to 51 per 1,000 in the control group	(17 RCTs)
Adverse event (somnolence)	$\oplus \oplus \oplus \bigcirc$	75 per 1000 (51 to 114) in the pramipexole group compared	1998
	MODERATE ^a	to 39 per 1,000 in the control group	(7 RCTs)
Adverse event (augmentation)	$\oplus \oplus \oplus \bigcirc$	110 per 1000 (55 to 220) in the pramipexole group compared)825
	MODERATE ^a	to 27 per 1,000 in the control group	(2 RCTs)
Adverse event (augmentation)	$\Theta\ThetaOO$	147 per 1000 (266 to 355) in the pramipexole group	640
	LOW	compared to 0 per 1,000 in the control group	(7 observational studies)
Adverse event (dizziness)	$\Theta\Theta\Theta$	91 per 1000 (59 to 136) in the pramipexole group compared	1745
	MODERATE ^a	to 45 per 1,000 in the control group	(6 RCTs)
Adverse event (impulse control	ФООО	100 per 1000 (17 to 183) in the pramipexole group compared	50
disorder	VERY LOW ^c	to 0 per 1,000 in the control group	(1 observational study)

- a. 95% CI crosses CST.
- b. High I squared value with unexplained heterogeneity.
- c. Small sample size. 95% CI crosses CST.

Critical Outcomes

Figure S78. Pramipexole vs placebo (IRLS) [CST =-3.0 pts] RCTs¹⁻⁵

	pran	nipexo	ole	pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allen 2014	13.3	7.4	347	15.5	7.1	172	12.7%	-2.20 [-3.52, -0.88]	-
Ferini-Strambi 2008	-13.4	9.3	178	-9.6	9.4	179	11.1%	-3.80 [-5.74, -1.86]	
Hogl 2011	-13.7	10.2	162	-11.1	10.1	159	10.4%	-2.60 [-4.82, -0.38]	
Inoue 2010	7.3	8.1	20	18.7	9.1	18	4.2%	-11.40 [-16.90, -5.90]	
Ma 2012	-15.9	9.2	195	-11.4	8.8	92	10.4%	-4.50 [-6.71, -2.29]	→
Montagna 2011	-14.2	10	203	-8.1	9.9	199	11.1%	-6.10 [-8.05, -4.15]	
Oertel 2007	-12.3	9	224	-5.7	9.6	114	10.6%	-6.60 [-8.72, -4.48]	
Partinen 2006	-15	7	86	-6.1	6.8	21	7.8%	-8.90 [-12.16, -5.64]	
Winkelman 2006	-13.5	9.3	258	-9.3	9.3	86	10.2%	-4.20 [-6.47, -1.93]	
Zhang 2015	-13.2	7.1	102	-9.4	6.1	102	11.4%	-3.80 [-5.62, -1.98]	
Total (95% CI)			1775			1142	100.0%	-4.86 [-6.20, -3.52]	•
Heterogeneity: Tau ² =	3.23; Ch	ii = 34	.41, df	= 9 (P <	0.000	11); l²=	74%	-	-20 -10 0 10 20
Test for overall effect:	Z = 7.10	(P ≤ 0.	.00001)					Favors pramipexole Favors placebo

^{1.} Change scores not reported in Inoue 2010 and Allen 2014 so posttreatment data were compared.

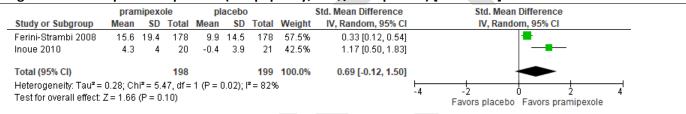
- 2. Data reported in Allen 2014 pooled across 2 different doses.
- 3. Data pooled across several countries in Hogl 2015 study.
- 4. SEs reported in Montagna 2011, Partinen 2006, Zhang 2015, and Oertel 2007 studies were converted to SDs.
- 5. Data pooled across 3 different doses for Partinen 2006 and Winkelman 2006 studies.

Figure S79. Pramipexole vs placebo (QOL, RLS QOL Abetz) [CST = +5 pt] RCT¹

	pran	nipexo	ole	pla	acebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Allen 2014	74.4	12.8	358	73.2	14	179	27.2%	1.20 [-1.24, 3.64]	-	
Ferini-Strambi 2008	17.5	18.7	178	11.6	13.1	178	24.0%	5.90 [2.55, 9.25]		
Montagna 2011	20	18.7	203	11.7	14.9	199	24.2%	8.30 [5.00, 11.60]	_ 	
Ninkelman 2006	20	13.1	254	13.5	12.9	85	24.6%	6.50 [3.32, 9.68]	-	
Total (95% CI)			993			641	100.0%	5.35 [2.05, 8.66]	•	
Heterogeneity: Tau² = 8.92; Chi² = 14.17, df = 3 (P = 0.003); I² = 79% Test for overall effect: Z = 3.17 (P = 0.002) Test for overall effect: Z = 3.17 (P = 0.002) Test for overall effect: Z = 3.17 (P = 0.002)										

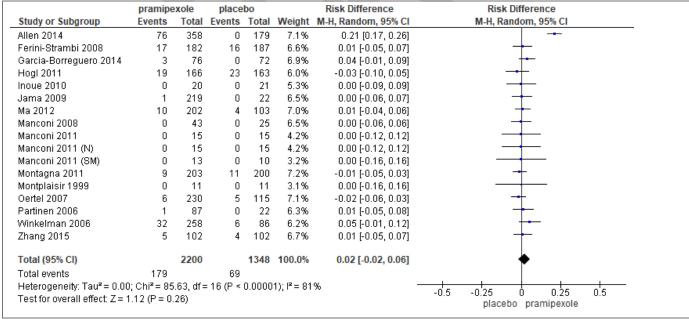
1. Data were pooled across 3 different doses and reported SEs were converted to SDs for Winkleman 2006 study.

Figure S80. Pramipexole vs placebo (Sleep quality, PSQI/MOS pooled) [CST = -0.2] RCT^{1,2}



- 1. Median change [P25%, P75%] converted to mean change (SD) for MOS measures reported in Ferini-Strambi 2008.
- 2. Inoue 2010 reported on sleep quality using the PSQI.

Figure S81. Pramipexole vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



29

Figure S82. Pramipexole vs placebo (Adverse event, augmentation) [CST = 5%] RCT¹

	pramipe	xole	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2014	27	345	0	179	68.3%	0.08 [0.05, 0.11]	_
Hogl 2011	28	152	9	149	31.7%	0.12 [0.05, 0.20]	
Total (95% CI)		497		328	100.0%	0.09 [0.04, 0.14]	•
Total events	55		9				
Heterogeneity: Tau ^z =	= 0.00; Chi ^a	= 1.95,	df = 1 (P	= 0.16); I ^z = 49%	6	
Test for overall effect:	Z = 3.57 (F	o.00	04)				-0.2 -0.1 0 0.1 0.2 placebo pramipexole

^{1.} Study duration for Allen 2014 and Hogl 2011 was 1 year and 6 months, respectively. Data from Hogl 2011 was normalized to 1 year.

Figure S83. Pramipexole pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Observational

	posttreat	ment	pretreati	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bassetti 2011	2	39	0	39	14.7%	0.05 [-0.03, 0.13]	+-
Ferini-Strambi 2002	5	60	0	60	14.9%	0.08 [0.01, 0.16]	-
Inoue 2010 (JNS)	6	141	0	141	16.1%	0.04 [0.01, 0.08]	-
Lipford 2012	21	50	0	50	12.2%	0.42 [0.28, 0.56]	
Silber 2003	20	60	0	60	13.0%	0.33 [0.21, 0.45]	
Takahashi 2017	21	231	0	231	16.1%	0.09 [0.05, 0.13]	-
Winkelman 2004	19	59	0	59	13.0%	0.32 [0.20, 0.44]	
Total (95% CI)		640		640	100.0%	0.18 [0.08, 0.27]	•
Total events	94		0				
Heterogeneity: Tau² = Test for overall effect:			•	0.0000	l1); l² = 93	9%	-0.5 -0.25 0 0.25 0.5 pretreatment posttreatment

Figure S84. Pramipexole vs placebo (Adverse event, somnolence) [CST = 5%] RCT

	pramipe	xole	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2014	26	358	0	179	25.1%	0.07 [0.04, 0.10]	-
Hogl 2011	11	166	8	163	16.3%	0.02 [-0.03, 0.07]	-
Inoue 2010	2	20	3	21	1.9%	-0.04 [-0.24, 0.16]	
Ma 2012	25	202	9	103	10.8%	0.04 [-0.03, 0.11]	+-
Oertel 2007	6	224	3	114	21.6%	0.00 [-0.04, 0.04]	+
Partinen 2006	3	87	0	22	10.5%	0.03 [-0.04, 0.11]	 -
Winkelman 2006	26	254	4	85	13.8%	0.06 [-0.00, 0.11]	-
Total (95% CI)		1311		687	100.0%	0.04 [0.01, 0.06]	•
Total events	99		27				
Heterogeneity: Tau² = Test for overall effect:	•		'	P = 0.0	7); I² = 48	%	-0.5 -0.25 0 0.25 0.5 placebo pramipexole

Figure S85. Pramipexole vs placebo (Adverse event, dizziness) [CST = 5%] RCT

	<u> </u>			·		<u>, , , , , , , , , , , , , , , , , , , </u>	
	pramipe	exole	place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Allen 2014	32	358	0	179	24.2%	0.09 [0.06, 0.12]	•
Ma 2012	28	202	9	103	16.7%	0.05 [-0.02, 0.12]	 ■−
Montplaisir 1999	4	11	0	11	2.4%	0.36 [0.07, 0.66]	
Oertel 2007	8	224	4	114	22.4%	0.00 [-0.04, 0.04]	+
Winkelman 2006	25	254	6	85	17.9%	0.03 [-0.04, 0.09]	+
Zhang 2015	8	102	8	102	16.5%	0.00 [-0.07, 0.07]	+
Total (95% CI)		1151		594	100.0%	0.04 [-0.00, 0.09]	•
Total events	105		27				
Heterogeneity: Tau ² :	= 0.00; Chi ^a	² = 18.40	D, df = 5 (i	P = 0.0	02); $I^2 = 73$	3%	-1 -0.5 0 0.5 1
Test for overall effect	: Z= 1.79 (I	P = 0.07	")				placebo pramipexole

Figure S86. Pramipexole pre- vs posttreatment (Adverse events, impulse control disorder) [CST = 5%] Observational

	posttreat	tment	pretreat	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Lipford 2012	5	50	0	50		0.10 [0.01, 0.19]	
						•	-0.2 -0.1 0 0.1 0.2
							pretreatment posttreatment



Rotigotine

Summary of Findings (GRADE)

Table S5 Rotigotine in adults with RLS

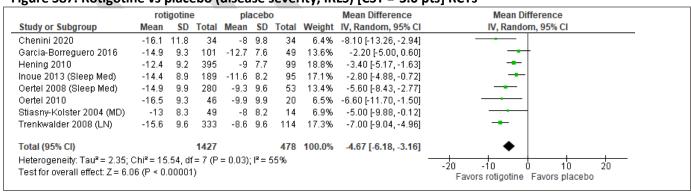
References: Chenini 2020, Garcia-Borreguero 2016, Hening 2010, Inoue 2013 (Sleep Med), Oertel 2008 (Sleep Med), Oertel 2010, Stiasny-Kolster 2004 (MD), Trenkwalder 2008 (LN), Inoue 2013 (PNBP), Oertel 2011, Stiasny-Kolster 2013

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Rotigotine vs Placebo or Control	
Disease severity	$\oplus \oplus \oplus \oplus$	The mean difference in the rotigotine group was 4.7 points	1905
[IRLS]	HIGH	lower (6.2 lower to 3.2 lower) compared to control	(8 RCTs)
Quality of life	$\oplus\oplus\oplus\bigcirc$	The mean difference in the rotigotine group was 4.5 points	1310
[RLS QOL Abetz]	MODERATE ^a	lower (8.2 higher to 0.8 lower) compared to control	(4 RCTs)
Sleep quality	$\oplus\oplus\oplus\bigcirc$	The mean difference in the rotigotine group was 0.2 SD	995
[PSQI/MOS pooled]	MODERATE ^a	higher (0.06 lower to 0.34 higher) compared to control	(4 RCTs)
Adverse events leading to study	$\oplus\oplus\oplus\bigcirc$	115 per 1000 (99 to 132) in the rotigotine group compared to	1927
withdrawal	MODERATE ^a	51 per 1,000 in the control group	(8 RCTs)
Adverse event (somnolence)	$\oplus \oplus \oplus \bigcirc$	119 per 1000 (94 to 144) in the rotigotine group compared to	855
	MODERATE ^a	39 per 1,000 in the control group	(3 RCTs)
Adverse event (dizziness)	$\oplus \oplus \oplus \bigcirc$	50 per 1000 (37 to 63) in the rotigotine group compared to 45	1369
	MODERATE ^a	per 1,000 in the control group	(4 RCTs)
Adverse event (application site	$\oplus \oplus \bigcirc \bigcirc$	335 per 1000 (304 to 366) in the rotigotine group compared	1205
reaction)	LOW ^{a,b}	to 27 per 1,000 in the control group	(5 RCTs)
Adverse event (augmentation)	Ф000	48 per 1000 (36 to 60) in the rotigotine group compared to 0	1164
	VERY LOW ^{a,b}	per 1,000 in the control group	(3 observational studies)

a. 95% CI of mean difference crossed CST.

Critical Outcomes

Figure S87. Rotigotine vs placebo (disease severity, IRLS) [CST =-3.0 pts] RCTs^{1,2}



^{1.} Data pooled across different drug dosages for Hening 2010, Inoue 2013, Oertel 2008, Stiasny-Kolster 2004, and Trenkwalder 2008.

b. High I-squared value with unexplained heterogeneity.

^{2.} SEM converted to SD prior to pooling data for Stiasny-Kolster 2004.

Figure S88. Rotigotine vs placebo (QOL, RLS QOL) [CST = -5 pts] RCT¹

	rotig	gotine	•	pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Hening 2010	-12.3	11.2	365	-10.7	11.5	99	31.5%	-1.60 [-4.14, 0.94]	
Oertel 2008 (Sleep Med)	-15.9	12.6	280	-12.4	15.5	53	24.1%	-3.50 [-7.93, 0.93]	
Oertel 2010	-15.5	14.5	46	-10.3	14.5	20	14.3%	-5.20 [-12.81, 2.41]	
Trenkwalder 2008 (LN)	-15.4	13.9	333	-7.3	13.5	114	30.1%	-8.10 [-10.99, -5.21]	-
Total (95% CI)			1024			286	100.0%	-4.53 [-8.21, -0.85]	•
Heterogeneity: Tau² = 9.53 Test for overall effect: Z = 2	•		df=3(P = 0.01	l); l²=	73%			-20 -10 0 10 20 Favors rotigotine Favors placebo

^{1.} Data pooled across different drug dosages for Hening 2010, Oertel 2008, and Trenkwalder 2008.

Figure S89. Rotigotine vs placebo (Sleep quality, PSQI and MOS pooled) [CST = SMD of 0.2] RCTs¹⁻³

<u> </u>		•		-					
	rot	igotine	е	pl	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Garcia-Borreguero 2016	17	19.9	101	13.2	18.2	49	17.4%	0.20 [-0.15, 0.54]	
Hening 2010	15	19.4	395	11	18.8	99	41.7%	0.21 [-0.01, 0.43]	
Inoue 2013 (Sleep Med)	3.1	3.2	189	2.5	2.4	95	33.3%	0.20 [-0.04, 0.45]	
Oertel 2010	13.7	19.8	46	10.8	19.9	21	7.6%	0.14 [-0.37, 0.66]	
Total (95% CI)			731			264	100.0%	0.20 [0.06, 0.34]	•
Heterogeneity: Tau² = 0.00	; Chi² = 1	0.05, d	lf=3 (P	= 1.00)	; I² = 0	%			-1 -0.5 0 0.5 1
Test for overall effect: Z = 2	.73 (P =	0.006))						Favors placebo Favors rotigotine

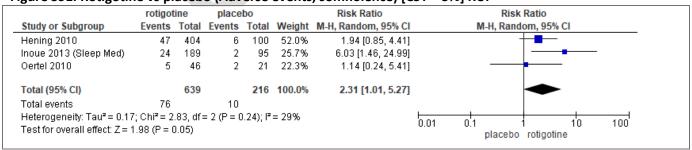
- 1. Data pooled across different drug dosages for Hening 2010 and Inoue 2013.
- 2. Inoue 2013 reported the PSQI. All other studies reported on the MOS.
- 3. Data from the MOS subscales were pooled within studies.

Figure S90. Rotigotine vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs¹

	rotigot	ine	place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chenini 2020	0	34	2	34	5.2%	0.20 [0.01, 4.02]	
Garcia-Borreguero 2016	4	101	0	49	5.5%	4.41 [0.24, 80.35]	- •
Hening 2010	82	404	4	100	20.6%	5.07 [1.91, 13.51]	_ -
Inoue 2013 (Sleep Med)	13	189	2	95	14.3%	3.27 [0.75, 14.18]	 •
Oertel 2008 (Sleep Med)	12	280	3	53	17.1%	0.76 [0.22, 2.59]	
Oertel 2010	2	46	1	21	7.7%	0.91 [0.09, 9.52]	- +
Stiasny-Kolster 2004 (MD)	0	49	1	14	4.8%	0.10 [0.00, 2.33]	
Trenkwalder 2008 (LN)	54	341	8	117	24.7%	2.32 [1.14, 4.72]	-
Total (95% CI)		1444		483	100.0%	1.72 [0.81, 3.65]	•
Total events	167		21				
Heterogeneity: Tau² = 0.46; (Chi ² = 13.1	10, df=	7 (P = 0.	07); l² =	47%		1004
Test for overall effect: Z = 1.4			•				0.001 0.1 1 10 1000 placebo rotigotine

^{1.} Data pooled across different drug dosages for Hening 2010, Inoue 2013, Oertel 2008, Stiasny-Kolster 2004, and Trenkwalder 2008.

Figure S91. Rotigotine vs placebo (Adverse events, somnolence) [CST = 5%] RCT¹



33

1. Data pooled across different drug dosages for studies.

Figure S92. Rotigotine vs placebo (Adverse events. dizziness/vertigo) [CST = 5%] RCT¹

	rotigot	ine	place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Hening 2010	21	404	6	100	42.8%	0.87 [0.36, 2.09]	
Oertel 2008 (Sleep Med)	12	285	4	55	28.8%	0.58 [0.19, 1.73]	
Oertel 2010	3	46	0	21	4.3%	3.28 [0.18, 60.73]	
Trenkwalder 2008 (LN)	18	341	3	117	24.1%	2.06 [0.62, 6.86]	+-
Total (95% CI)		1076		293	100.0%	1.01 [0.55, 1.85]	*
Total events	54		13				
Heterogeneity: Tau² = 0.02 Test for overall effect: Z = 0	•		3 (P = 0	.36); l²	= 6%		0.01 0.1 1 10 100 placebo rotigotine

1. Data pooled across different drug dosages for Hening 2010.

Figure S93. Rotigotine vs placebo (Adverse events, application site reaction) [CST = 5%] RCT

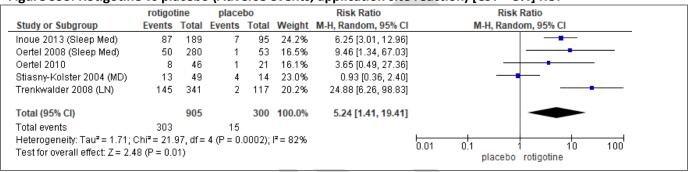


Figure S94. Rotigotine pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Open-label¹⁻³

	Posttreat	ment	Pretreat	ment		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Inoue 2013 (PNBP)	10	185	0	185	33.1%	0.05 [0.02, 0.09]	-
Oertel 2011	39	295	0	295	32.8%	0.13 [0.09, 0.17]	
Stiasny-Kolster 2013	7	684	0	684	34.1%	0.01 [0.00, 0.02]	†
Fotal (95% CI)		1164		1164	100.0%	0.06 [-0.05, 0.17]	•
Total events	56		0				
Heterogeneity: Tau² = 0 Test for overall effect: Z			df=2(P<	0.0000	1); I² = 98	%	-1 -0.5 0 0.5 1 pretreatment posttreatment

- 1. Inoue 2013 treatment duration was 1 year. Augmentation was defined by MPI criteria. Augmentation was evaluated by an independent panel of experts as well as by the individual investigators, similar to Oertel 2011. Augmentation in 10 of 185 Japanese patients met the MPI criteria, including clinically significant augmentation in 5 of these patients. One of these 5 patients discontinued administration because of augmentation. Study was of 1 year duration. The final dose used in this study was 1 mg/24 h in27.0%, 2 mg/24 h in 35.7% and 3 mg/24 h in 37.3%. Concomitant use of other RLS treatments was prohibited.
- 2. Oertel 2011 treatment duration was 5 years. Computer screening identified 145 German patients with suspected augmentation of symptoms. 107 patients showed signs of augmentation after exclusion of patients who met MPI criteria only after discontinuation of treatment or who had not initially responded to treatment. 69 patients met MPI criteria for augmentation, of whom 39 met MPI criteria for clinically significant augmentation on at least one visit. Discontinuation of therapy due to augmentation occurred in 12 patients, 4 of whom received EMA-approved doses. Study was of 5 years duration. At the end of maintenance almost half (49%) of patients were on 4 mg/24 h and few patients received the two lowest doses. 112 (39%) did not have a dose adjustment during maintenance. After the first year of maintenance, few patients needed dose adjustments: 151 of 290 (52%) in year 1; 36 of 220 (16%) in year 2; 26 of 191 (14%) in year 3; 16 of 159 (10%) in year 4; and ten of 147 (7%) in year 5. 41% (90/220) of patients started year 2 on 4 mg/24 h rotigotine. Concomitant use of other RLS treatments was prohibited.
- 3. Stiasny-Kolster 2013 treatment duration was 3 months. Mean rotigotine dose of longest duration was 2.4 ± 1.4 mg/24 h. The study only reported the number of patients who withdrew from the study due to augmentation, not the incidence of augmentation.

Supplemental material 34

Ropinirole

Summary of Findings (GRADE)

Table S13 Ropinirole in adults with RLS

References: Adler 2004, Allen 2004, Beneš 2011, Bliwise 2005, Bogan 2006, Garcı´a-Borreguero 2012, Giorgi 2013, Kushida 2008, Saletu 2000, Saletu 2010, Trenkwalder 2004 (JNNP), Walters 2004, Allen 2011, Giorgi 2013

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)	
	(GRADE)	Ropinirole vs Placebo or Control		
Disease severity	$\oplus\oplus\oplus\bigcirc$	The mean difference in the ropinirole group was 4.0 points	1314	
[IRLS]	MODERATE ^a	lower (5.4 lower to 2.6 lower) compared to control	(7 RCTs)	
Quality of life	$\oplus \oplus \oplus \bigcirc$	The mean difference in the ropinirole group was 3.8 points	768	
[RLS QOL Abetz}	MODERATE ^a	higher (1.8 higher to 5.8 lower) compared to control	(3 RCTs)	
Sleep quality	$\oplus\oplus\oplus\bigcirc$	The mean difference in the ropinirole group was 0.17 SD	615	
[MOS pooled]	MODERATE ^a	higher (0 to 0.35 higher) compared to control	(3 RCTs)	
Adverse events leading to study	$\oplus \oplus \oplus \bigcirc$	83 per 1000 (52 to 125) in the ropinirole group compared to	2067	
withdrawal	MODERATE ^a	52 per 1,000 in the control group	(8 RCTs)	
Adverse event (augmentation)	$\Theta\Theta\Theta\bigcirc$	21 per 1000 (9 to 33) in the ropinirole group compared to	1072	
	MODERATE ^a	2 per 1,000 in the control group	(3 RCTs)	
Adverse event (augmentation)	ФФОО	669 per 1,000 (613 to 726) in the ropinirole group compared	266	
[definite/highly suggestive]	LOW	to 0 per 1,000 in the control group	(1 observational study)	
Adverse event (somnolence)	$\oplus \oplus \oplus \bigcirc$	115 per 1000 (84 to 166) in the ropinirole group compared to	1430	
	MODERATE ^a	52 per 1,000 in the control group	(4 RCTs)	
Adverse event (dizziness)	$\oplus \oplus \oplus \bigcirc$	108 per 1000 (66 to 166) in the ropinirole group compared to	1315	
	MODERATE ^a	41 per 1,000 in the control group	(4 RCTs)	
a. 95% CI crosses CST	MODERATE	41 per 1,000 in the control group	(4 KCIS)	

Critical Outcomes

Figure S95. Ropinirole vs placebo (disease severity, IRLS) [CST =-3.0 points] RCTs¹⁻⁴

	Rop	iniro	le	Pla	icebo)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Adler 2004	13	12	22	24.7	7.2	22	4.6%	-11.70 [-17.55, -5.85]	
Benes 2011	-14.7	9	171	-9.9	9.1	60	13.7%	-4.80 [-7.47, -2.13]	
Bliwise 2005	14.3	3.8	9	20.7	4.1	13	10.6%	-6.40 [-9.74, -3.06]	
Bogan 2006	-13.5	8.2	186	-9.8	8.3	191	19.9%	-3.70 [-5.37, -2.03]	
Garcia-Borreguero 2012	-15.9	6.8	80	-13.4	6.3	67	16.8%	-2.50 [-4.62, -0.38]	
Trenkwalder 2004 (JNNP)	-11	8.7	146	-8	8.7	138	17.4%	-3.00 [-5.02, -0.98]	
Walters 2004	-11.2	7.7	102	-8.7	7.8	107	17.0%	-2.50 [-4.60, -0.40]	
Total (95% CI)			716			598	100.0%	-3.98 [-5.36, -2.60]	•
Heterogeneity: Tau² = 1.77;	Chi²= 13	.28, 0	df = 6 (F	o = 0.04); l² =	55%		-	-20 -10 0 10 20
Test for overall effect: $Z = 5.0$	66 (P < 0	.0000	11)						Favors ropinirole Favors placebo

- 1. Posttreatment values entered for Adler 2004, Garcia-Borreguero 2012, and Bliwise 2005 as change scores were not available.
- 2. Calculated SDs from 95% CI data reported in Benes 2011.
- 3. Calculated SDs from 2SE data reported in Bogan 2006.
- 4. Calculated SDs from SE data reported in Trenkwalder 2004 and Walters 2004.

Figure S96. Ropinirole vs placebo (QOL, RLS QOL) [CST = +5 pts] RCTs^{1,2}

	Roj	pinirol	е	Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bogan 2006	16.9	14.2	176	12.4	14.2	186	46.6%	4.50 [1.57, 7.43]	_
Giorgi 2013	18.5	13.7	94	16.5	13.7	103	27.2%	2.00 [-1.83, 5.83]	
Walters 2004	17.4	14.3	102	12.9	14.5	107	26.2%	4.50 [0.59, 8.41]	
Total (95% CI)			372			396	100.0%	3.82 [1.82, 5.82]	•
Heterogeneity: Tau ² = Test for overall effect:				-	0.55);	²= 0%			-10 -5 0 5 10
restion overall ellect.	. Z = 5.75	· (i – c	,.0002)						Favors placebo Favors ropinirole

- 1. Calculated SDs from 2SE data reported in Bogan 2006.
- 2. Calculated SDs from SE data reported in Giorgi 2013.

Figure S97. Ropinirole vs placebo (sleep quality, MOS pooled) [CST = 0.2] RCTs^{1,2}

	Ropinirole Placebo				acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allen 2004	9.6	16.4	27	7.4	16	25	9.9%	0.13 [-0.41, 0.68]	- •
Bogan 2006	18	16.8	175	16.7	17.6	186	56.0%	0.08 [-0.13, 0.28]	-
Giorgi 2013	12.7	13.2	97	8.2	13.2	105	34.2%	0.34 [0.06, 0.62]	 —■
Total (95% CI)			299			316	100.0%	0.17 [-0.00, 0.35]	•
Heterogeneity: Tau ² :	= 0.00; CI	hi = 2.	25, df=	2 (P =	0.32);	P= 119	%	-	-1 -05 0 05 1
Test for overall effect	: Z=1.93	P = 0	1.05)						Favors placebo Favors ropinirole

- 1. Calculated SDs from 2SE data reported in Bogan 2006.
- 2. Calculated SDs from SE data reported in Giorgi 2013 and Allen 2004.

Figure S98. Ropinirole vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs

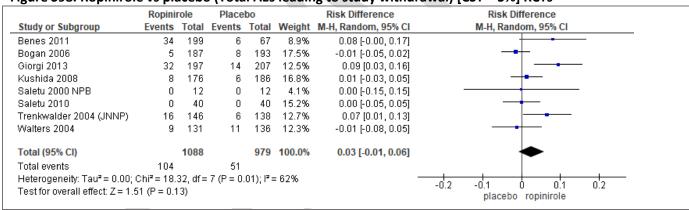
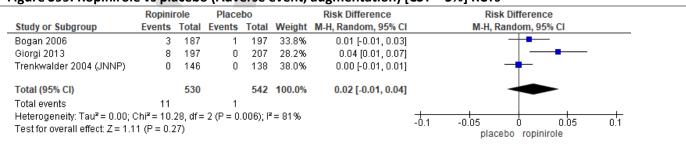


Figure S99. Ropinirole vs placebo (Adverse event, augmentation) [CST = 5%] RCTs¹⁻³



- 1. Bogan 2006 treatment duration was 12 weeks.
- 2. Giorgi 2013 treatment duration was 26 weeks.
- 3. Trenkwalder 2004 treatment duration was 12 weeks.

Figure S100. Ropinirole pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Observational¹

	erence	Risk Difference	Risk Difference	ment	pretreat	tment	posttreat	
Giorgi 2012 9 260 0 260 0.02 (0.01 0.05)	m, 95% CI	I M-H, Random, 95% CI	M-H, Random, 95% CI	Total	Events	Total	Events	Study or Subgroup
0 209 0 209 0.03 [0.01, 0.03]		 	0.03 [0.01, 0.05]	269	0	269	8	Giorgi 2013
-ò.1 -o.o5 ò pretreatment p	0.05 0.1 posttreatment	-ò.1 -o.05 ò o.ò5 o.º pretreatment posttreatment						

^{1.} Giorgi 2013 treatment duration was 40 weeks for the open-label phase.

Figure S101. Ropinirole pre- vs posttreatment (Adverse event, definite/highly suggestive likelihood of augmentation) [CST = 5%]

			pretreat	ment	Risk Difference	Risk Difference				
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Rai	ndom, 95% CI		
Allen 2011	178	266	0	266	0.67 [0.61, 0.73]				+	
						-1	-0.5	Ó	0.5	
							pretreatme	nt posttreatn	nent	

1. Allen 2011 mean treatment duration is 2.7 ± 2.4 years.

Figure S102. Ropinirole vs placebo (Adverse event, somnolence) [CST = 5%] RCTs

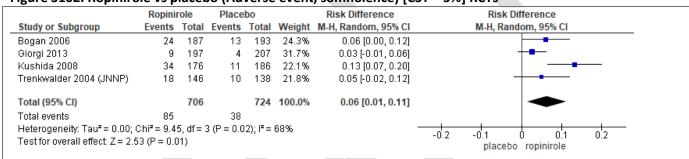


Figure S103. Ropinirole vs placebo (Adverse event, dizziness) [CST = 5%] RCTs

	Ropinii	role	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Benes 2011	17	197	2	67	24.1%	0.06 [-0.00, 0.11]	
Bogan 2006	18	187	11	193	27.0%	0.04 [-0.01, 0.09]	 •
Giorgi 2013	20	197	6	207	33.5%	0.07 [0.02, 0.12]	
Walters 2004	20	131	6	136	15.5%	0.11 [0.04, 0.18]	
Total (95% CI)		712		603	100.0%	0.07 [0.04, 0.09]	•
Total events	75		25				
Heterogeneity: Tau² = Test for overall effect:				P = 0.4	6); I² = 09	6	-0.2 -0.1 0 0.1 0.2 placebo ropinirole

Bupropion

Summary of Findings (GRADE)

Table S14 Bupropion in adults with RLS

References: Bayard 2011

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Bupropion vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊕⊜ MODERATEª	The mean difference in the bupropion group was 2.8 points lower (7.3 lower to 1.7 higher) compared to control	60 (1 RCT)
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATE ^a	142 per 1000 (37 to 503) in the bupropion group compared to 129 per 1,000 in the control group	60 (1 RCT)
a 95% CL crosses CST	WIODERATE	129 per 1,000 in the control group	(I KCI)

Critical Outcomes

Figure S104. Buproprion vs placebo (disease severity, IRLS) [CST = -3 points] RCT

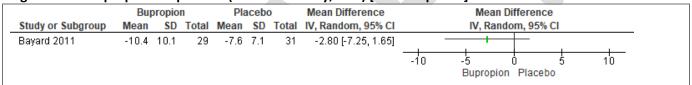
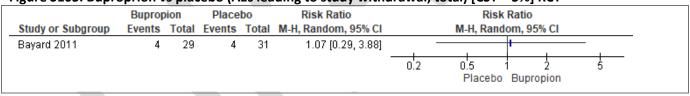


Figure S105. Buproprion vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT



Small sample size. h.

Carbamazepine

Summary of Findings (GRADE)

Table S15 Carbamazepine in adults with RLS

References: Lundvall 1983, Telstad 1984, Zucconi 1989

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Carbamazepine vs Placebo or Control	
Disease severity [Subjective frequency of RL sensations]	⊕⊕⊕⊜ MODERATEª	The mean difference in the carbamazepine group was 1.1 days/wk lower (3.1 day/wk lower to 0.9 days/wk higher) compared to control	12 (1 RCT)
Disease severity [Subjective severity ratings]	⊕⊕⊕○ MODERATE ^a	The mean difference in the carbamazepine group was 3.0 points lower (8.7 lower to 2.7 higher) compared to control	12 (1 RCT)
PLM frequency [Myoclonus Index]	⊕○○○ VERY LOW ^a	The mean PLM frequency pre-post difference was 1.4 jerks/hr higher (19.3 jerks/hr lower to 22.1 jerks/hr higher)	9 (1 observational study)
Sleep latency [PSG]	⊕○○○ VERY LOW ^{a,b}	The mean sleep latency pre-post difference was 25.7 minutes lower (48.3 minutes lower to 3.1 minutes higher)	9 (1 observational study)
WASO [PSG]	⊕○○○ VERY LOW ^{a,b}	The mean WASO pre-post difference was 65.1 minutes lower (126.4 minutes lower to 3.8 minutes lower)	9 (1 observational study
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATE ^{a,b}	67 per 1000 (15 to 188) in the carbamazepine group compared to 21 per 1,000 in the control group	184 (2 RCTs)
Adverse events leading to study withdrawal	⊕○○○ VERY LOW ^{a,b}	0 per 1000 in the carbamazepine group compared to 0 per 1,000 in the control group	9 (1 observational study)
Adverse event (dizziness)	⊕⊕⊕○ MODERATE ^{a,b}	167 per 1000 (-132 to 465) in the carbamazepine group compared to 0 per 1,000 in the control group	12 (1 RCT)

^{95%} CI crosses CST.

Critical Outcomes

Figure S106. Carbamazepine vs placebo for adults with RLS (Disease severity, RL sensations days/week) [No CST] RCT

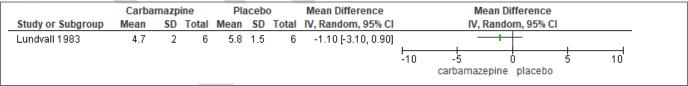


Figure S107. Carbamazepine vs placebo for adults with RLS (Disease severity, subj severity ratings) [No CST] **RCT**

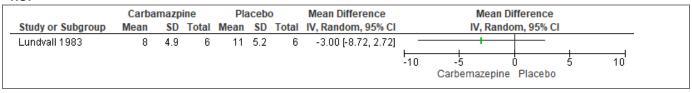


Figure S108. Carbamazepine vs placebo for adults with RLS (AEs leading to study withdrawal, total) [CST = 5%] RCT

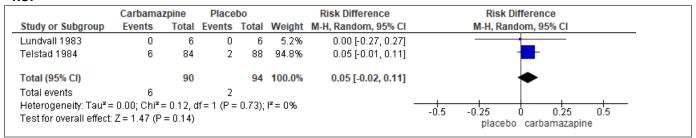


Figure S109. Carbamazepine pre- vs posttreatment for adults with RLS (AEs leading to study withdrawal, total) [CST = 5%] Observational

	Posttreatment Pretreatment				Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Zucconi 1989	0	9	0	9	0.00 (-0.19, 0.19) -	-0.2 -0.1 0 0.1 0.2 pretreatment posttreatment

Figure S110. Carbamazepine vs placebo for adults with RLS (Adverse events, dizziness) [CST = 5%] RCT

	Carbama	zpine	Place	bo	Risk Difference	Ri	sk Difference	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H,	Random, 95% CI	
Lundvall 1983	1	6	0	6	0.17 [-0.19, 0.53]			
						-1 -0.5	0 0.5	1
						pla	cebo carbamazepine	

Important Outcomes

Figure S111. Carbamazepine pre- vs posttreatment (PLM Freq, Myoclonus Index) [No CST] Observational¹

	Postt	reatm	ent	Pretr	eatme	ent	Mean Difference		Mea	an Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, R	andom, 95%	CI	
Zucconi 1989	29.2	26.9	9	27.8	16.7	9	1.40 [-19.29, 22.09]		. —	-	— .	
								-50	-25	Ó	25	50
									posttreatn	nent pretre	atment	

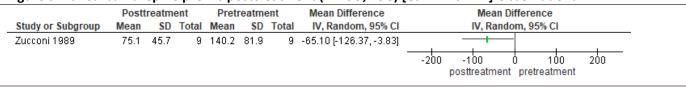
^{1.} Standard deviations were calculated from individual patient data in Zucconi 1989.

Figure S112. Carbamazepine pre- vs posttreatment (sleep latency, PSG) [CST = -10 min] Observational¹

	Posttreatment		Preti	eatme	ent	Mean Difference						
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rand	lom, 95%	CI	
Zucconi 1989	11.9	9.2	9	37.6	33.3	9	-25.70 [-48.27, -3.13]		 	-		
								-50	-25 posttreatmen	ό t pretrea	25 atment	50

^{1.} Standard deviations were calculated from individual patient data in Zucconi 1989.

Figure S113. Carbamazepine pre- vs posttreatment (WASO, PSG) [CST = -10 min] Observational¹



^{1.} Standard deviations were calculated from individual patient data in Zucconi 1989.

Clonazepam

Summary of Findings (GRADE)

Table S16 Clonazepam in adults with RLS

References: Boghen 1986, Montagna 1984, Saletu 2001

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Clonazepam vs Placebo or Control	No of Participants (studies)
PLM frequency	⊕⊕⊕⊜	The mean difference in the clonazepam group was 0.6 PLMs/hr lower (20.7 PLMs/hr lower to 19.4 PLMs/hr higher) compared to control	20
[PLMI]	MODERATEª		(1 RCT)
Sleep latency	⊕⊕⊕⊜	The mean difference in the clonazepam group was 3.2 minutes lower (14.8 mins lower to 8.4 minutes higher) compared to control	20
[PSG]	MODERATE ^{a,b}		(1 RCT)
WASO	⊕⊕⊕⊜	The mean difference in the clonazepam group was 28.3 minutes lower (40.0 mins lower to 16.8 minutes lower) compared to control	20
[PSG]	MODERATEª		(1 RCT)
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATE ^{a,c}	0 per 1000 in the clonazepam group compared to 0 per 1,000 in the control group	44 (3 RCTs)
Adverse event (sleepiness)	⊕⊕⊕⊜ MODERATEª,¢	330 per 1000 (-170 to 830) in the clonazepam group compared to 0 per 1,000 in the control group	12 (1 RCT)

- a. Small sample size.
- b. 95% CI crosses CST.
- c. Cannot determine for certain whether adverse events were directly attributed to the drug.

Critical Outcomes

Figure S114. Clonazepam vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCTs

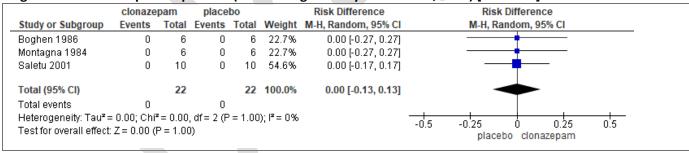


Figure S115. Clonazepam vs placebo (Adverse event, sleepiness) [CST = 5%] RCT

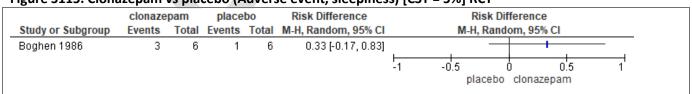


Figure S116. Clonazepam vs placebo (PLM Freq, PLMI) [No CST] RCT

	clon	azepa	m	pla	cebo	0	Mean Difference		Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	om, 95% CI	
Saletu 2001	31.5	24.6	10	32.1	21	10	-0.60 [-20.65, 19.45]	-50	-25	25	50
										Favors placebo	

Figure S117. Clonazepam vs placebo (Sleep latency, PSG) [CST = -10 min] RCT

			•	•					
	clon	azepa	ım	pla	cebo	0	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI	
Saletu 2001	16.2	16.1	10	19.4	9.4	10	-3.20 [-14.75, 8.35]		
								-20 -10 0 10	20
								Favors clonazepam Favors placebo	

Figure S118. Clonazepam vs placebo (WASO, PSG) [CST = -10 min] RCT

	clon	azepa	ım	pla	acebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Saletu 2001	31.3	32.7	10	99.9	66.6	10	-68.60 [-114.59, -22.61]	
								-200 -100 0 100 200 Favors clonazepam Favors placebo

Valerian

Summary of Findings (GRADE)

Table S6 Valerian in adults with RLS

References: Cuellar 2009

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Valerian vs Placebo or Control	
Disease severity	$\oplus\oplus\oplus\bigcirc$	The mean difference in the valerian group was 1.3 points	37
[IRLS]	MODERATE ^a	higher (5.1 lower to 7.7 higher) compared to control	(1 RCT)
Sleep quality	$\Theta\Theta\bigcirc\bigcirc$	The mean difference in the valerian group was 0.1 points	37
[PSQI]	LOW ^b	higher (3.2 lower to 3.5 higher) compared to control	(1 RCT)
Adverse events leading to study	$\Theta\Theta\bigcirc\bigcirc$	83 per 1000 (-71 to 238) in the valerian group compared to 0	48
withdrawal	LOW ^{a,c}	per 1,000 in the control group	(1 RCT)
Adverse event (dizziness)	ФООО	42 per 1000 (-38 to 122) in the valerian group compared to 0	48
	VERY LOW ^{b,c}	per 1,000 in the control group	(1 RCT)

- a. Small sample size. 95% CI crosses CST.
- b. Small sample size. 95% CI crosses both sides of CST.
- c. Cannot determine for certain whether adverse events were directly attributed to the drug.

Critical Outcomes

Figure S119. Valerian vs placebo for adults with RLS (Disease severity, IRLS) [CST = -3 pts] RCT

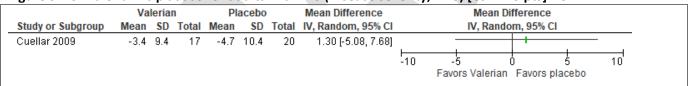


Figure S120. Valerian vs placebo for adults with RLS (Sleep quality, PSQI) [CST = -3 pts] RCT

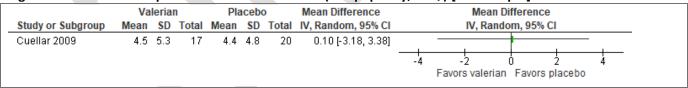


Figure S121. Valerian vs placebo for adults with RLS (AEs leading to study withdrawal, Total) [CST = -5%] RCT

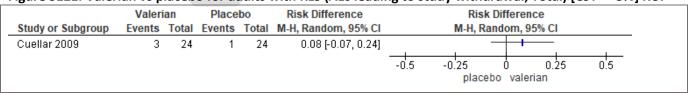


Figure S122. Valerian vs placebo for adults with RLS (Adverse event, dizziness) [CST = -5%] RCT

	Valeri	an	Placebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Cuellar 2009	1	24	0	24	0.04 [-0.07, 0.15]	
						-0.2 -0.1 0 0.1 0.2 placebo valerian



Valproic Acid

Summary of Findings (GRADE)

Table S7 Valproic Acid in adults with RLS

[RLS intensity score, 0-10] Disease severity [RLS duration during 24 hrs] PLM Frequency [PLMI] WASO Disease severity ⊕⊕○○ LOWa LOWa Disease severity ⊕⊕○○ LOWa Disease severity LOWa Disease severity ⊕⊕○○ LOWa	Valproic acid vs Placebo or Control The mean difference in the valproic acid group volumer (3.9 lower to 0.5 higher) compared to control The mean difference in the valproic acid group volumes lower (292.8 lower to 189.8 higher) control The mean difference in the valproic group was 5	ntrol (1 RCT) was 51.5 14 mpared to (1 RCT) 5.2 PLMs/hr 14
[RLS intensity score, 0-10] Disease severity [RLS duration during 24 hrs] PLM Frequency [PLMI] WASO □ Disease severity □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □	lower (3.9 lower to 0.5 higher) compared to con The mean difference in the valproic acid group v minutes lower (292.8 lower to 189.8 higher) con control	ntrol (1 RCT) was 51.5 14 mpared to (1 RCT) 5.2 PLMs/hr 14
Disease severity [RLS duration during 24 hrs] PLM Frequency [PLMI] WASO	The mean difference in the valproic acid group winutes lower (292.8 lower to 189.8 higher) control	was 51.5 14 (1 RCT) 5.2 PLMs/hr 14
PLM Frequency [PLMI] WASO LOWa LOWa LOWa LOWa	minutes lower (292.8 lower to 189.8 higher) concontrol	5.2 PLMs/hr 14
PLM Frequency	control	5.2 PLMs/hr 14
PLMI] LOW³ WASO ⊕⊕○○		·
PLMI] LOW³ WASO ⊕⊕○○		·
44 00	lower (41.5 PLMs/hr lower to 31.1 PLMs/hr high to control	her) compared (1 RCT)
[PSG] LOW ^a	The mean difference in the valproic acid group v	was 3.3 14
	minutes lower (22.4 lower to 15.8 higher) components	pared to (1 RCT)
Adverse events leading to study $\oplus \oplus \bigcirc \bigcirc$	0 per 1000 in the valproic acid group compared	d to 14
withdrawal LOW ^a	0 per 1,000 in the control group	(1 RCT)

Critical Outcomes

Figure S123. Valproic acid vs placebo for adults with RLS (Disease severity, RLS intensity 0-10 VAS) [No CST] **RCT**

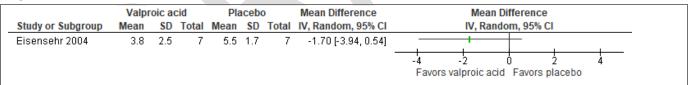


Figure S124. Valproic acid vs placebo for adults with RLS (Disease severity, RLS duration – min. during 24 hrs) [No CST] RCT

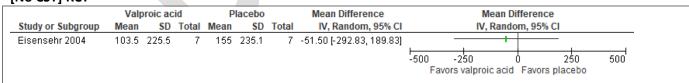


Figure S125. Valproic acid vs placebo for adults with RLS (AEs leading to study withdrawal, Total) [CST = 5%] **RCT**

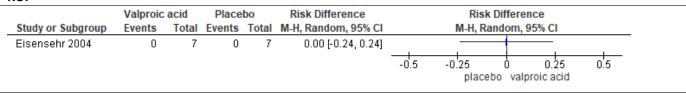


Figure S126. Valproic acid vs placebo for adults with RLS (PLM Freq, PLMI) [No CST] RCT

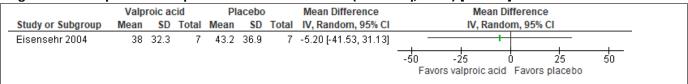


Figure S127, Valproic acid vs placebo for adults with RLS (WASO, PSG) [CST = -10 min] RCT

	Valpi	roic ac	cid	Pl	acebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Eisensehr 2004	18.5	15.4	7	21.8	20.6	7	-3.30 [-22.35, 15.75]	-50 -25 0 25 50 Favors valproic acid Favors placebo



Cabergoline

Summary of Findings (GRADE)

Table S8 Cabergoline in adults with RLS

References: Oertel 2006, Stiasny-Kolster 2004, Beneš 2004, Trenkwalder 2007, Zucconi 2003

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Cabergoline vs Placebo or Control	
Disease severity	$\oplus \oplus \oplus \bigcirc$	The mean difference in the cabergoline group was 12.5	124
[IRLS]	MODERATE ^a	points lower (17.2 lower to 7.9 lower) compared to control	(2 RCTs)
Quality of life	$\Theta\Theta\Theta\bigcirc$	The mean difference in the cabergoline group was 12.3	40
[RLS QOL Kohnen]	MODERATE ^a	points lower (22.3 lower to 2.3 lower compared to control	(1 RCT)
Sleep latency	$\Theta\Theta\Theta$	The mean difference in the cabergoline group was 17.7	40
[PSG]	MODERATE ^{a,b}	minutes higher (6.9 lower to 42.3 higher) compared to	(1 RCT)
		control	
PLM Frequency	$\Theta\Theta\Theta\Theta$	The mean difference in the cabergoline was 32.8 PLMs/hr	40
[PLMI]	MODERATE ^a	lower (56.8 PLMs/hr lower to 8.8 PLMs/hr lower)	(1 RCT)
		compared to control	
Adverse events leading to study	$\oplus \oplus \oplus \bigcirc$	81 per 1000 (24 to 139) in the cabergoline group	128
withdrawal	MODERATE ^a	compared to 0 per 1,000 in the control group	(2 RCTs)
Adverse event (dizzeness/vertigo)	000	70 per 1000 (2 to 1000) in the cabergoline group	128
	LOW ^{a,b,c}	compared to 95 per 1,000 in the control group	(2 RCTs)
Adverse event (augmentation)	Ф000	36 per 1000 (21 to 51) in the cabergoline group compared	1116
	VERY LOW ^b	to 41 per 1,000 in the control group	(4 observational studies)

- a. Small sample size
- b. 95% CI crosses CST
- c. High I-squared with unexplained heterogeneity.

Critical Outcomes

Figure S128. Cabergoline vs placebo (Disease severity, IRLS) [CST = -3 pts] RCTs¹

	cab	ergolir	1e	pla	ceb)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Oertel 2006	-23.7	11.2	20	-7.9	11	20	34.9%	-15.80 [-22.68, -8.92]	
Stiasny-Kolster 2004 (N)	-14.1	10.7	62	-3.3	8	22	65.1%	-10.80 [-15.07, -6.53]	-
Total (95% CI)			82			42	100.0%	-12.54 [-17.21, -7.87]	•
Heterogeneity: Tau² = 3.96	-		-	= 0.23)	2 =	32%			-20 -10 0 10 20
Test for overall effect: Z = 5	.26 (P <	0.0000	01)						Favors cabergoline Favors placebo

^{1.} Data pooled across 3 doses for Stiasny-Kolster 2004.

Figure S129. Cabergoline vs placebo (QOL, RLS-QOL Kohnen) [CST = -2.5 pts] RCTs

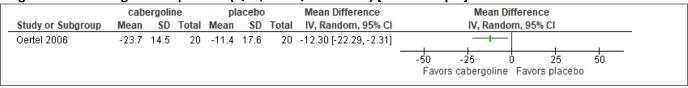
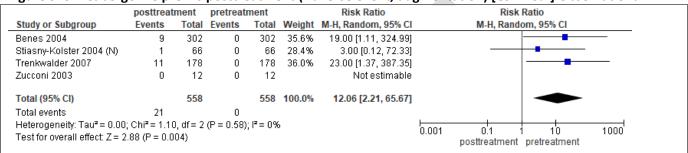


Figure S130. Cabergoline vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCTs

	cabergo		place			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Oertel 2006	3	23	0	20	49.6%	6.13 [0.34, 111.85]	
Stiasny-Kolster 2004 (N)	4	63	0	22	50.4%	3.23 [0.18, 57.77]	-
Total (95% CI)		86		42	100.0%	4.44 [0.57, 34.36]	
Total events	7		0				
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 0.0$	09, df=	1 (P = 0.3)	76); l ^z =	0%		
Test for overall effect: $Z = 1$.			·				0.005 0.1 1 10 200 placebo cabergoline

Figure S131. Cabergoline pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Observational¹



- 1. Pre- vs posttreatment data entered from RCT by Trenkwalder 2007 as control was levodopa. Treatment duration was 30 weeks.
- 2. Benes 2004 duration of treatment was 6 months.
- 3. Stiasny-Kolster 2004 duration of treatment was 47 weeks.
- 4. Zucconi 2003 duration of treatment was 2 months.

Figure S132. Cabergoline vs placebo (Adverse event; dizziness or vertigo) [CST = 5%] RCTs

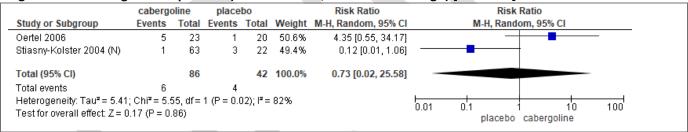


Figure S133. Cabergoline vs placebo (PLM Freq, PLMI) [No CST] RCTs

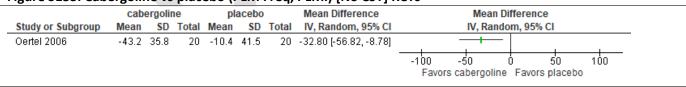
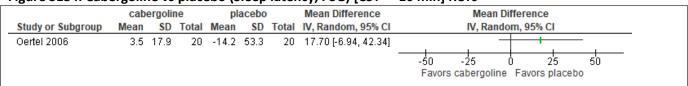


Figure S134. Cabergoline vs placebo (Sleep latency, PSG) [CST = -10 min] RCTs



PICO 2: Adult Populations with RLS and ESRD

Gabapentin in adults with RLS and CKD/ESRD

Summary of Findings (GRADE)

Table S20 Gabapentin in adults with RLS and CKD/ESRD

References: Thorp 2001, Ali 2020, Razazian 2015

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Gabapentin vs Placebo or Control	
Disease severity [IRLS]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the gabapentin group was 18.6 points lower (21.6 lower to 15.5 lower)	56 (2 observational studies)
Sleep Quality [PSQI]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the gabapentin group was 10.3 points lower (13.3 lower to 7.3 lower) compared to control	56 (2 observational studies)
Adverse events leading to study withdrawal	⊕⊕⊜⊜ LOW ^{a,b,c}	125 per 1,000 (37 fewer to 287 more) in the gabapentin group compared to 22 per 1,000 in the control group	32 (1 RCT)
Adverse event (somnolence)	⊕⊕⊜⊜ LOW ^{a,b,c}	125 per 1,000 (37 fewer to 287 more) in the gabapentin group compared to 73 per 1,000 in the control group	32 (1 RCT)

- a. Small sample size.
- b. Cannot determine whether adverse events were directly attributed to the intervention. Specific adverse events may be more serious than others.
- c. 95% CI crosses CST

Critical Outcomes

Figure S135. Gabapentin pre- vs posttreatment (Disease severity, IRLS) [CST =-5.0 pts] Observational

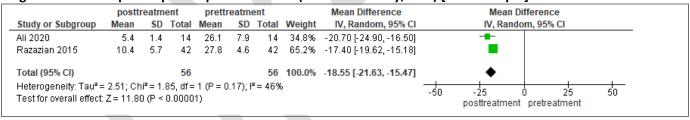


Figure S136. Gabapentin pre- vs posttreatment (Sleep quality, PSQI) [CST =-5.0 pts] Observational

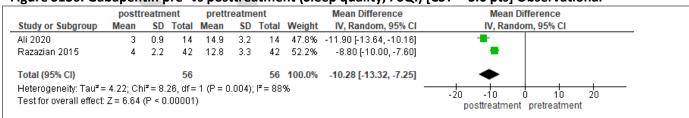


Figure S137. Gabapentin vs placebo (AEs leading to study withdrawal, total) [CST =5%] RCT

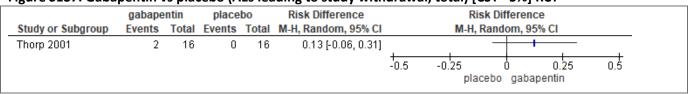


Figure S138. Gabapentin pre- vs posttreatment (AEs leading to study withdrawal, total) [CST =10%] Observational

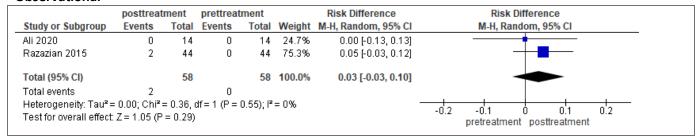


Figure S139. Gabapentin vs placebo (Adverse event, somnolence/lethargy) [CST =5%] RCT

	gabape	entin	placebo		Risk Difference	Risk Difference					
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, R	Random,	95% CI		
Thorp 2001	2	16	0	16	0.13 [-0.06, 0.31]				+ ,	_	
						-0.5	-0.25 plac	o ebo ga	0.2 bapenti		0.5

Figure S140. Gabapentin pre- vs posttreatment (Adverse event, somnolence) [CST =10%] Observational

	posttreat	tment	prettreat	ment	Risk Difference		Ris	k Differen	ce	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, R	Random, 95	5% CI	
Razazian 2015	6	44	0	44	0.14 [0.03, 0.24]			-		
						-1	-0.5	0	0.5	1
							pretreatm	nent postt	reatment	t

IV iron sucrose in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S21 IV iron sucrose in adults with RLS and ESRD

Certainty of the evidence	Absolute Difference	No of Participants (studies)	
(GRADE)	Gabapentin vs Placebo or Control		
⊕⊕⊕О морератеа	The mean difference in the IV iron sucrose group was 6.6 points	32 (1 RCT)	
	0 per 1,000 (110 fewer to 110 more) in the IV iron sucrose group	32	
MODERATE ^a	compared to the control group	(1 RCT)	
	(GRADE) ⊕⊕⊕○ MODERATE ^a ⊕⊕⊕○	(GRADE) Gabapentin vs Placebo or Control ⊕⊕⊕○ The mean difference in the IV iron sucrose group was 6.6 points MODERATE ^a lower (8.2 lower to 5.0 lower) compared to control ⊕⊕⊕○ 0 per 1,000 (110 fewer to 110 more) in the IV iron sucrose group	

Critical Outcomes

Figure S141. IV Iron Sucrose vs placebo (disease severity, IRLS) [CST= -3 points] RCT

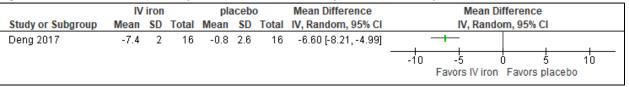
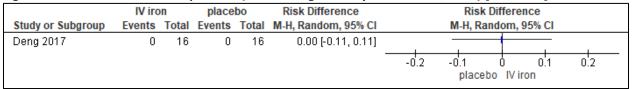


Figure S142. IV Iron sucrose vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT



Vitamin C in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S22 Vitamin C in adults with RLS and ESRD

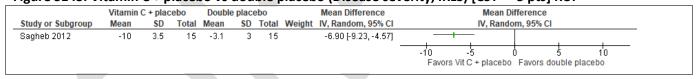
References: Sagheb 2012			
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Vitamin C vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊜⊜ LOW ^{a,b}	The mean difference in the vitamin c group was 6.9 points lower (9.2 lower to 4.6 lower) compared to control	30 (1 RCT)

a. As baseline vitamin deficiencies are important in this context and as it was not reported in the population selected, rated down for indirectness.

b. Small sample size.

Critical Outcomes

Figure S143. Vitamin C + placebo vs double placebo (Disease severity, IRLS) [CST = -3 pts] RCT



Levodopa in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S23 Levodopa in adults with RLS and ESRD

References: Trenkwalder 1995, Ali 2020, Micozkadioglu 2004, Pellecchia 2004, Razazian 2015

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Levodopa vs Placebo or Control	
Disease severity	$\oplus \oplus \bigcirc\bigcirc$	The mean difference in the levodopa group was 0.2 points	22
[CGI-S]	LOW ^{a,b}	lower (1.0 lower to 0.6 higher) compared to control	(1 RCT)
Disease severity	ФООО	The mean pre-post difference in the levodopa group was	52
IRLS	VERY LOW ^a	14.1 points lower (16.4 lower to 11.9 higher)	(2 observational studies)
Sleep quality	ФООО	The mean pre-post difference in the levodopa group was 7.2	52
[PSQI]	VERY LOW ^a	points lower (10.1 lower to 4.3 higher)	(2 observational studies)
PLM frequency	$\oplus \oplus \oplus \bigcirc$	The mean difference in the levodopa group was 28 PLMs/hr	22
[PLMI]	MODERATE ^a	lower (74.9 lower to 18.9 higher) compared to control	(1 RCT)
Adverse events leading to study	$\oplus \oplus \bigcirc \bigcirc$	0 per 1000 in the levodopa group compared to	22
withdrawal	LOW ^{a,b}	0 per 1,000 in the control group	(1 RCT)
Adverse events leading to study	ФООО	20 per 1000 (-30 to 80) in the levodopa group compared to	69
withdrawal	VERY LOW ^{a,c}	0 per 1,000 in the control group	(3 observational studies)

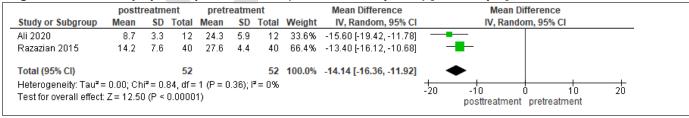
- Small sample size.
- 95% CI crosses both sides of CST.
- 95% CI crosses CST.

Critical Outcomes

Figure S144. Levodopa vs placebo (Disease severity, CGI-S) [CST = -0.5] RCT

	Lev	odop	a	Pla	cebo)	Mean Difference		Mea	n Diff	ference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Ra	indon	n, 95% CI	
Trenkwalder 1995	6.3	1	11	6.5	0.9	11	-0.20 [-1.00, 0.60]				_	
								-4	-2 Favors levodo	0 opa l	2 Favors placebo	4
*Crossover study, same pa	articipants	recei	ved plac	cebo and	levod	lopa						

Figure S145. Levodopa pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational¹



1. Ali 2020 and Razazian 2015 RCTs compared levodopa to gabapentin so pre- vs posttreatment data used for comparison.

Figure S146. Levodopa pre- vs posttreatment (Sleep quality, PSQI) [CST = -3 pts] Observational¹

U		•						1 1/ 1/ 6					
	posttr	eatme	ent	pretr	eatme	ent		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
Ali 2020	4.7	2.8	12	13.6	3.4	12	44.0%	-8.90 [-11.39, -6.41]	-				
Razazian 2015	7.1	3.8	40	13	2.7	40	56.0%	-5.90 [-7.34, -4.46]	•				
Total (95% CI)			52			52	100.0%	-7.22 [-10.14, -4.30]	•				
Heterogeneity: Tau² = Test for overall effect:				•	.04); l	²= 76%	5		-20 -10 0 10 20 posttreatment pretreatment				

^{1.} Ali 2020 and Razazian 2015 RCTs compared levodopa to gabapentin so pre- vs posttreatment data used for comparison.

Figure S147. Levodopa vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT

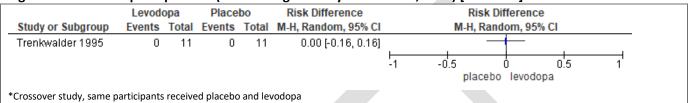
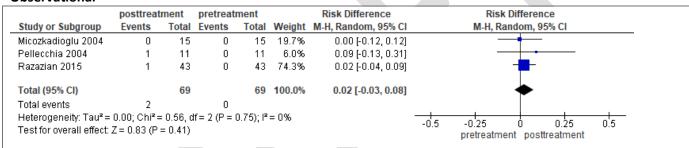
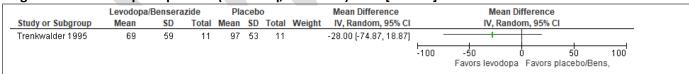


Figure S148. Levodopa pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational^{1,2}



- 1. Micozkadioglu 2004, and Razazian 2015 RCTs compared levodopa to gabapentin so pre- vs posttreatment data used for comparison.
- 2. Pellecchia 2004 RCT compared levodopa to ropinirole so pre- vs posttreatment data used for comparison.

Figure S149. Levodopa vs placebo (PLM Freq, PLMI PSG) RCTs [No CST]



Rotigotine in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S24 Rotigotine in adults with RLS and ESRD

References: Dauvilliers 2016

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Rotigotine vs Placebo or Control	
Disease severity	$\oplus \oplus \oplus \bigcirc$	The mean difference in the rotigotine group was 7 .3 points lower	25
[IRLS]	MODERATE ^{a,b}	(13.7 lower to 0.9 lower) compared to control	(1 RCT)
Quality of life			25
[RLS-QOL Kohnen]			(1 RCT)
PLM frequency	$\oplus \oplus \oplus \bigcirc$	The mean difference in the rotigotine group was 34 points lower	25
[PLMI]	MODERATE ^a	(57.5 lower to 10.5 lower) compared to control	(1 RCT)
Sleep latency	$\oplus \oplus \bigcirc\bigcirc$	The mean difference in the rotigotine group was 31.7 minutes	25
[PSG]	LOW ^{a,c}	lower (79.2 lower to 15.8 higher) compared to control	(1 RCT)
WASO	$\Theta\Theta\bigcirc\bigcirc$	The mean difference in the rotigotine group was 22.8 minutes	25
[PSG]	LOW ^{a,c}	lower (64.2 lower to 18.6 higher) compared to control	(1 RCT)
Adverse events leading to study	$\Theta\ThetaOO$	100 per 1000 (-31 to 231) in the rotigotine group compared to 0	30
withdrawal	LOW ^{a,c}	per 1,000 in the control group	(1 RCT)
Adverse event (augmentation)	$\Theta\Theta\Theta\bigcirc$	The study did not report on the incidence of augmentation.	30
	MODERATE ^a		(1 RCT)

- a. Small sample size
- b. 95% CI crosses CST
- c. 95% CI crosses both sides of CST

Critical Outcomes

Figure S150. Rotigotine vs placebo (disease severity, IRLS) [CST =-3.0 pts] RCT

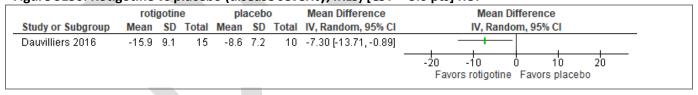


Figure S151. Rotigotine vs placebo (QOL, RLS-QOL Kohnen) [CST = -2.5 pts] RCT

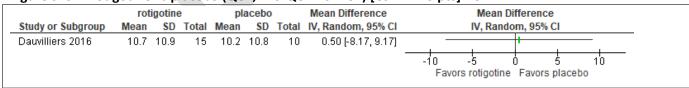
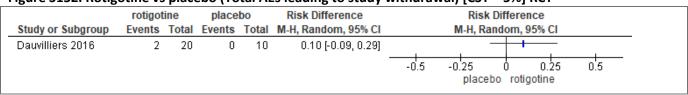


Figure S152. Rotigotine vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT



Supplemental material 54
Jan 2024

Figure S153. Rotigotine vs placebo (PLM Freq, PLMI) [No CST] RCT

•	U	•		•			,					
	rot	igotine	е	pla	ceb	0	Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	m, 95% CI		
Dauvilliers 2016	-23.7	38.7	15	10.3	21	10	-34.00 [-57.52, -10.48]					
								-100	-50 (50	100	
									Favors rotigotine	Favors placebo		

Figure S154. Rotigotine vs placebo (sleep latency, PSG) [CST = -10 min] RCT

	rot	igotine	9	placebo Mean Difference					Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rand	om, 95% CI			
Dauvilliers 2016	-18.9	83.9	15	12.8	34.4	10	-31.70 [-79.21, 15.81]			\vdash			
								-100	-50	Ò :	50	100	
									Favors rotigotine	Favors pla	cebo		

Figure S155. Rotigotine vs placebo (WASO, PSG) [CST = -10 min] RCT

	rot	igotine	9	pl	placebo		Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	om, 95% CI			
Dauvilliers 2016	-28.8	52.1	15	-6	51.5	10	-22.80 [-64.20, 18.60]		- , 		,		
								-100	-50	Ó	50	100	
									Favors rotigotine	Favors pla	acebo		

PICO 3: Adults with PLMD

Triazolam

Summary of Findings (GRADE)

Table S25 Triazolam in adults with PLMD

References: Bonnet 1991. Doghramii 1991

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Triazolam vs Placebo or Control	
Excessive daytime sleepiness	$\oplus\oplus\oplus\bigcirc$	The mean difference in the triazolam group was 3.4 minutes	30
[MSLT]	MODERATE ^{a,b}	higher (0.13 lower to 6.93 higher) compared to control	(1 RCT)
PLM frequency	$\Theta\Theta\Theta$	The mean difference in the triazolam group was 21.3 PLMs/hr	30
[PLMI]	MODERATE ^a	lower (44.5 lower to 1.9 higher)compared to control	(1 RCT)
WASO	$\oplus \oplus \oplus \bigcirc$	The mean difference in the triazolam group was 11.7 minutes	30
[PSG]	MODERATE ^{a,b}	lower (8.5 lower to 31.9 higher) compared to control	(1 RCT)
Sleep latency	$\Theta\Theta\Theta$	The mean difference in the triazolam group was 1.7 minutes	30
[PSG]	MODERATE ^{a,b}	higher (1.1 lower to 14.5 higher) compared to control	(1 RCT)
Adverse events leading to study	$\oplus\oplus\oplus\bigcirc$	0 per 1000 in the triazolam group compared to 0 per 1,000 in the	48
withdrawal	MODERATE ^a	control group	(2 RCTs)

b. 95% CI crosses CST

Critical Outcomes

Figure S156. Triazolam vs placebo for adults with PLMD (excessive daytime sleepiness, MSLT) [CST = 1 min] RCT¹

	Tria	zolar	n	Pla			Mean Difference	Mean Differe	ence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 9	15% CI
Doghramji 1991	9	5.4	15	5.6	4.4	15	3.40 [-0.13, 6.93]		
								-10 -5 0	5 10
								Favors placebo Fav	ors triazolam

^{1.} Posttreatment data used as change score data were not reported in Doghramji 1991.

Figure S157. Triazolam vs placebo for adults with PLMD (AEs leading to study withdrawal, total) [CST = 5%] RCT

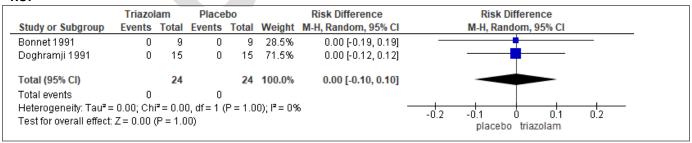


Figure S158. Triazolam vs placebo for adults with PLMD (PLMI) RCT1

	Tria	azolan	n	Placebo Mean Difference			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI				
Doghramji 1991	38.6	34.6	15	59.9	30.1	15	-21.30 [-44.51, 1.91]	-50 -25 0 25 50 Favors triazolam Favors placebo				

^{1.} Posttreatment data used as change score data were not reported in Doghramji 1991.

Figure S159. Triazolam vs placebo for adults with PLMD (Sleep latency, PSG) [CST = -10 min] RCTl¹

		•						7.				
	Tria	izolai	m	Pla	acebo)	Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI				
Doghramji 1991	4.8	4.8	15	3.1	2.6	15	1.70 [-1.06, 4.46]	++-				
								-10 -5 0 5 10				
								Favors triazolam Favors placebo				

1. Posttreatment data used as change score data were not reported in Doghramji 1991.

Figure S160. Triazolam vs placebo for adults with PLMD (WASO, PSG) [CST = -10 min] RCT¹

	Tria	azolan	n	Pla	Placebo		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI			
Doghramji 1991	36.2	35.7	15	24.5	17.9	15	11.70 [-8.51, 31.91]	-50 -25 0 25 50 Favors triazolam Favors placebo			

1. Posttreatment data used as change score data were not reported in Doghramji 1991.

Valproic Acid

Summary of Findings (GRADE)

Table S26 Valproic Acid in adults with PLMD

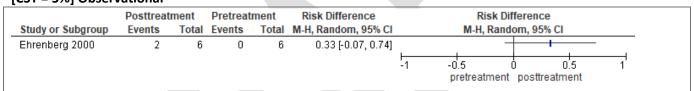
References: Ehrenberg 2000

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Valproic acid vs Placebo or Control	
PLM Frequency [PLMI]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the valproic group was 11.3 PLMs/hr lower (17.5 PLMs/hr lower to 5.1 PLMs/hr lower)	6 (1 observational study)
Adverse events leading to study withdrawal	⊕○○○ VERY LOW ^a	333 per 1000 (-44 to 711) in the valproic acid group compared to 0 per 1,000 in the control group	6 (1 observational study)

Small sample size.

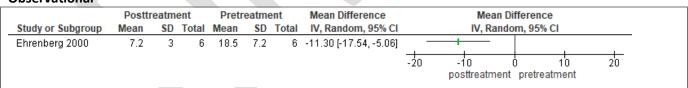
Critical Outcomes

Figure S161. Valproic acid pre- vs posttreatment for adults with PLMD (AEs leading to study withdrawal, Total) [CST = 5%] Observational



Important Outcomes

Figure S162. Valproic acid pre- vs posttreatment for adults with PLMD (PLM Freq, PLMI) [No CST] Observational¹



^{1.} Ranges reported in Ehrenberg 2000 were converted to SD.

^{95%} CI crosses CST

PICO 4: Pediatric Populations with RLS

Oral Iron

Summary of Findings (GRADE)

Table S27 Oral iron in children with RLS

References: Gurbani 2019, Rosen 2019

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)		
	(GRADE)	Oral iron vs Placebo or Control			
Disease severity [P-RLS-SS]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the oral iron group was 2.5 points lower (4.7 lower to 0.3 lower)	18 (1 RCT)		
Disease severity [IRLS]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the oral iron group was 10.5 points lower (15.4 lower to 5.6 lower)	18 (1 RCT)		
PLM frequency [PLMI]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the oral iron group was 10.5 PLMs/hr lower (15.4 lower to 6.4 lower)	95 (2 observational studies)		
Adverse events leading to study withdrawal	⊕○○○ VERY LOW ^a	1 per 1,000 in the oral iron group compared to 0 per 1,000 in the control group	95 (2 observational studies)		
a. Small sample size	VERT LOW	o per 1,000 in the control group	(2 observational studies		

Critical Outcomes

Figure S163. Ferrous sulfate pre- vs posttreatment (Disease severity, P-RLS-SS) [No CST] Observational

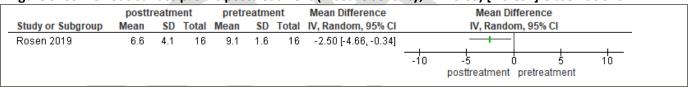


Figure S164. Ferrous sulfate pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational

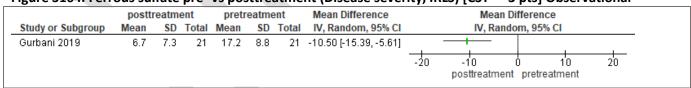


Figure S165. Ferrous sulfate pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

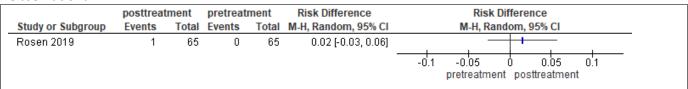
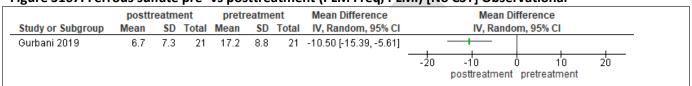


Figure S166. Ferrous sulfate pre- vs posttreatment (adverse event leading to withdrawal, total) [CST = 5%] Observational

	posttreatment		pretreat	ment	Risk Difference	Risk Difference						
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Ran	dom, 95% C	1			
Gurbani 2019	0	30	0	30	0.00 [-0.06, 0.06]				_			
						-0.1	-0.05 pretreatmen		05 ment	0.1		

Figure S167. Ferrous sulfate pre- vs posttreatment (PLM Freq, PLMI) [No CST] Observational



No Recommendation

'No Recommendation' is used in the guideline development process when there was value in the findings of included studies but further research and innovation for the intervention is needed.

PICO 1: Adults with RLS

Intravenous (IV) Iron Sucrose

Summary of Findings (GRADE)

Table S28 IV Iron Sucrose in adults with RLS

References: Earley 2009, Grote 2009

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	IV Iron Sucrose vs Placebo or Control	
Disease severity [IRLS]	⊕⊕⊜⊝ LOW ^{b,c}	The mean difference in the IV iron sucrose was 0.98 points lower (5.24 lower to 3.29 higher) compared to control	78 (2 RCTs)
Adverse events leading to study withdrawal	⊕⊕⊕⊜ MODERATEª	84 per 1000 in the IV iron sucrose group compared to 26 per 1,000 in the control group	78 (2 RCTs)

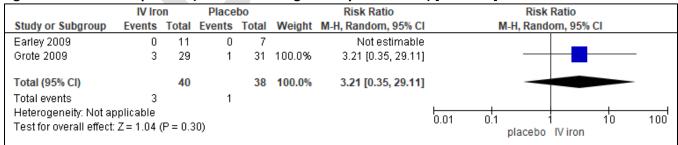
- a. 95% confidence interval crossed the clinical significance threshold.
- b. $I^2 = 85\%$ with unexplained heterogeneity.
- c. 95% confidence interval crosses both sides of clinical significance threshold and small sample size (<100).

Critical Outcomes

Figure S168. IV Iron sucrose vs placebo (RLS severity, IRLS) [CST =-3.0 points] RCTs

	IV	Iron		Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Earley 2009	-10.1	5.1	11	-12	11.5	7	22.2%	1.90 [-7.14, 10.94]	
Grote 2009	-8.7	9.4	29	-6.9	9.7	31	77.8%	-1.80 [-6.63, 3.03]	-
Total (95% CI)			40			38	100.0%	-0.98 [-5.24, 3.29]	•
Heterogeneity: Tau² = Test for overall effect:				i=1 (P=	= 0.48)	;	%		-20 -10 0 10 20 Favors IV iron Favors placebo

Figure S169. IV Iron vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



Clonidine

Summary of Findings (GRADE)

Table S29 Clonidine in adults with RLS

References: Wagner 1996

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference	No of Participants (studies)
		Clonidine vs Placebo or Control	
PLM Frequency [PLMI]	⊕⊕⊕⊜ MODERATE ^a	The mean difference in the clonidine group was 12.2 PLMs/night higher (15.6 lower to 40 higher) compared to control	20 (1 RCT)
Sleep latency [PSG]	⊕⊕⊕⊜ MODERATE ^{a,b}	The mean difference in the clonidine groups was 17.5 minutes lower (33.7 lower to 1.3 lower) compared to control	20 (1 RCT)
Adverse events leading to study withdrawal	⊕○○○ LOWa,c	0 per 1000 in the clonidine group compared to 0 per 1,000 in the control group	20 (1 RCT)
Adverse event (sleepiness)	⊕⊕⊕⊜ MODERATE ^{a,b}	500 per 1000 (190 to 810) in the clonidine group compared to 0 per 1,000 in the control group	20 (1 RCT)
Adverse event (lightheadedness)	⊕⊕⊕⊜ MODERATE ^{a,b}	600 per 1000 (158 to 1000) in the clonidine group compared to 200 per 1,000 in the control group	20 (1 RCT)

- Small sample size.
- 95% CI crosses CST
- 95% CI crosses CST on both sides

Critical Outcomes

Figure S170. Clonidine vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT

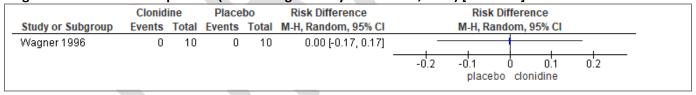


Figure S171. Clonidine vs placebo (Adverse event, sleepiness) [CST = 5%] RCT

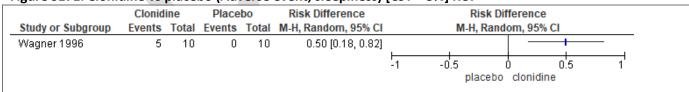


Figure S172. Clonidine vs placebo (Adverse event, lightheadedness) [CST = 5%] RCT

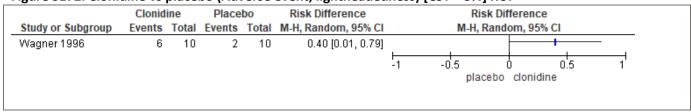


Figure S173. Clonidine vs placebo (PLM Freq, PLMI) [No CST] RCT

	Clo	nidine		Pla	Placebo		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI				
Wagner 1996	43.2	36.4	10	31	26.3	10	12.20 [-15.63, 40.03]	- - - - - - - - - - 				
							•	-50 -25 0 25 50				
								Favors clonidine Favors placebo				

Figure S174. Clonidine vs placebo (Sleep latency, PSG) [CST = -10 min] RCT

	Clo	nidine	9	Pla	Placebo		Mean Difference	Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI			IV, Rando	m, 95% (CI	
Wagner 1996	11.9	10.7	10	29.4	23.8	10	-17.50 [-33.67, -1.33]	-50		25	<u> </u>	 25	 50
										clonidine	Favors		

Botulinum

Summary of Findings (GRADE)

Table S30 Botulinum in adults with RLS

References: Mittal 2018, Nahab 2018

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Botulinum vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊜⊝ LOWª	The mean difference in the botulinum group was 2.3 points lower (9.0 lower to 4.4 higher) compared to control	12 (1 RCT)
Adverse events leading to study withdrawal	⊕⊕⊜⊝ LOWª	0 per 1000 in the botulinum group compared to 0 per 1,000 in the control group	60 (2 RCTs)

Very small sample size. 95% CI crossed CST in both directions.

Critical Outcomes

Figure S175. Botulinum toxin vs placebo (Disease severity, IRLS) [CST =-3.0 pts] RCT

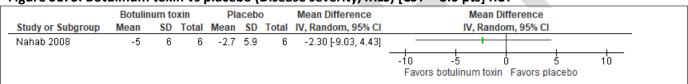
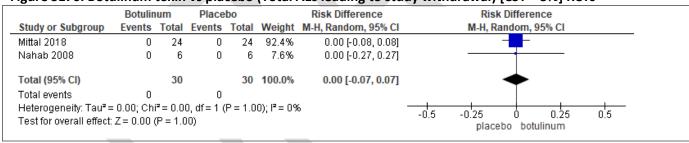


Figure S176. Botulinum toxin vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



Perampanel

Summary of Findings (GRADE)

Table S31 Perampanel in adults with RLS

References: Garcia-Borreguero 2017

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference	No of Participants (studies)
	(GRADL)	Perampanel vs Placebo or Control	
Disease severity	\oplus	The mean pre-post difference in the perampanel group was	20
[IRLS]	VERY LOW ^a	12.2 points lower (15.1 lower to 9.3 lower)	(1 observational study)
PLM frequency	Ф000	The mean pre-post difference in the perampanel group was	20
[PLMI]	VERY LOW ^a	23.4 PLMs/hr lower (26.5 lower to 20.3 lower)	(1 observational study)
Sleep latency	ФООО	The mean pre-post difference in the perampanel group was	20
[PSG]	VERY LOW ^{a,b}	11.9 minutes lower (18.1 lower to 5.7 lower)	(1 observational study)
WASO	ФООО	The mean pre-post difference in the perampanel group was	20
[PSG]	VERY LOW ^a	49.2 minutes lower (63.4 lower to 35.0 higher)	(1 observational study)
Adverse events leading to study	Ф000	50 per 1000 (-80 to 180) in the perampanel group compared	20
withdrawal	VERY LOW ^a	to 0 per 1,000 in the control group	(1 observational study)
Adverse event (dizziness)	ФООО	300 per 1000 (90 to 510) in the perampanel group	20
	VERY LOW ^{a,b}	compared to 0 per 1,000 in the control group	(1 observational study)
Adverse event (somnolence)	Ф000	100 per 1000 (-50 to 250) in the perampanel group	20
	VERY LOW ^a	compared to 0 per 1,000 in the control group	(1 observational study)

b. 95% CI crosses CST.

Critical Outcomes

Figure S177. Perampanel pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational

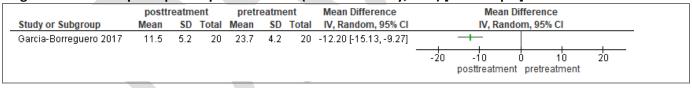


Figure S178. Perampanel pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

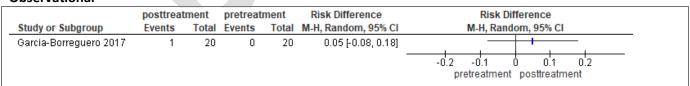


Figure S179. Perampanel pre- vs posttreatment (Adverse event, dizziness) [CST = 5%] Observational

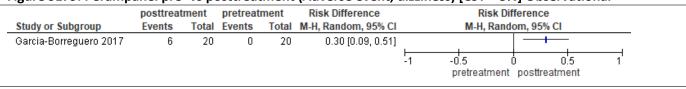


Figure S180. Perampanel pre- vs posttreatment (Adverse event, somnolence) [CST = 5%] Observational

	posttreat	tment	pretreatment		Risk Difference	Risk Difference				
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI		M-H, Random, 95% CI			
Garcia-Borreguero 2017	2	20	0	20	0.10 [-0.05, 0.25]	-0.5	-0.25 0 0.25 0.5 pretreatment posttreatment			

Important Outcomes

Figure S181 Perampanel pre- vs posttreatment (PLM Freq, PLMI) [No CST] Observational

	posttreatment			pretreatment			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI		
Garcia-Borreguero 2017	4.4	2	20	27.8	6.8	20	-23.40 [-26.51, -20.29]	+		
								-50 -25 0 25 50		
								posttreatment pretreatment		

Figure S182. Perampanel pre- vs posttreatment (Sleep latency, PSG) [CST = -10 min] Observational

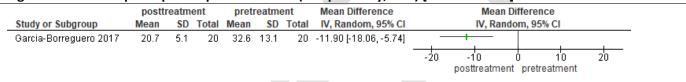


Figure S183. Perampanel pre- vs posttreatment (WASO, PSG) [CST = -10 min] Observational

	postt	reatm	ent	preti	reatme	ent	Mean Difference		Me	ean Differen	ce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, F	Random, 95	% CI	
Garcia-Borreguero 2017	40	19.4	20	89.2	26.1	20	-49.20 [-63.45, -34.95]		<u> </u>			
								-100	-50	- 6	50	100
									posttreat	ment pretr	eatment	

Vitamin D

Summary of Findings (GRADE)

Table S32 Vitamin D in adults with RLS

References: Wali 2019, Tutunc	u 2020, Wali 2015		
Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Vitamin D vs Placebo or Control	
Disease severity [IRLS]	⊕⊕⊖⊝ LOWª	The mean difference in the vitamin D group was 4.2 points higher (4.1 lower to 12.5 higher) compared to control	22 (1 RCT)
Disease severity [IRLS]	⊕⊕○○ LOWª	The mean pre-post difference in the vitamin D group was 9.8 points lower (10.6 lower to 5.1 lower) compared to control	48 (2 observational studies)

- a. High I-squared value with unexplained heterogeneity.
- b. Small sample size. 95% CI crosses CST.
- c. Small sample size. 95% CI crosses both sides of CST.

Critical Outcomes

Figure S184. Vitamin D vs placebo (Disease severity, IRLS) [CST = -3 pts] RCT¹

	vita	vitamin D		pla	acebo		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Wali 2019	14.5	8.2	12	10.3	11.1	10	4.20 [-4.10, 12.50]	
								-20 -10 0 10 20
								Favors vitamin D Favors placebo

^{1.} Posttreatment scores from both groups were compared as change scores were not reported in the Wali 2019 study. Differences in baseline scores for both vitamin and placebo (i.e., 14.6 ± 4.5 and 16.1 ± 6.2 , respectively) were reported. This difference may account for an underestimation or overestimation of the mean difference in disease severity between the two groups.

Figure S185. Vitamin D pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational¹

	posttr	eatme	ent	pretreatment			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
Tutuncu 2020	21	2.9	12	24.9	5.1	12	51.0%	-3.90 [-7.22, -0.58]	=		
Wali 2015	10	6.8	12	26	5	12	49.0%	-16.00 [-20.78, -11.22]	-		
Total (95% CI)			24			24	100.0%	-9.82 [-21.68, 2.03]	•		
Heterogeneity: Tau² = 68.80; Chi² = 16.63, df = 1 (P < 0.0001); l² = 94% Teet for everyll effect: 7 = 1.63 (P = 9.10)								-50 -25 0 25 50			
Heterogeneity: Tau 2 = 68.80; Chi 2 = 16.63, df = 1 (P < 0.0001); P = 94% Test for overall effect: Z = 1.62 (P = 0.10)									-50 -25 0 25 50 posttreatment pretreatment		

1. Ranges reported in Wali 2015 were converted to SD.

Yoga

Summary of Findings (GRADE)

Table S33 Yoga in adults with RLS

References: Innes 2020, Innes 2013

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Yoga vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊜⊝ LOW ^{a,b}	The mean difference in the yoga group was 5.3 points lower (9.6 lower to 1.1 lower) compared to control	40 (1 RCT)
Sleep quality [PSQI]	⊕⊕⊜⊝ LOW ^{a,b}	The mean difference in the yoga group was 1.2 points lower (3.2 lower to 0.8 higher) compared to control	40 (1 RCT)
Sleep quality [MOS pooled]	⊕○○○ VERY LOW ^{a,b}	The pre-post s tandardized mean difference in the yoga group was 1.1 SD higher (0.17 higher to 2.1 higher)	20 (1 observational study)

Inadequate blinding.

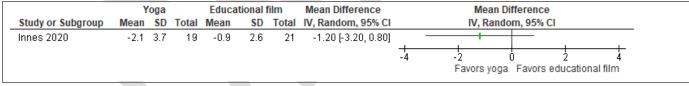
Critical Outcomes

Figure S186. Yoga vs educational film (Disease severity, IRLS) [CST = -3 pts.] RCT¹

	Yoga Educational film			Mean Difference		Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Random, 95% CI		
Innes 2020	-9.4	7.4	19	-4.1	6.2	21	-5.30 [-9.55, -1.05]				
								-10	-5 () ;	5 10
									Favors yoga	Favors edu	ucational film

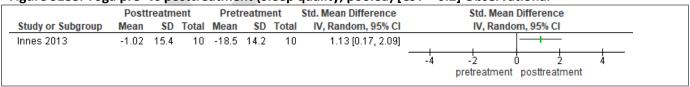
^{1.} SE data were converted to SD.

Figure S187. Yoga vs educational film (Sleep quality, PSQI) [CST = -3 pts] RCT¹



^{1.} SE data were converted to SD.

Figure S188. Yoga pre- vs posttreatment (Sleep quality, pooled) [CST = 0.2] Observational



68

Small sample size. 95% CI crosses CST.

Acupuncture

Summary of Findings (GRADE)

Table S34 Acupuncture in adults with RLS

References: Raissi 2017

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Acupuncture vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the acupuncture group was 2.5 points lower (10 lower to 5 higher) compared to control	33 (1 RCT)
Sleep quality [PSQI]	⊕⊕⊜⊝ LOW ^{a,c}	The mean difference in the acupuncture group was 2.5 points higher (1.9 lower to 6.9 higher) compared to control	33 (1 RCT)

- Inadequate blinding.
- Small sample size. 95% CI crosses both sides of CST.
- Small sample size. 95% CI crosses CST.

Critical Outcomes

Figure S189. Acupuncture + gabapentin vs gabapentin (Disease severity, IRLS) [CST = -3 pts] RCT

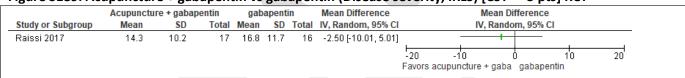
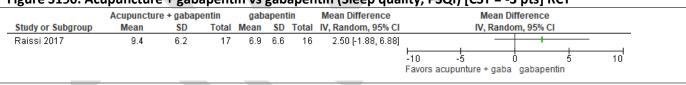


Figure S190. Acupuncture + gabapentin vs gabapentin (Sleep quality, PSQI) [CST = -3 pts] RCT



Cognitive Behavioral Therapy

Summary of Findings (GRADE)

Table S35 Cognitive behavioral therapy in adults with RLS

References: Hornyak 2008

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	CBT vs Placebo or Control	
Disease severity [IRLS]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the CBT group was 7.0 points lower (10.8 lower to 3.2 lower)	25 (1 observational study)
Quality of life [RLS QOL Kohnen]	⊕○○○ VERY LOW ^a	The mean pre-post difference in the CBT group was 7.4 points lower (13.7 lower to 1.1 lower)	25 (1 observational study)

a. Small sample size.

Critical Outcomes

Figure S191. CBT pre- vs posttreatment (Disease severity, IRLS) [CST = -3 points] Observational

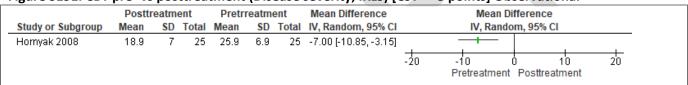
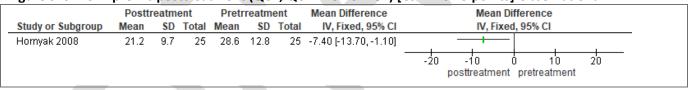


Figure S192. CBT pre- vs posttreatment (QOL, QOL-RLS Kohnen) [CST = -0.25 points] Observational



Near Infrared Light Therapy

Summary of Findings (GRADE)

Table S36 Near infrared light therapy in adults with RLS

References: Mitchell 2011 (PTP)

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	Near infrared light therapy vs Placebo or Control	
Disease severity	$\Theta\Theta\Theta$	The mean difference in the near infrared group was 8.3 points	34
[IRLS]	MODERATE ^a	lower (12.3 lower to 4.3 lower) compared to control	(1 RCT)

a. Small sample size.

Critical Outcomes

Figure S193. Near infrared vs sham control (Disease severity, IRLS) [CST = - 3 pts] RCT¹

	Near infrared light		Sham	cont	rol	Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI				
Mitchell 2011 (PTP)	-12.7	7.7	17	-4.4	3.6	17	-8.30 [-12.34, -4.26]					
							•	-20	-10	 	10	20
								Favo	ors near infrare	ed Favoi	rs sham	control

^{1.} The Mitchell 2011 RCT studied the efficacy of near infrared light (890 nm) versus sham control. The sham control consisted of the same device; however, the manufacturer disabled the control unit so that no light or other energy was emitted, but the panel showed the same 10 illuminated bars as the treatment unit.

Tramadol

Summary of Findings (GRADE)

Table S37 Tramadol in adults with RLS

References: Lauerma 1999

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)	
	(GRADE)	Tramadol vs Placebo or Control		
Disease severity	ФООО	The mean pre-post difference in the tramadol group was	10	
[Subjective Distress, 0-100]	VERY LOW ^a	80.2 points lower (90.7 lower to 69.7 lower)	(1 observational study)	
Adverse events leading to study	ФООО	0 per 1000 in the tramadol group compared to 0 per 1,000	12	
withdrawal	VERY LOW ^a	in the control group	(1 observational study)	
Adverse event (dizziness)	Ф000	83 per 1000 (-73 to 240) in the tramadol group compared to	12	
	VERY LOW ^a	0 per 1,000 in the control group	(1 observational study)	
a. Small sample size.				

Critical Outcomes

Figure S194. Tramadol pre- vs posttreatment (Disease severity, subj distress 0-100 scale) [No CST] Observational

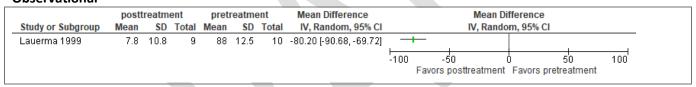


Figure S195. Tramadol pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

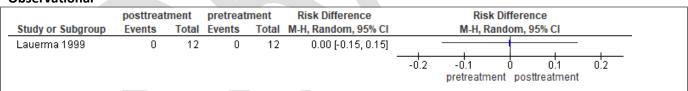
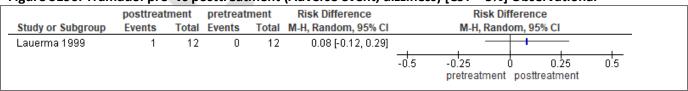


Figure S196. Tramadol pre- vs posttreatment (Adverse event, dizziness) [CST = 5%] Observational



72

Transcranial Magnetic Stimulation

Summary of Findings (GRADE)

Table S9 Transcranial magnetic stimulation in adults with RLS

References: Altunrende 2014

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Transcranial magnetic stimulation vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	•••	The mean difference in the TMS group was 15.9 points lower (19.9 lower to 11.9 lower) compared to control	19 (1 RCT)

a. Small sample size.

Critical Outcomes

Figure S197. Transcranial Magnetic Stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT¹

	T	MS		Sham	cont	rol	Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	m, 95% CI	
Altunrende 2014	12.7	5.1	11	28.6	3.8	8	-15.90 [-19.90, -11.90]	-20	-10 (Favors TMS	0 10 Favors sham	20 n control

1. No adverse events were reported.

b. There are concerns regarding the lack of improvement reported in the placebo group.

Transcutaneous Spinal Direct Current Stimulation

Summary of Findings (GRADE)

Table S39 Transcutaneous spinal DC stimulation in adults with RLS

References: Wang 2020

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference TSDCS vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊜⊝ LOW ^{a,b}	The mean difference in the TSDCS group was 8.4 points lower (13.6 lower to 3.2 lower) compared to control	30 (1 RCT)
Sleep quality [PSQI]	⊕⊕⊜⊜ LOW ^{a,c}	The mean difference in the TSCDS group was 1.6 points lower (4.2 lower to 1.0 higher) compared to control	30 (1 RCT)

- Study appears to be single-blinded.
- Small sample size.
- Small sample size. 95% CI crosses CST.

Critical Outcomes

Figure S198. Transcutaneous spinal DC stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT1

	Transcutan	eous Spina	al DC	Sham	cont	rol	Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		IV, Rando	m, 95% CI	
Wang 2020	15	7.4	15	23.4	7.2	15	-8.40 [-13.62, -3.18]				
								-20	-10 (0 10	20
								Favors	trans spinal DC	Favors sham contro	I

1. Posttreatment scores used as change scores were not reported in Wang 2020.

Figure S199. Transcutaneous spinal DC stimulation vs sham control (Sleep quality, PSQI) [CST = -3 pts] RCT¹

	Transcutan	eous Spina	al DC	Sham	cont	rol	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Wang 2020	10.3	3.7	15	11.9	3.6	15	-1.60 [-4.21, 1.01]	-10 -5 0 5 10 Favors trans spinal DC Favors sham control

1. Posttreatment scores used as change scores were not reported in Wang 2020.

PICO 2: Adult Populations with RLS and ESRD

Vitamin C + Vitamin E

Summary of Evidence (GRADE)

Table S40 Vitamin C + E in adults on hemodialysis with RLS

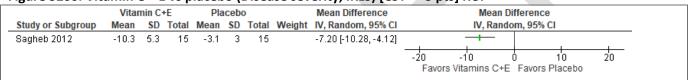
References: Sagheb 2012

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)	
	(GRADE)	Vitamin C + E vs Placebo or Control		
Disease severity	$\Theta\Theta\Theta\bigcirc$	The mean difference in the vitamin C + E group was 7.2 points	30	
[IRLS]	MODERATE ^a	lower (10.3 lower to 4.1 lower) compared to control	(1 RCT)	

a. Small sample size.

Critical Outcomes

Figure S200. Vitamin C + E vs placebo (Disease severity, IRLS) [CST = -3 pts] RCT



Vitamin E

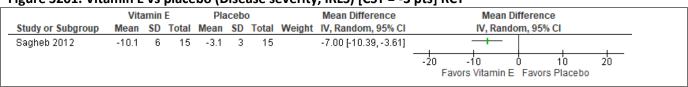
Summary of Evidence (GRADE)

Table S41 Vitamin in adults on hemodialysis with RLS

Outcomes	Certainty of the	Absolute Difference	No of Participants		
[Tool]	evidence		(studies)		
	(GRADE)	Vitamin E vs Placebo or Control			
Disease severity	$\Theta\Theta\Theta\Theta$	The mean difference in the vitamin E group was 7.0 points	30		
[IRLS]	MODERATE ^a	lower (10.4 lower to 3.6 lower) compared to control	(1 RCT)		

Critical Outcomes

Figure S201. Vitamin E vs placebo (Disease severity, IRLS) [CST = -3 pts] RCT



Other Interventions

The studies investigating these interventions were not considered for recommendations. These studies had limited data on critical or important outcomes and biased study designs or methods.

Alpha-Dihydroergocryptine

Bromocriptine

Cryotherapy

Deep brain stimulation for Parkinson's and RLS

Exercise

Foot Massage Heat therapy Hot/cold baths

Hypericin

Hydrocort is one

Istradefylline

Levetiracetam for children with ADHD and RLS

Light therapy

Magnesium with PLMD

Melatonin

Olive oil massage

Pneumatic compression

Pramipexole for spinal cord injury and RLS Pramipexole for type II diabetes and RLS

Refaximine

Relaxis

RESTIFFIC device

