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 ("wittmaack"[All Fields] AND "ekbom"[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 any 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

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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
        j. 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

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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
    l. 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

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UPDRS – Unified Parkinson's Disease Rating Scale

DRAFT

PICO 1: Adults with RLS

Gabapentin Enacarbil

Summary of Findings (GRADE)

Table S1 Gabapentin enacarbil in adults with RLS

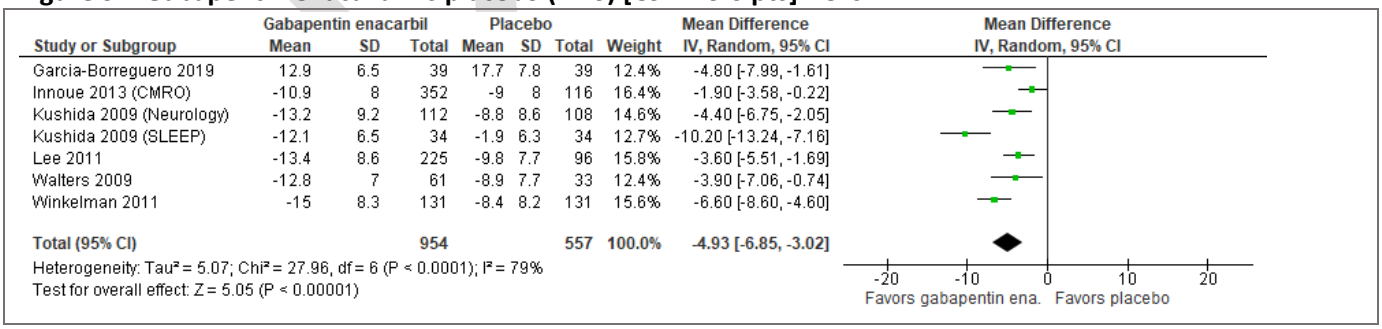
References: Garcia-Borreguero 2019, Innoue 2013, Kushida 2009 Neuro, Kushida 2009 SLEEP, Lee 2011, Walters 2009, Winkelman 2011, Lal 2011, Bogan 2010, Innoue 2012,

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Gabapentin Enacarbil vs Placebo or Control	No of Participants (studies)
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)	⨁⨁⨁⨁ **HIGH**	**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)

a. 95% CI crosses CST
b. small sample size

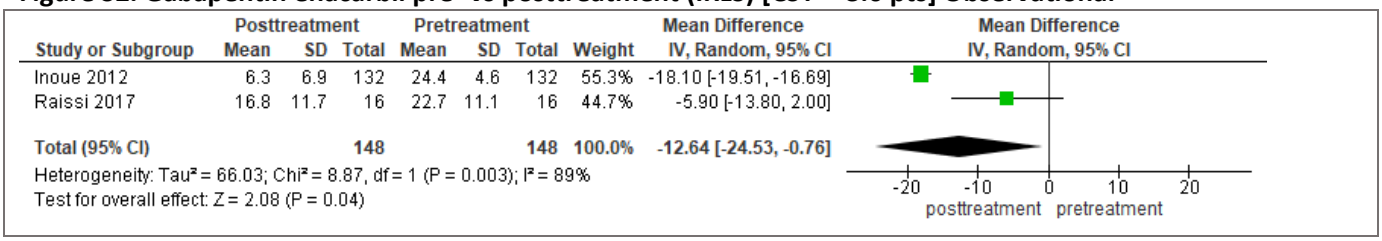
Critical Outcomes

Figure S1. Gabapentin enacarbil vs placebo (IRLS) [CST =-3.0 pts] RCTs[1]



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] Observational[1]



1. SEs reported in study were converted to SDs.

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

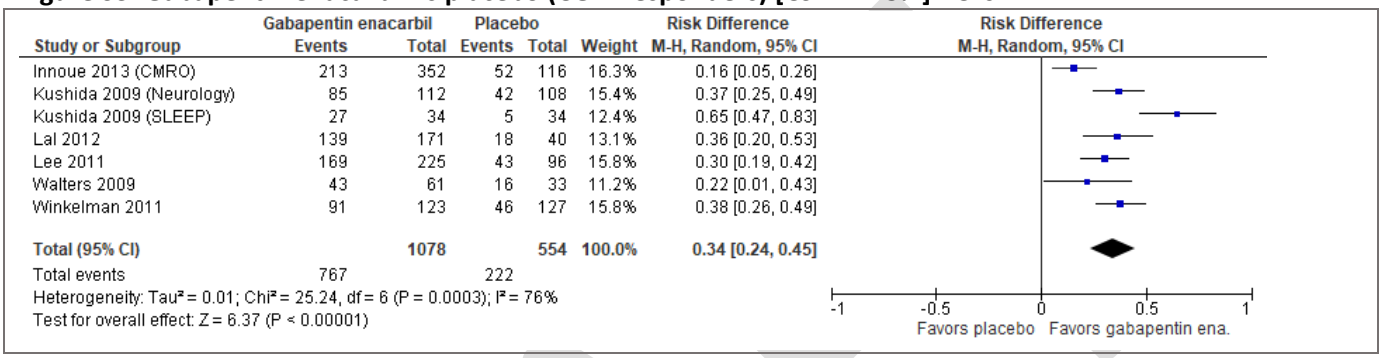


Figure S4. Gabapentin enacarbil pre- vs posttreatment (Disease severity, CGI-I responders) [CST = +15%] Observational

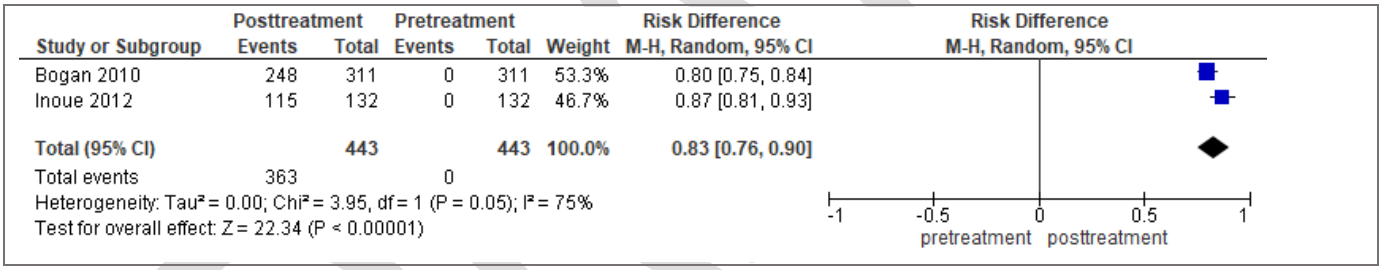


Figure S5. Gabapentin enacarbil vs placebo (PGI responders) [CST= +15%] RCTs

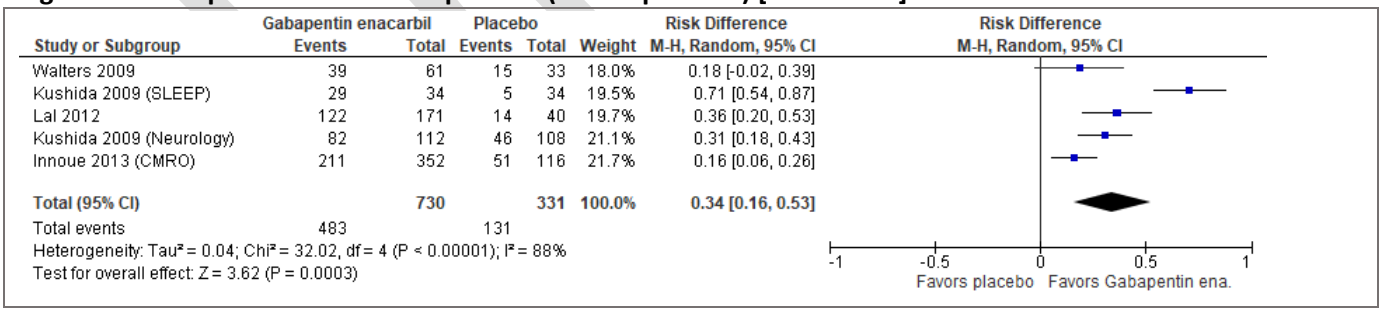


Figure S6. Gabapentin enacarbil pre- vs posttreatment (Disease severity, PGI-I responders) [CST = +15%] Observational

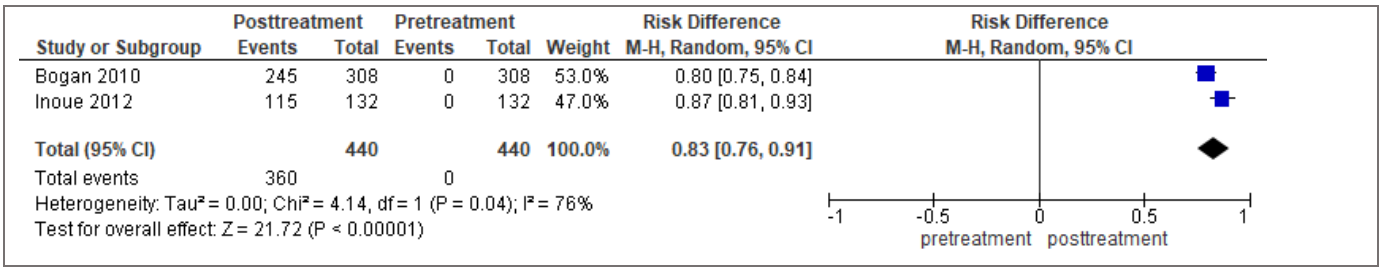
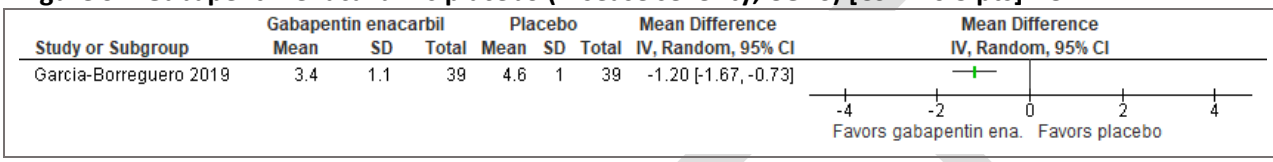
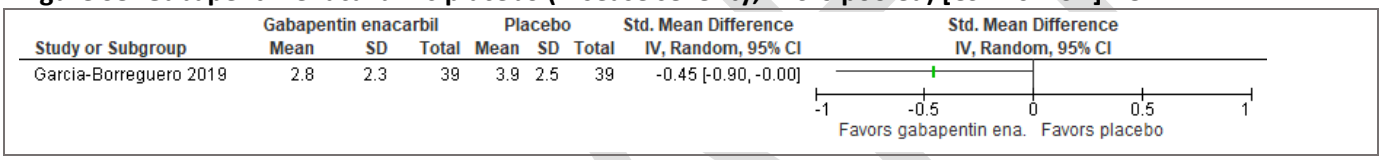


Figure S7. Gabapentin enacarbil vs placebo (Disease severity, CGI-S) [CST= -0.5 pts] RCT[1]



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] RCT[1]



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

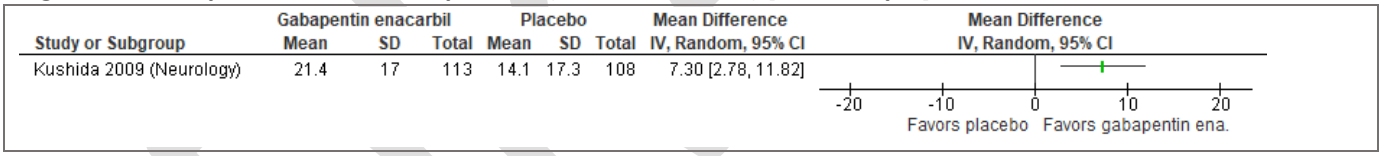
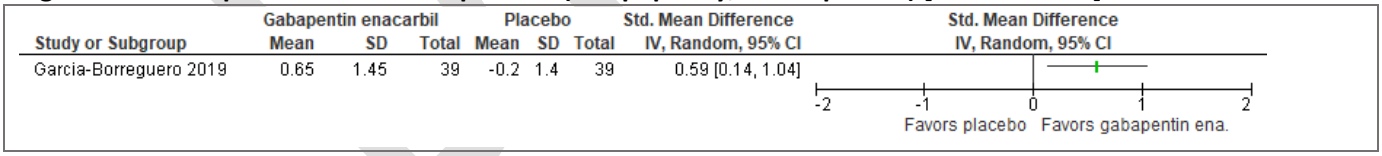
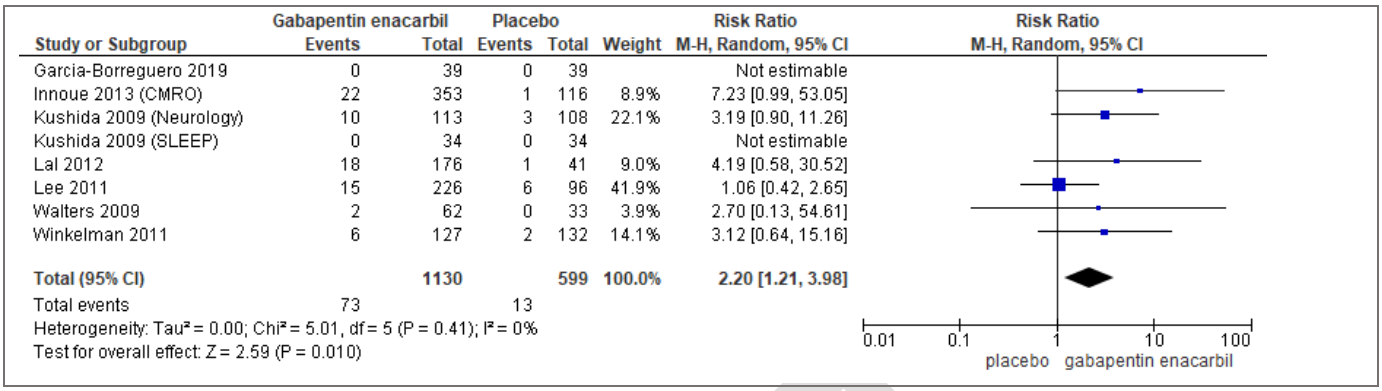


Figure S10. Gabapentin enacarbil vs placebo (Sleep quality, MOSS pooled) [CST = 0.2 SDs] RCT[1]



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] RCTs[1]



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

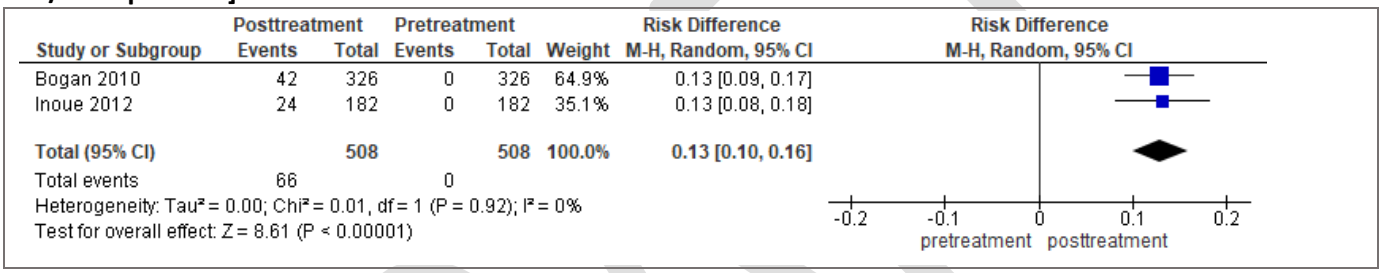
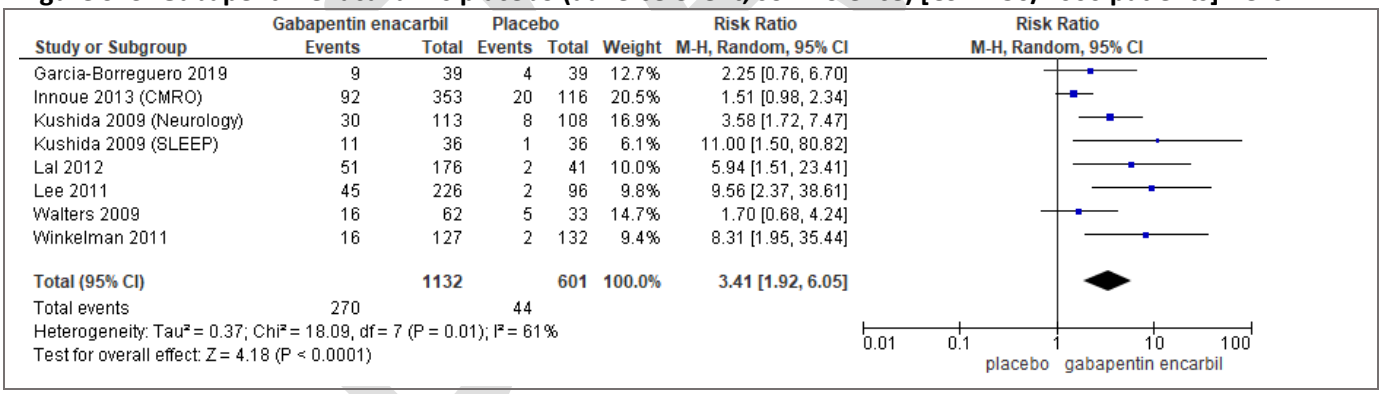


Figure S13. Gabapentin enacarbil vs placebo (adverse event, somnolence) [CST = 50/1000 patients] RCTs[1]



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

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

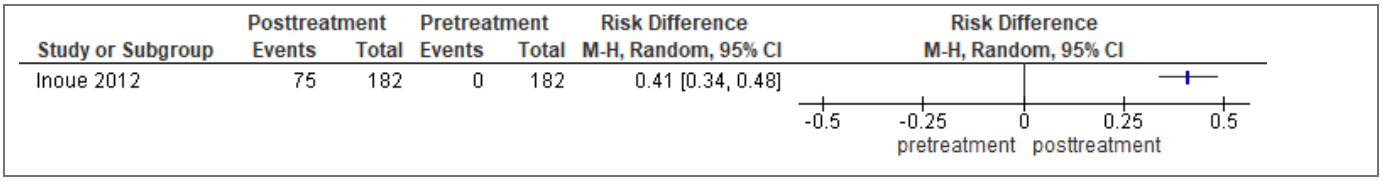
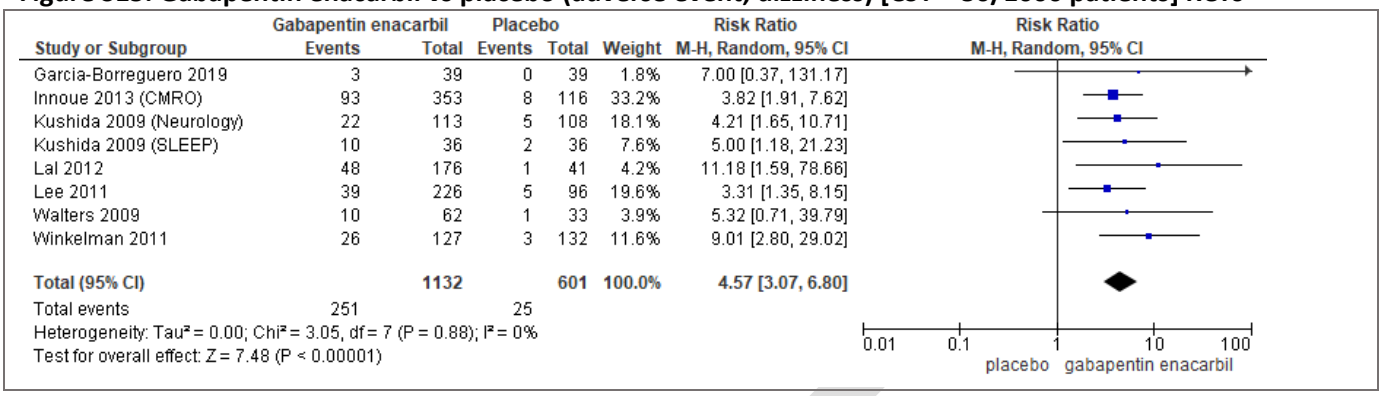
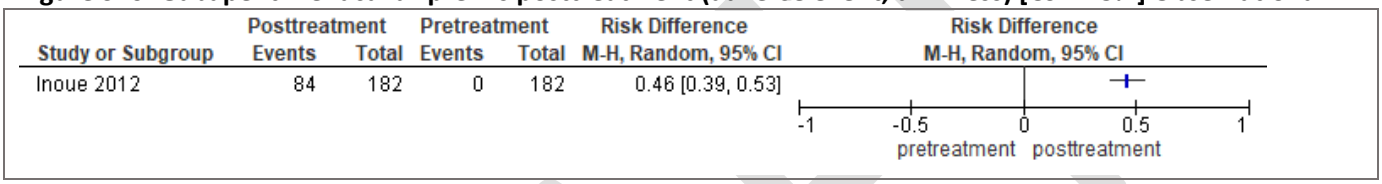


Figure S15. Gabapentin enacarbil vs placebo (adverse event, dizziness) [CST = 50/1000 patients] RCTs[1]



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



Important Outcomes

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

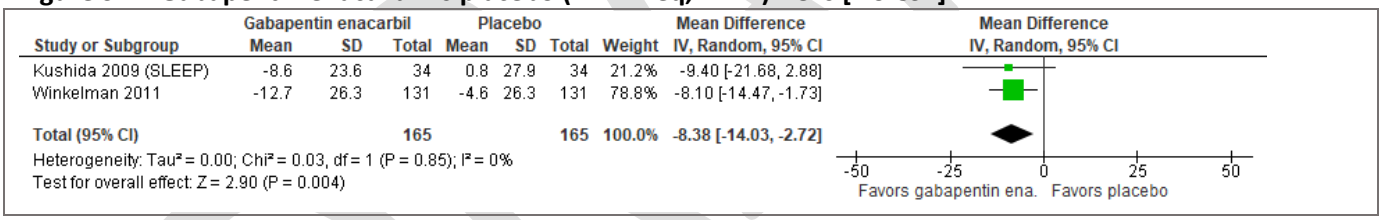


Figure S18. Gabapentin enacarbil vs placebo (Sleep latency, PSG) RCTs [CST =-10 min]

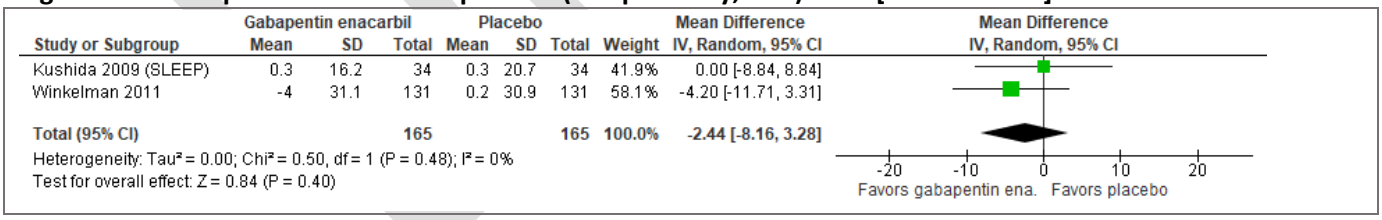
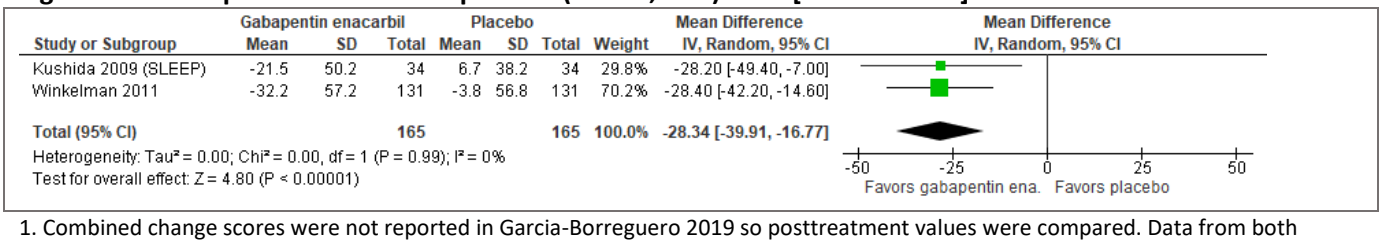


Figure S19. Gabapentin enacarbil vs placebo (WASO, PSG) RCTs [CST =-10 min]



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

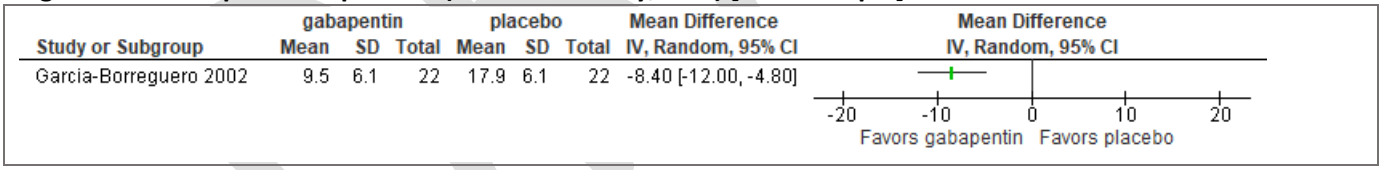
References: Garcia-Borreguero 2002, Saletu 2010, Happe 2001, Happe 2003, Raissi 2017, Adler 1997

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Gabapentin vs Placebo or Control	No of Participants (studies)
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]	⨁⨁⨁◯ **MODERATE**[a]	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	⨁⨁⨁⨁ **HIGH**	**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)	⨁⨁⨁◯ **MODERATE**[a]	**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)	⨁⨁⨁◯ **MODERATE**[a]	**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.
b. 95% CI crosses CST.

Critical Outcomes

Figure S20. Gabapentin vs placebo (Disease severity, IRLS) [CST =-3.0 pts] RCT[1]



1. SE reported in the study was converted to SD.

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

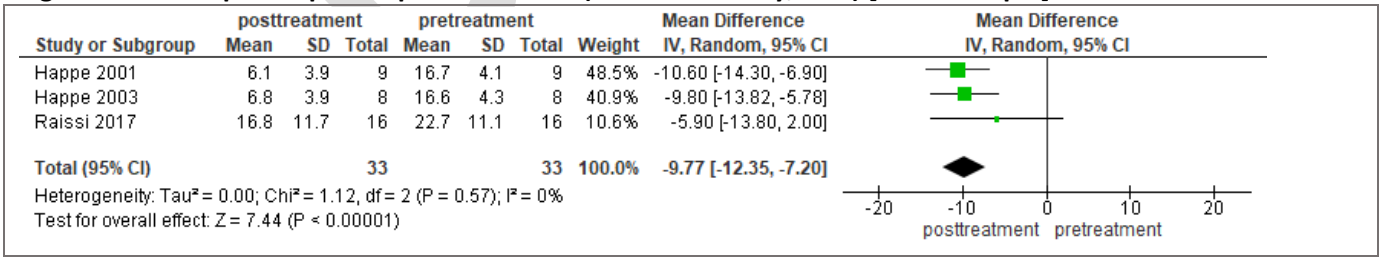
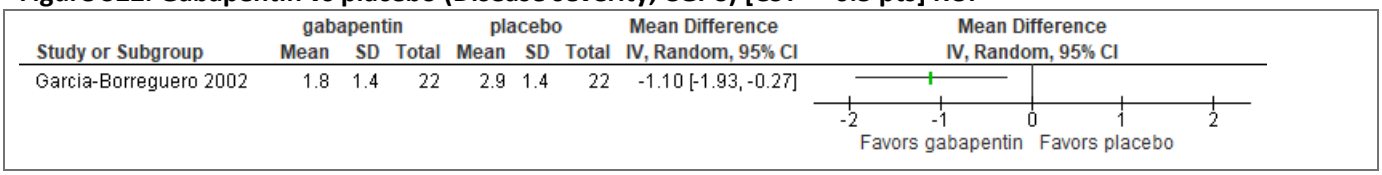


Figure S22. Gabapentin vs placebo (Disease severity, CGI-S) [CST = -0.5 pts] RCT[1]



1. SE reported in study was converted to SD.

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

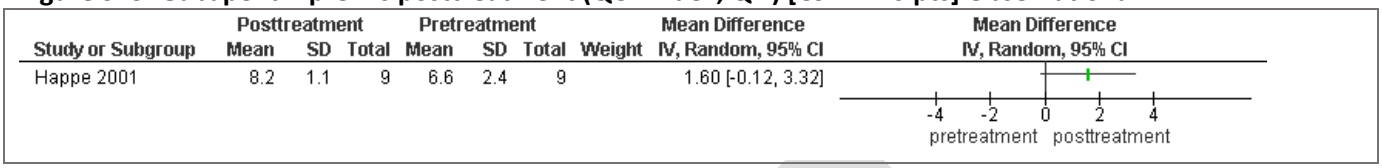
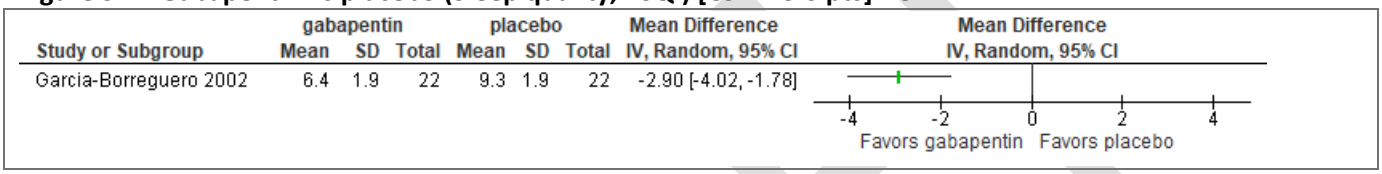


Figure S24. Gabapentin vs placebo (Sleep quality, PSQI) [CST =-3.0 pts] RCT[1]



1. SE reported in study was converted to SD.

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

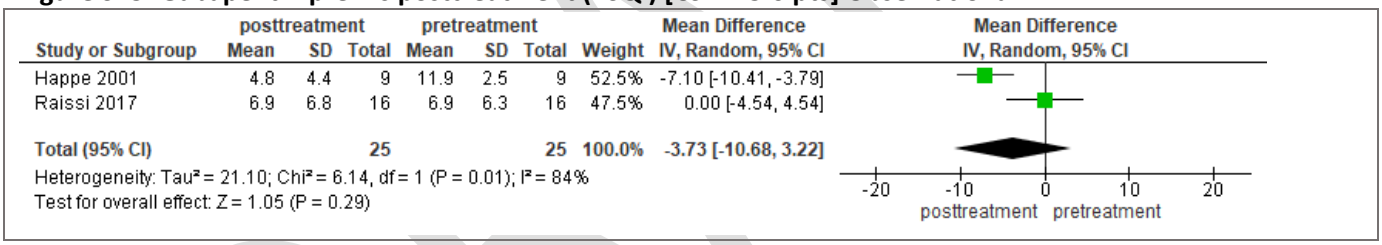


Figure S26. Gabapentin vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT

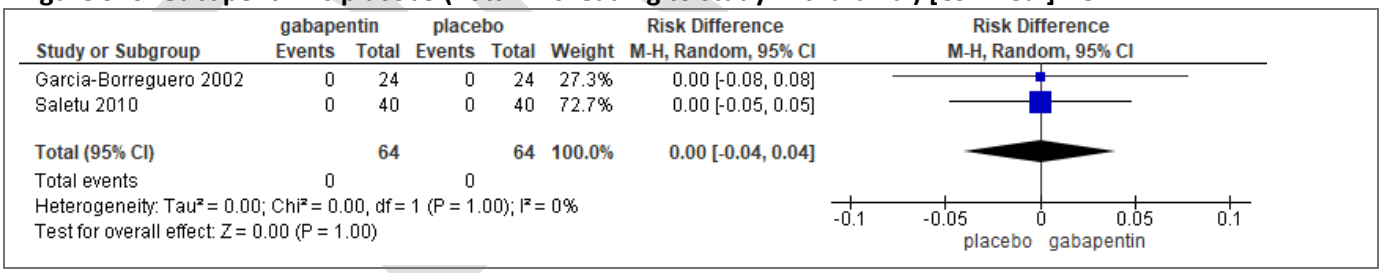


Figure S27. Gabapentin pre- vs posttreatment (Total AEs leading to study withdrawal) [CST = 10%] Observational

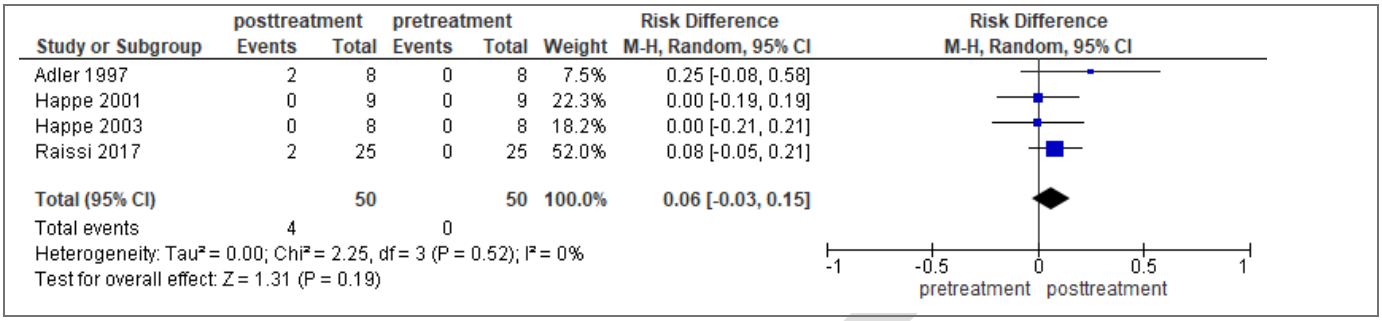


Figure S28. Gabapentin vs placebo (adverse event, somnolence) RCT [CST = 5%]

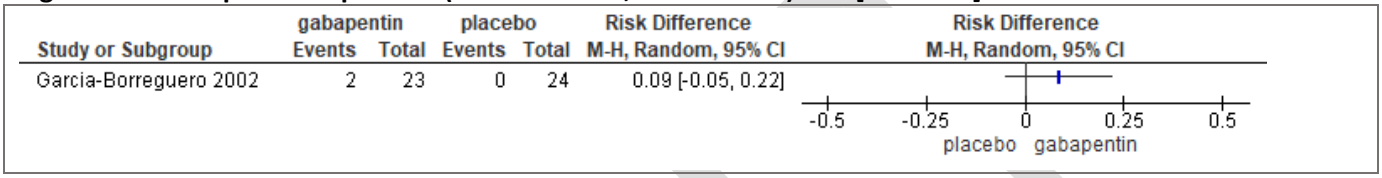


Figure S29. Gabapentin pre- vs posttreatment (adverse event, somnolence) Observational [CST = 10%]

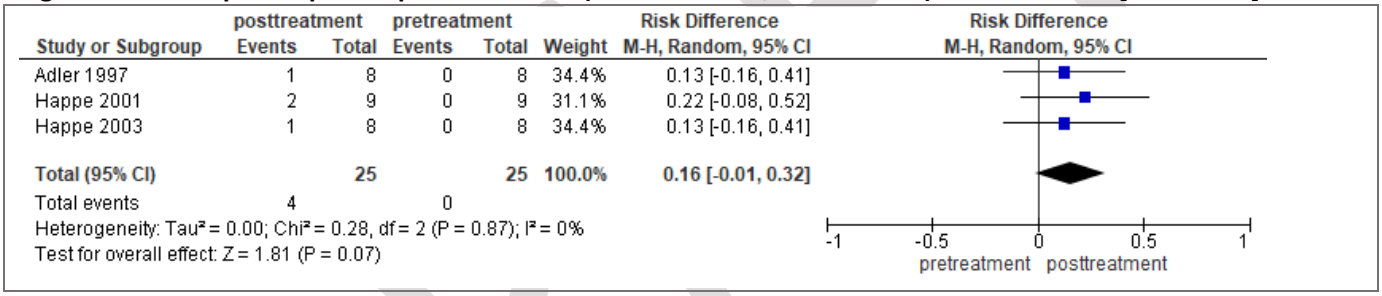


Figure S30. Gabapentin pre- vs posttreatment (adverse event, dizziness) Observational [CST = 10%]

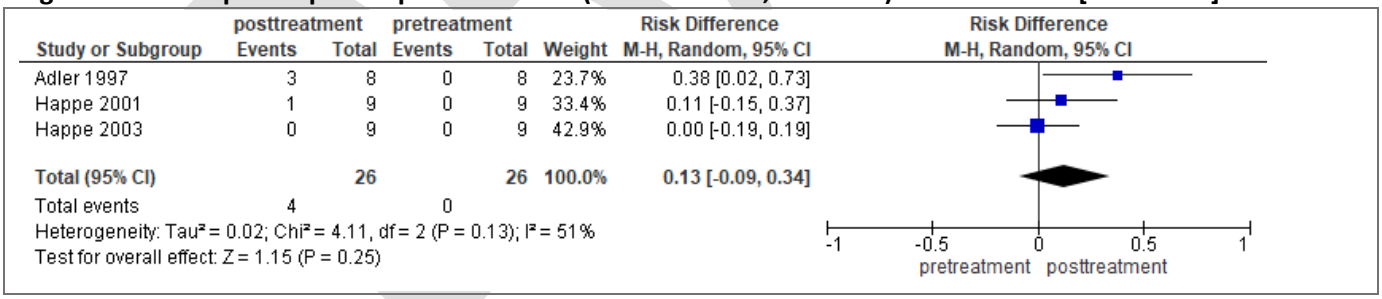
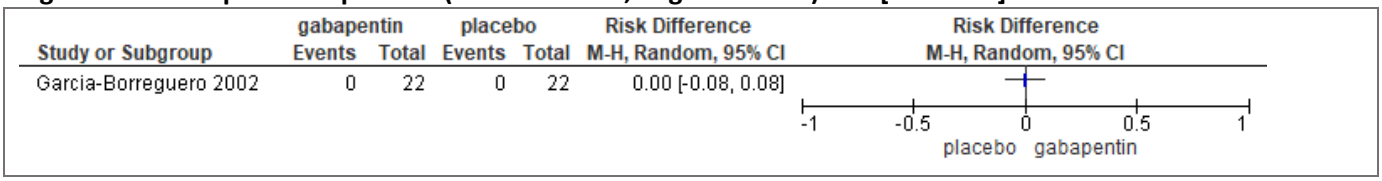
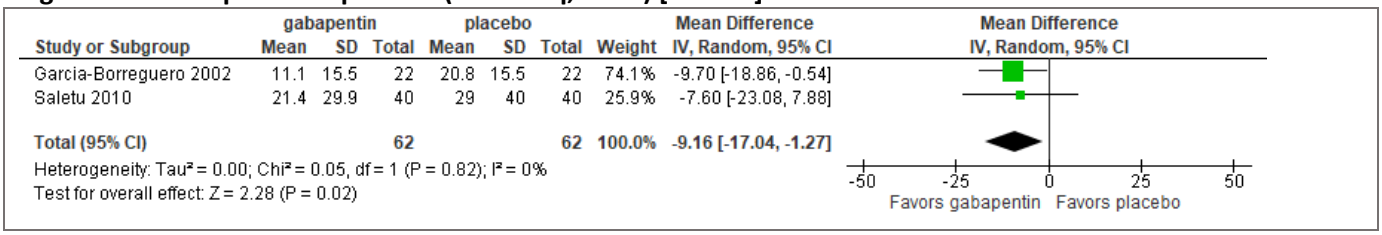


Figure S31. Gabapentin vs placebo (adverse event, augmentation) RCT [CST = 5%]



Important Outcomes

Figure S32. Gabapentin vs placebo (PLM Freq, PLMI) [No CST] RCT[1]



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]

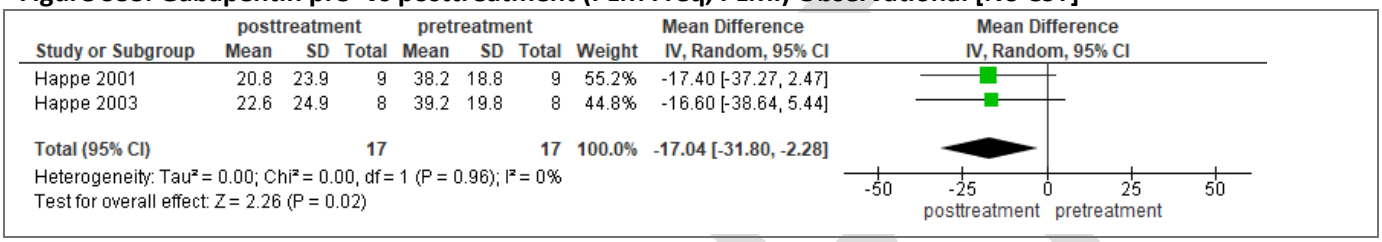
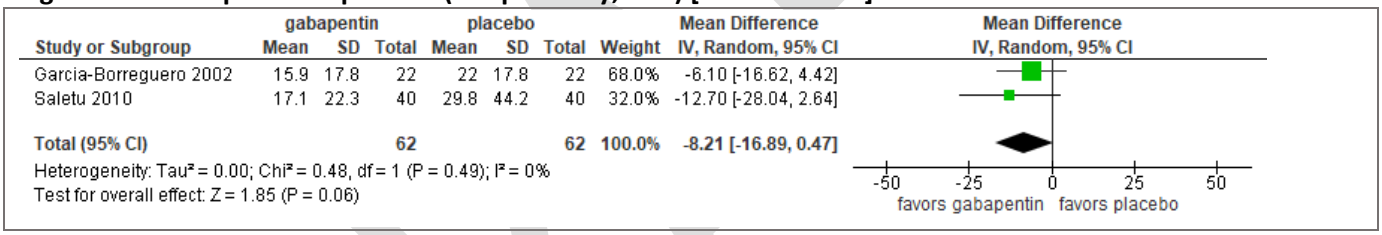
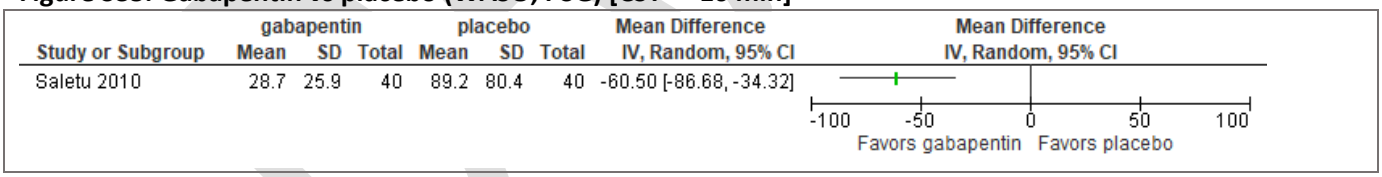


Figure S34. Gabapentin vs placebo (sleep latency, PSG) [CST = -10 min] RCT[1]



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

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



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

a. 95% CI crosses CST
b. small sample size

Critical Outcomes

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

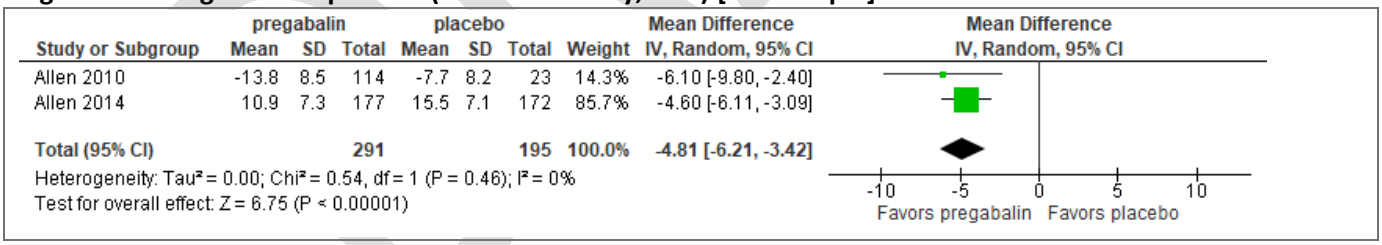


Figure S37. Pregabalin vs placebo (QOL, RLS-QOL Abetz) [CST = +5 pts] RCT

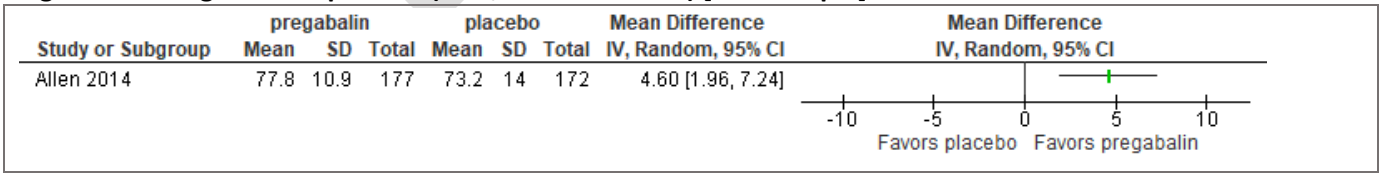
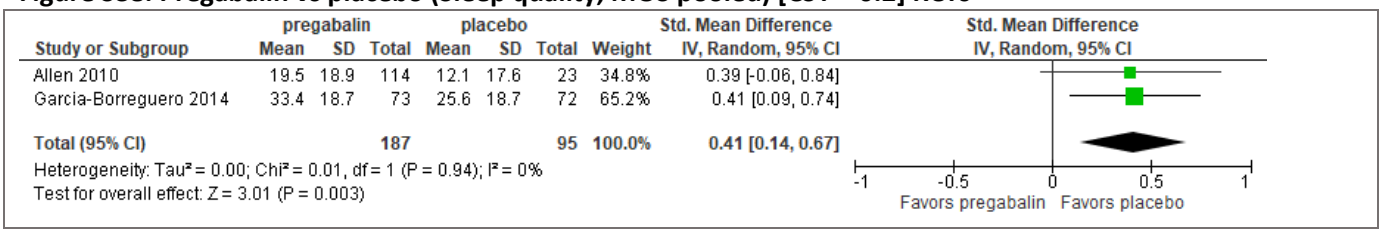


Figure S38. Pregabalin vs placebo (Sleep quality, MOS pooled) [CST = 0.2] RCTs[1,2]



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%] RCTs[1]

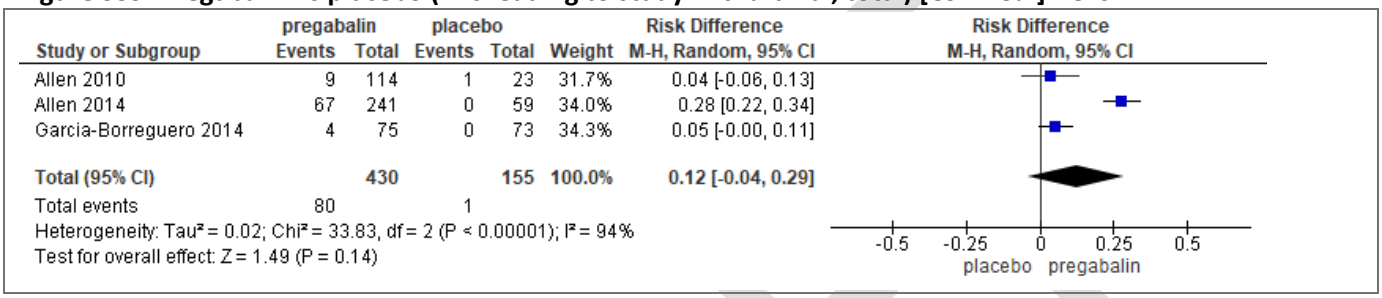


Figure S40. Pregabalin vs placebo (Adverse event, dizziness) [CST = 5%] RCT

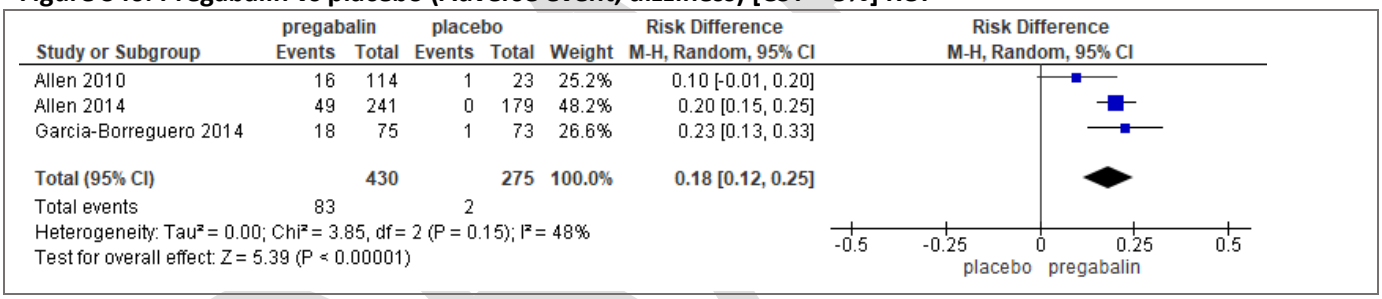
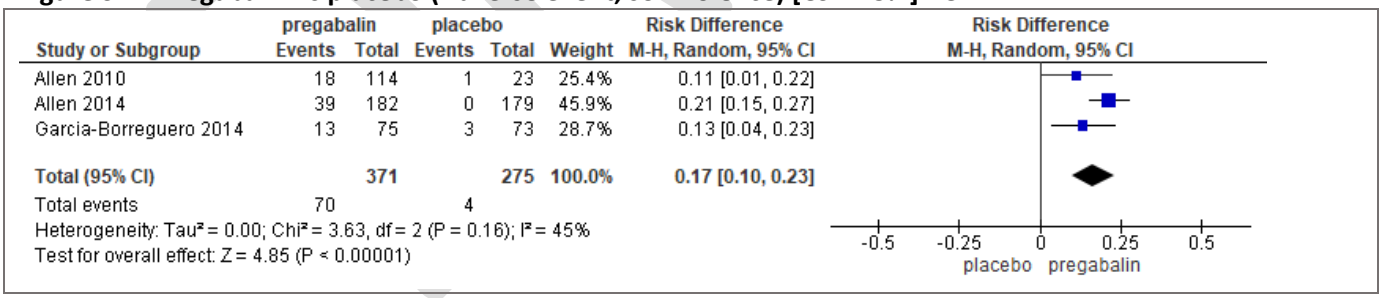
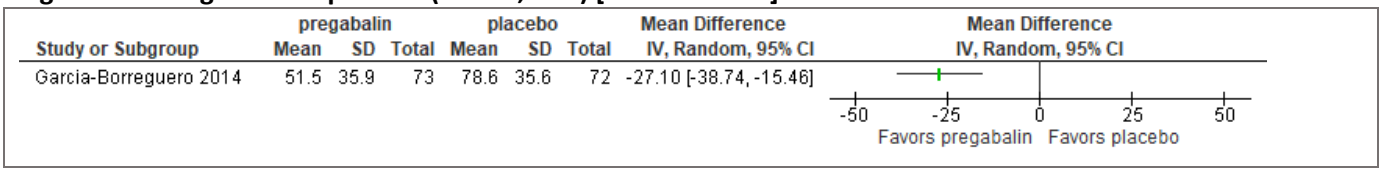


Figure S41. Pregabalin vs placebo (Adverse event, somnolence) [CST = 5%] RCT



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

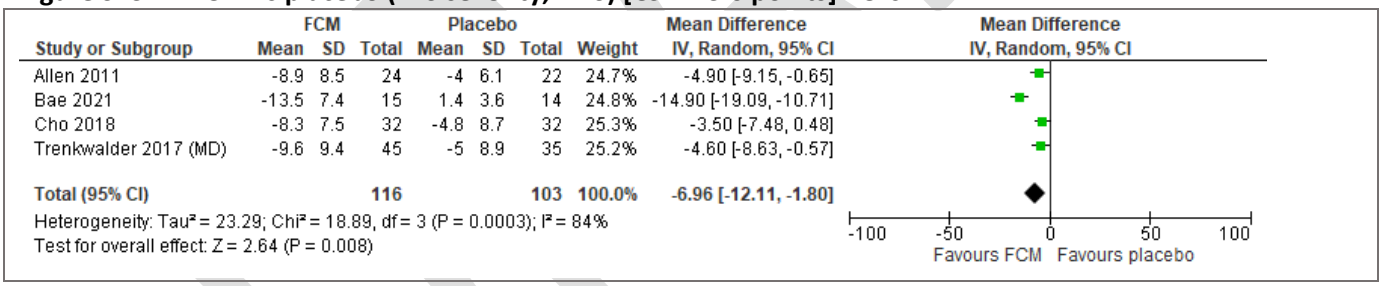
References: Allen 2011, Bae 2021, Cho 2018, Trenkwalder 2017

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference IV FCM vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⊕⊕⊕◯ **MODERATE**[a]	The mean difference in the IV FCM was **7.0 points lower** (12.11 lower to 1.8 lower) compared to control	219 (4 RCTs)
Quality of Life [RLS QOL – Abetz]	⊕⊕⊕◯ **MODERATE**[a]	The mean difference in the IV FCM group was **11.1 points higher** (0.3 lower to 22.5 higher) compared to control	136 (3 RCTs)
Sleep Quality [PSQI]	⊕◯◯◯ **VERY LOW**[b,c]	The mean difference in the IV FCM group was **2.5 points lower** (9.4 lower to 4.4 higher) compared to control	93 (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] RCTs[1]



1. Bae 2021 study included patients with iron deficiency anemia.

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

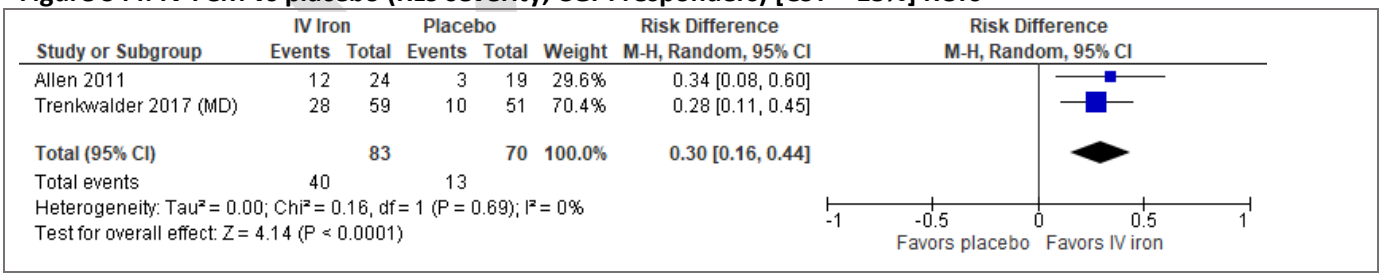


Figure S45. IV FCM vs placebo (RLS severity, PGI responders) [CST= 15%] RCT

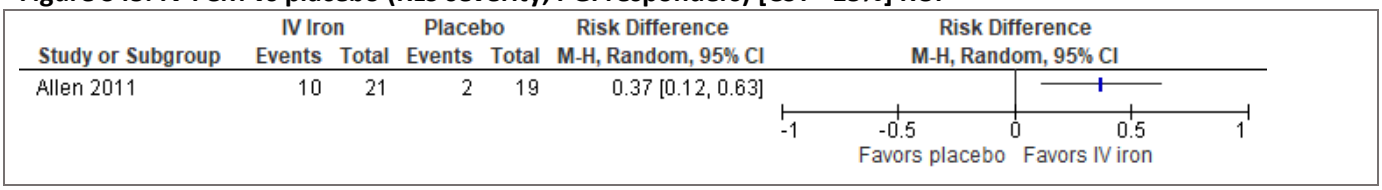


Figure S46. IV FCM vs placebo (RLS QOL – Abetz) [CST = +5 points] RCTs

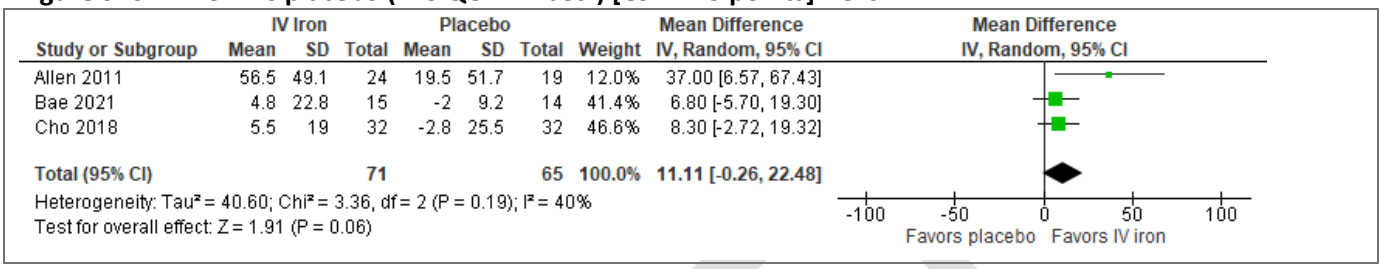


Figure S47. IV FCM vs placebo (Sleep quality, PSQI) [CST = -3 points] RCTs

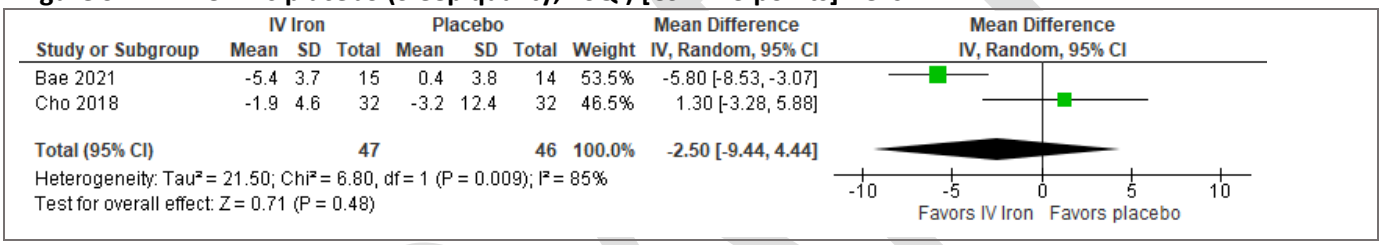
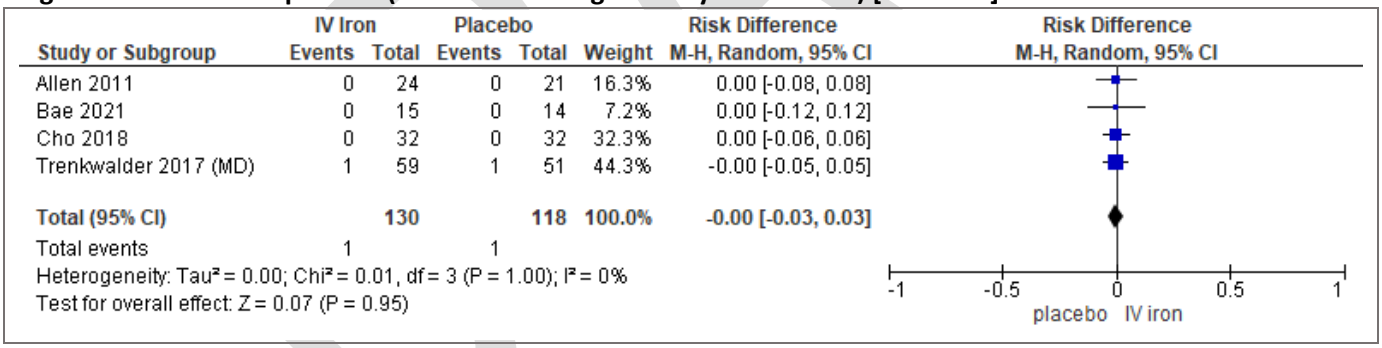


Figure S48. IV FCM vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



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 8 per 1,000 in the control group	59 (3 Obs)

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

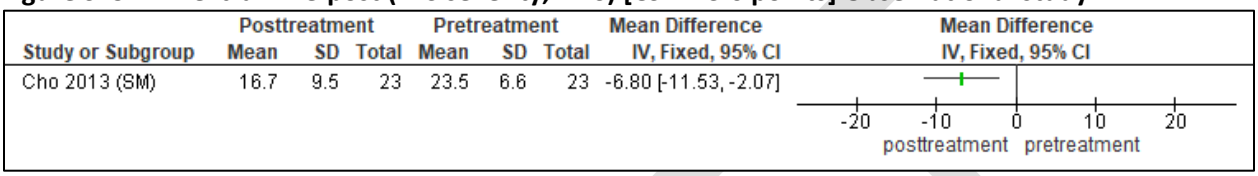
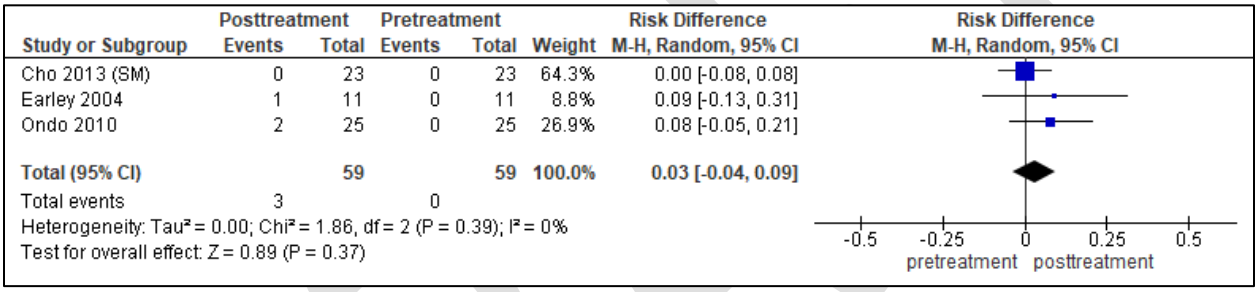


Figure S50. IV Dextran Pre-post (Total AEs leading to study withdrawal) [CST = 10%] Observational study



Oral Iron

Summary of Findings (GRADE)

Table S6 Oral iron in adults with RLS

References: Davis 2000, Wang 2009

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

a. Small sample size

Critical Outcomes

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

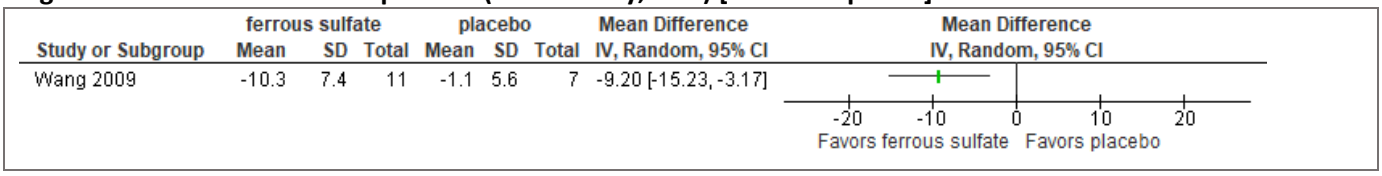
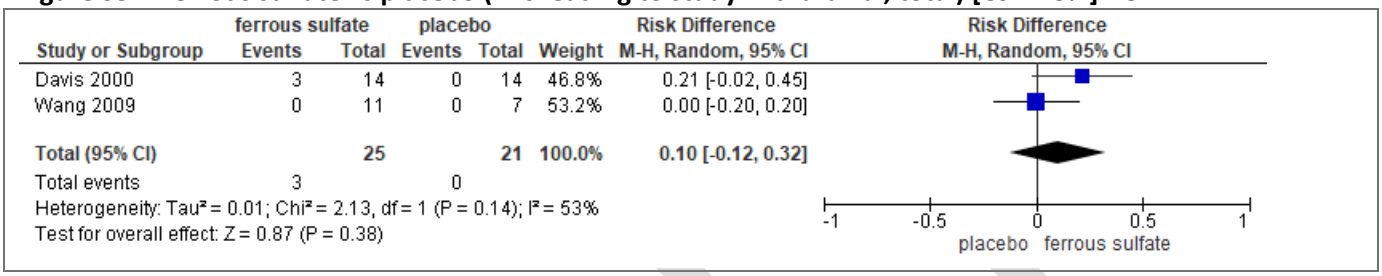


Figure S52. Ferrous sulfate vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT



DRAFT

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

a. Small sample size
b. 95% CI crosses CST

Critical Outcomes

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

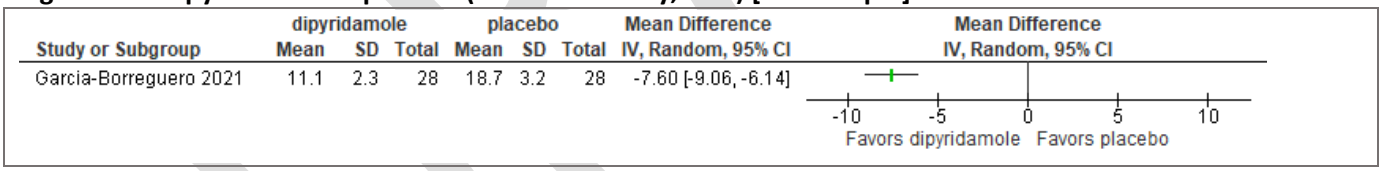


Figure S54. Dipyridamole vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT

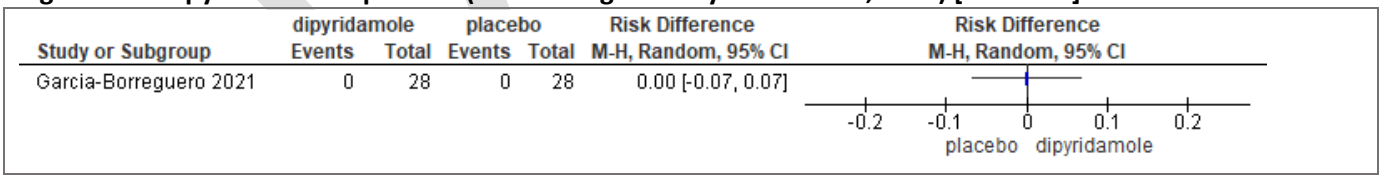


Figure S55. Dipyridamole vs placebo (Adverse event, dizziness) [CST = 5%] RCT

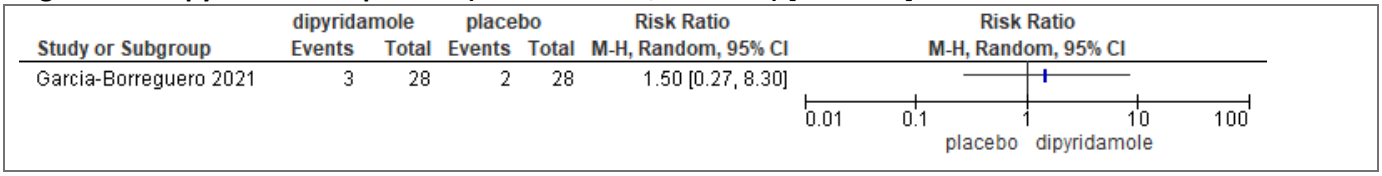


Figure S56. Dipyridamole pre- vs posttreatment (Adverse event, dizziness) [CST = 10%] Observational

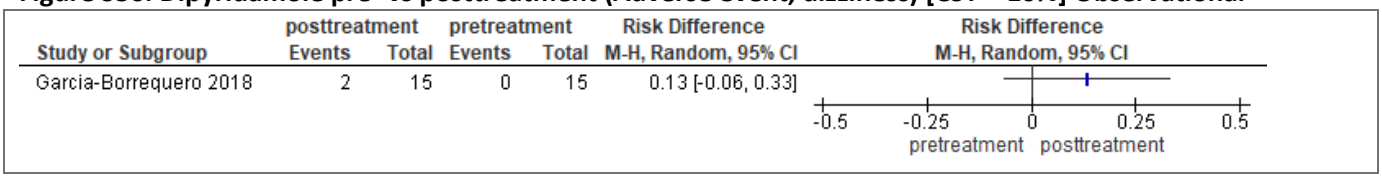
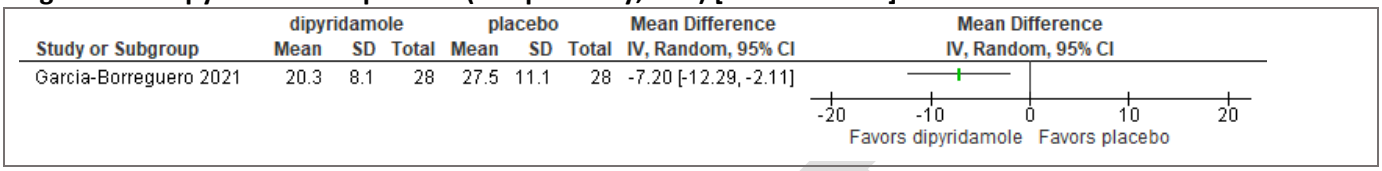
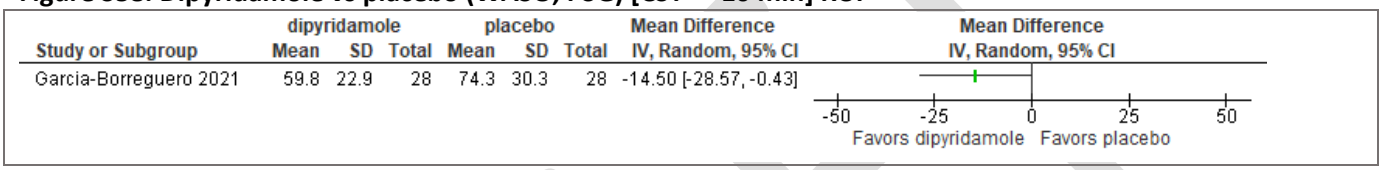


Figure S57. Dipyridamole vs placebo (Sleep latency, PSG) [CST = -10 min] RCT[1]



1. Posttreatment values were entered as change scores were not reported.

Figure S58. Dipyridamole vs placebo (WASO, PSG) [CST = -10 min] RCT[1]



1. Posttreatment values were entered as change scores were not reported.

DRAFT

Oxycodone

Summary of Findings (GRADE)

Table S8 Oxycodone in adults with RLS

References: Trenkwalder 2013, Walters 1993

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Oxycodone vs Placebo or Control	No of Participants (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]	⨁⨁⨁◯ **MODERATE**[a]	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)	⨁⨁◯◯ **LOW**[a,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)	⨁⨁◯◯ **LOW**[a,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]

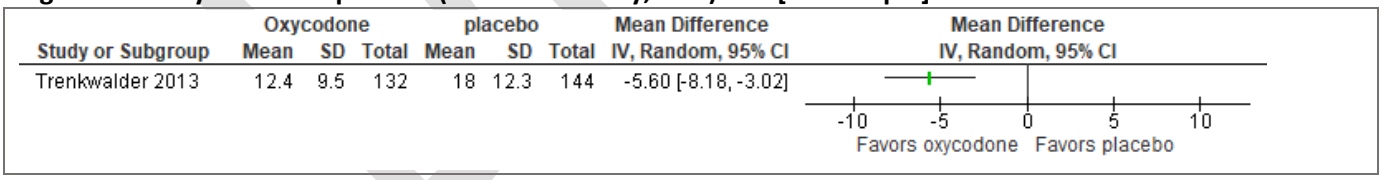


Figure S60. Oxycodone vs placebo (Sleep quality, MOS pooled) [CST = 0.2] RCT

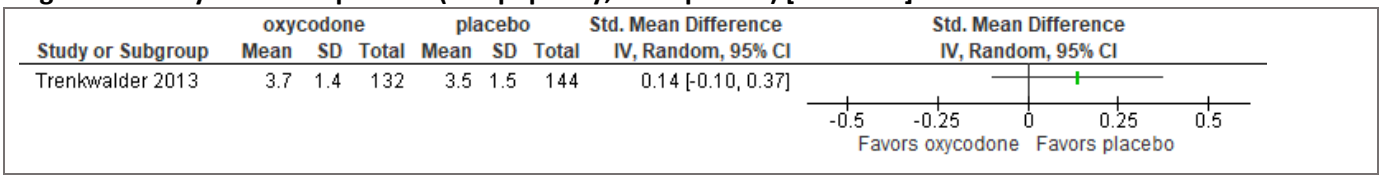


Figure S61. Oxycodone vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT

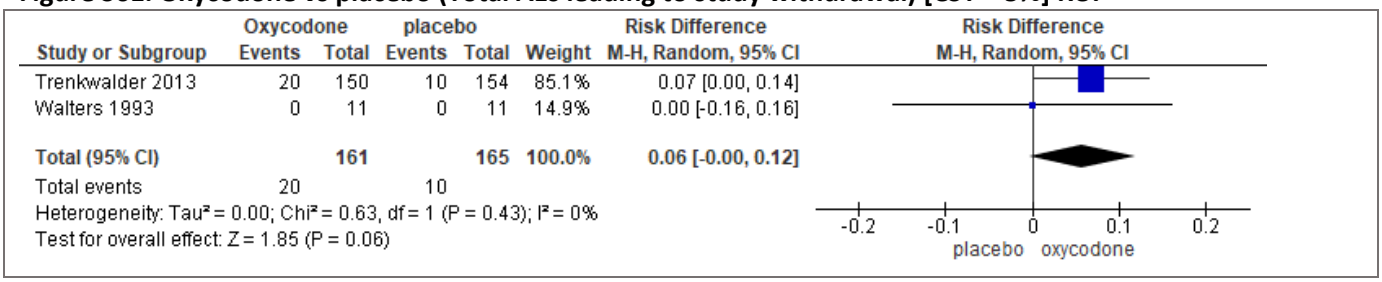


Figure S62. Oxycodone vs placebo (adverse event, fatigue) [CST = 5%] RCT

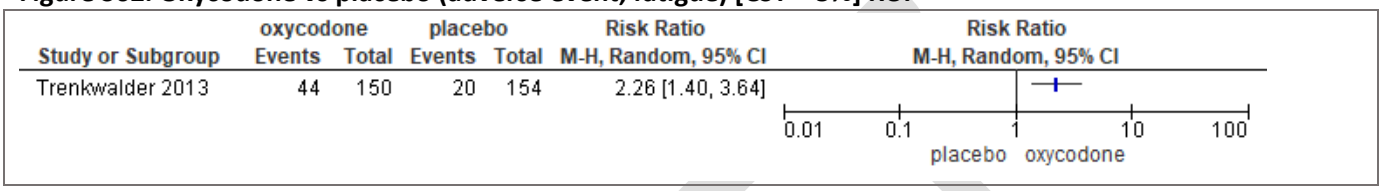


Figure S63. Oxycodone vs placebo (adverse event, somnolence) [CST = 5%] RCT

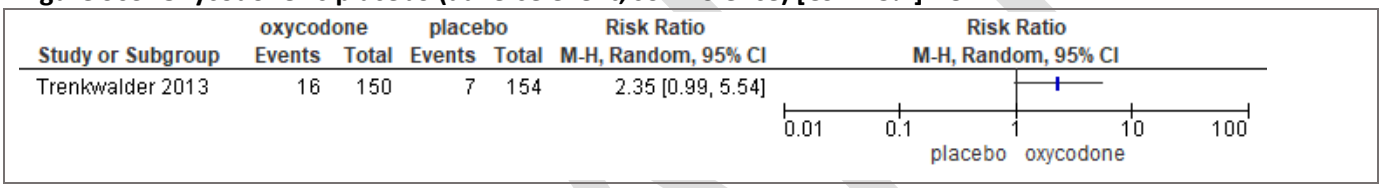
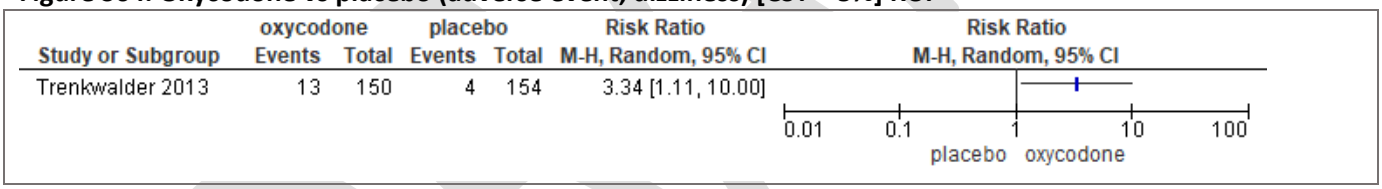


Figure S64. Oxycodone vs placebo (adverse event, dizziness) [CST = 5%] RCT



Important Outcomes

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

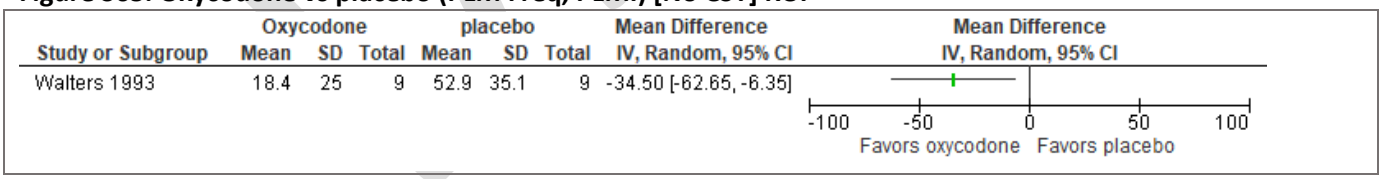
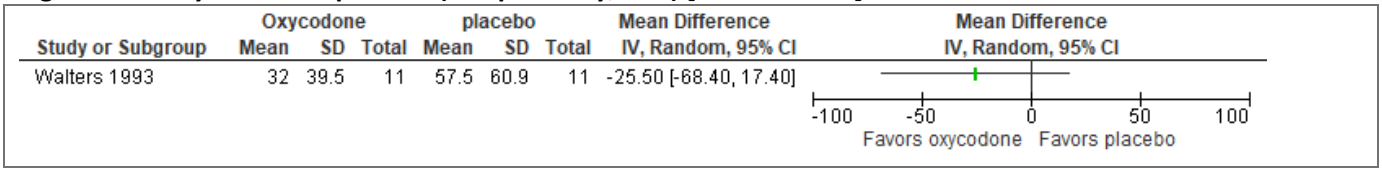


Figure S66. Oxycodone vs placebo (Sleep latency, PSG) [CST =-10 min] RCT



Peroneal Nerve Stimulation

Summary of Findings (GRADE)

Table S9 Peroneal Nerve Stimulation in adults with RLS

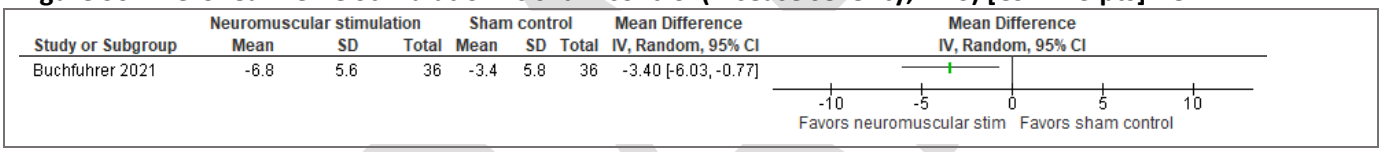
References: Buchfuhrer 2021

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]	⨁⨁◯◯ **LOW**[a,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.

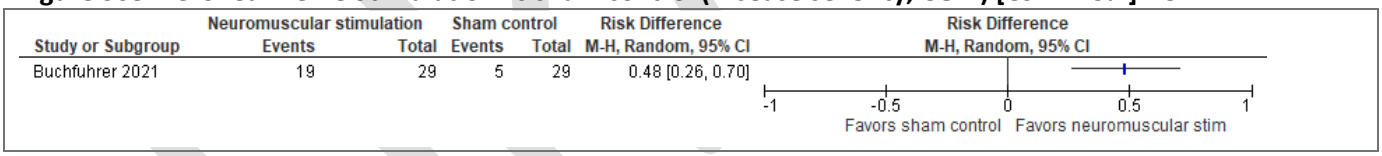
Critical Outcomes

Figure S67. Peroneal Nerve Stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT[1]



1. SEMs reported in study were converted to SDs.

Figure S68. Peroneal Nerve Stimulation vs sham control (Disease severity, CGI-I) [CST = 15%] RCT[1]



1. SEMs reported in study were converted to SDs.

Levodopa

Summary of Findings (GRADE)

Table S10 Levodopa in adults with RLS

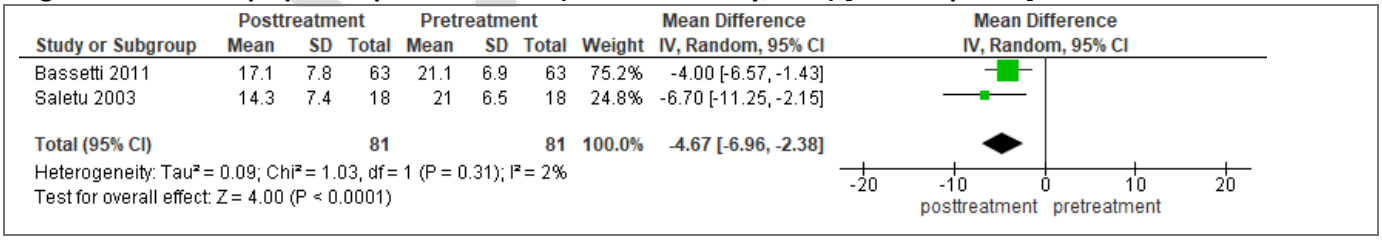
References: Beneš 1999, Eisensehr 2004, Trenkwalder 1995, Allen 1996, Bassetti 2011, Earley 1996, Hogl 2010, Saletu 2003, Trenkwalder 2003, Trenkwalder 2007

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Levodopa vs Placebo or Control	No of Participants (studies)
Disease severity [CGI-S]	⨁⨁◯◯ **LOW**[a]	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	⨁⨁◯◯ **LOW**[c,b]	**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] Observational[1]



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

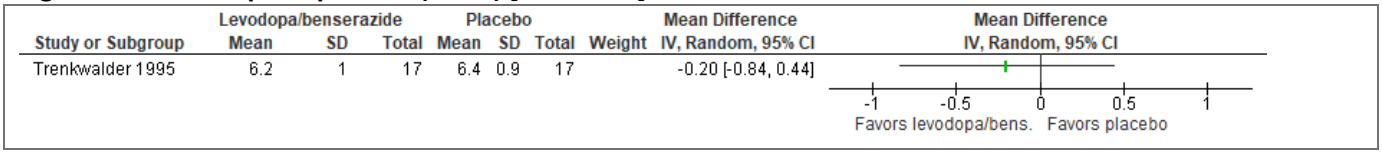


Figure S71. Levodopa pre- vs posttreatment (QOL index, RLS-QLI) [CST= +10 points] Observational

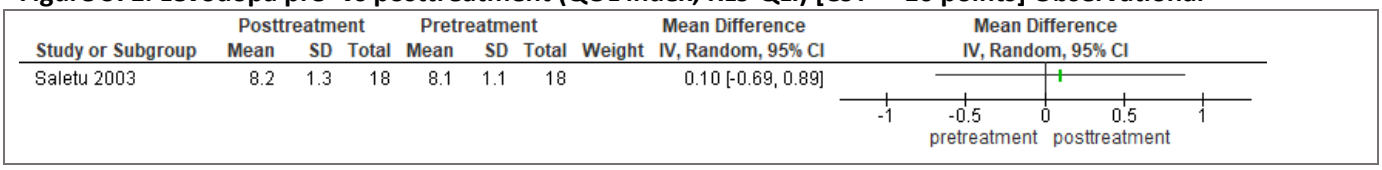


Figure S72. Levodopa pre- vs posttreatment (PSQI) [CST= -3.0 points] Observational

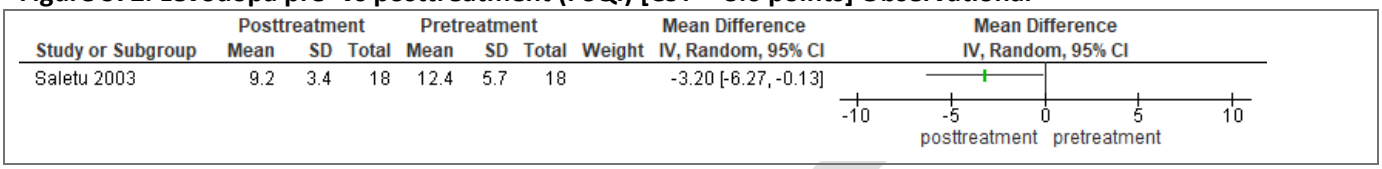


Figure S73. Levodopa vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs

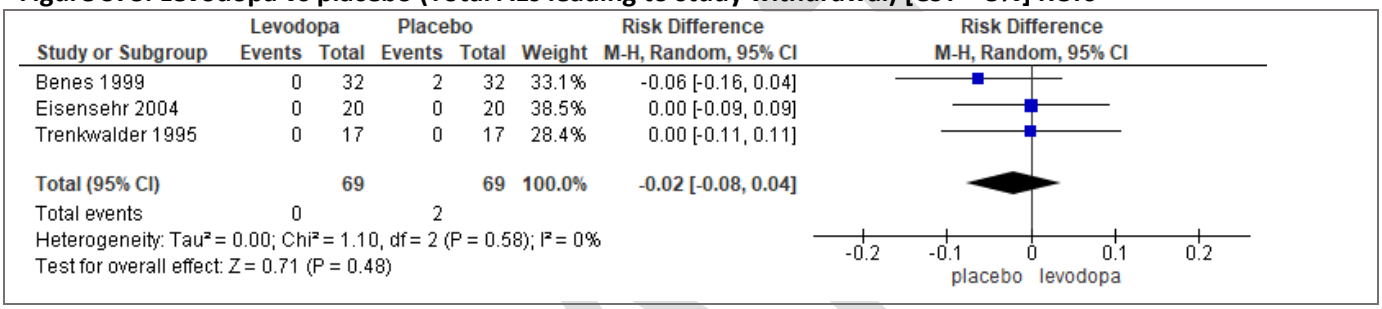


Figure S74. Levodopa vs placebo (adverse event, augmentation) [CST = 5%] RCT

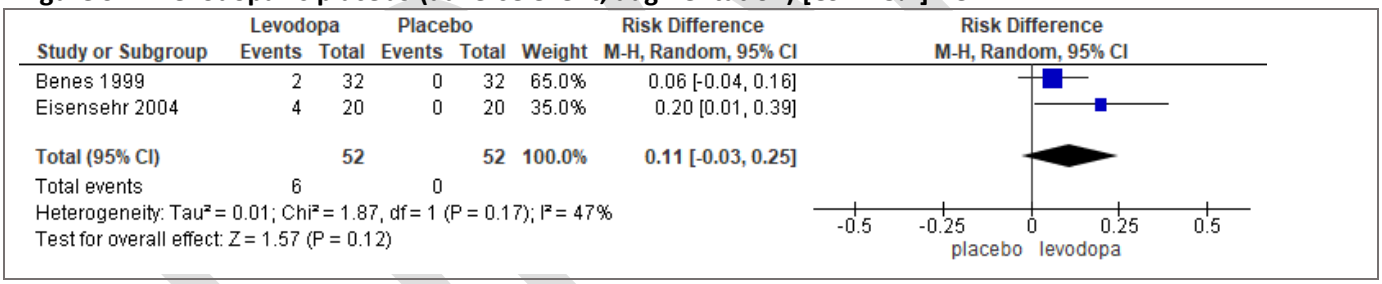
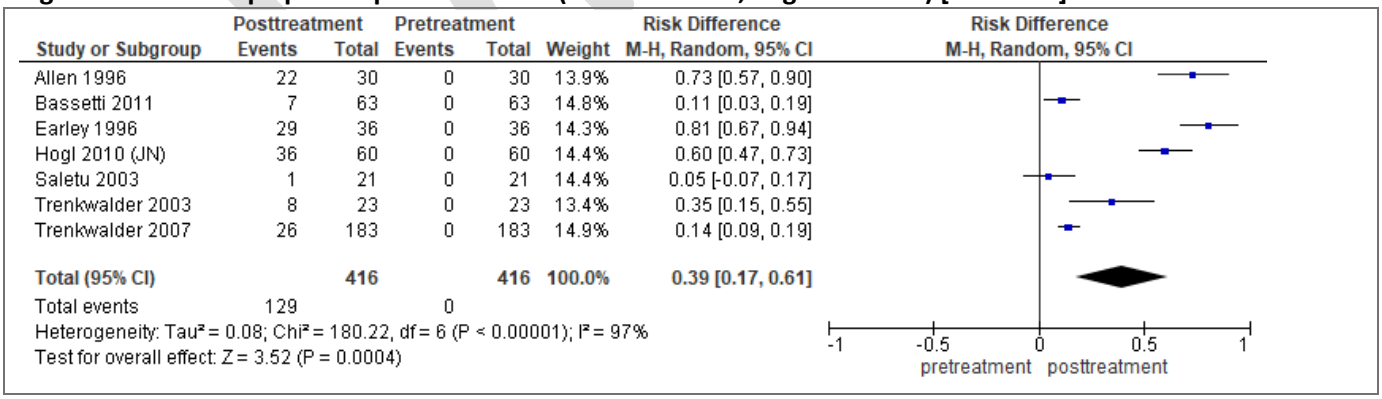
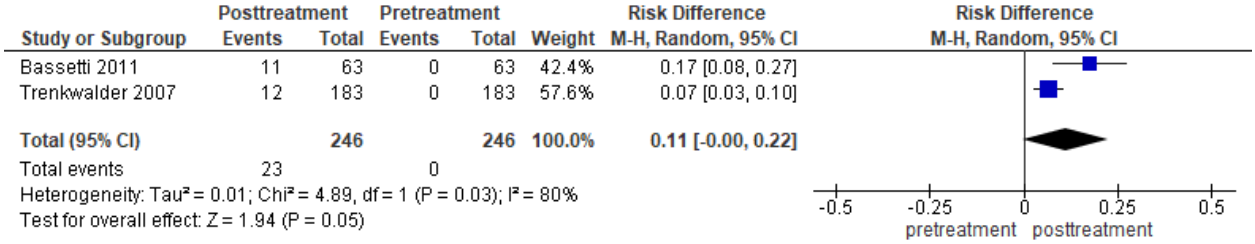


Figure S75. Levodopa pre- vs posttreatment (adverse event, augmentation) [CST = 5%] Observational[1-3]



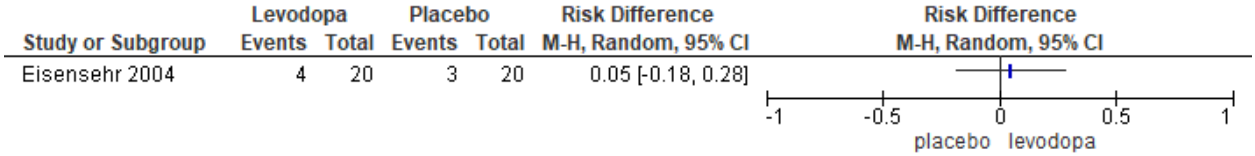
1. Bassetti 2011 RCT compared levodopa to pramipexole so pre-vs posttreatment data used for comparison.
2. Earley 1996 RCT compared levodopa to pergolide so pre- vs posttreatment data used for comparison.
3. Trenkwalder 2007 RCT compared levodopa to cabergoline so pre-vs posttreatment data used for comparison.

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



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



DRAFT

Pramipexole

Summary of Findings (GRADE)

Table S11 Pramipexole in adults with RLS

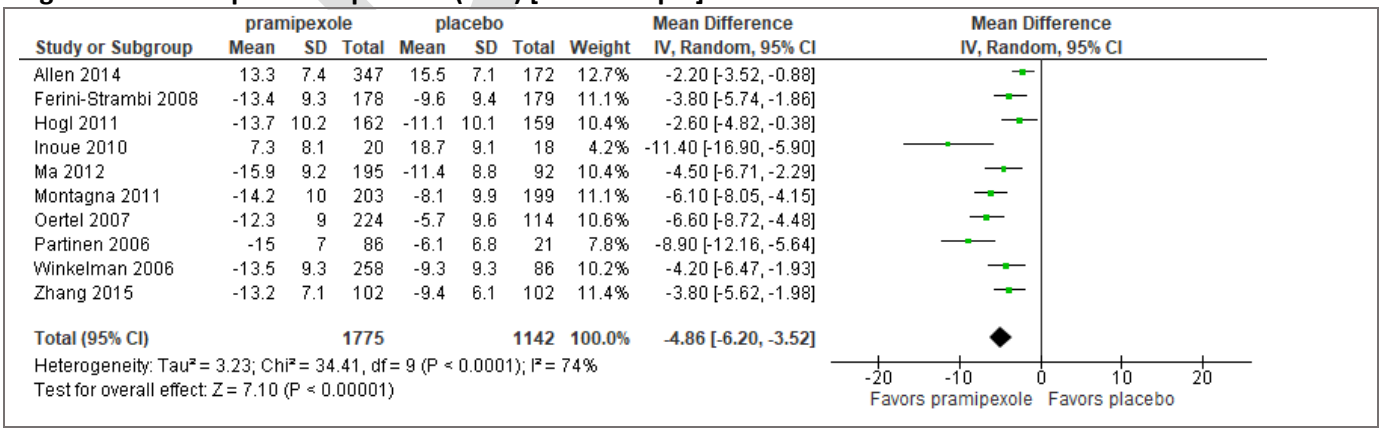
References: Allen 2014, Basetti 2011, Ferini-Strambi 2008, Garcia- Borreguero 2014, Hogl 2011, Inoue 2010, Jama 2009, Lipford 2012, Ma 2012, Manconi 2008, Manconi 2011, Manconi 2011 (N), Manconi 2011(SM), Montagna 2011, Montplaisir 1999, Oertel 2007, Partinen 2006, Silber 2003, Takahashi 2017, Winkelman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

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

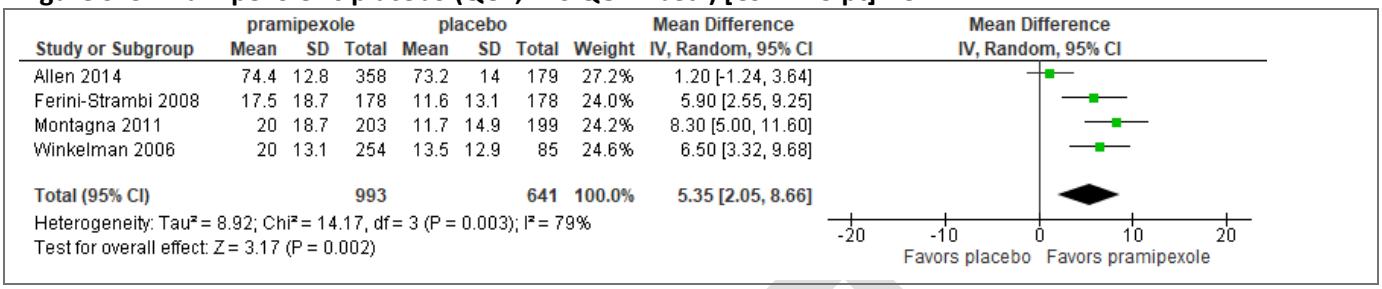
Figure S78. Pramipexole vs placebo (IRLS) [CST =-3.0 pts] RCTs[1-5]



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

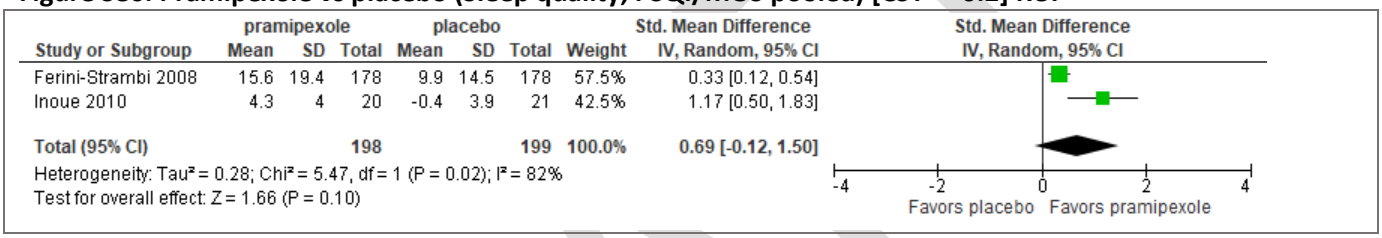
2. Data reported in Allen 2014 pooled across 2 different doses.
3. Data pooled across several countries in Hogl 2015 study.
4. SEs reported in Montagna 2011, Partinen 2006, Zhang 2015, and Oertel 2007 studies were converted to SDs.
5. Data pooled across 3 different doses for Partinen 2006 and Winkelman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

Figure S79. Pramipexole vs placebo (QOL, RLS QOL Abetz) [CST = +5 pt] RCT[1]



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

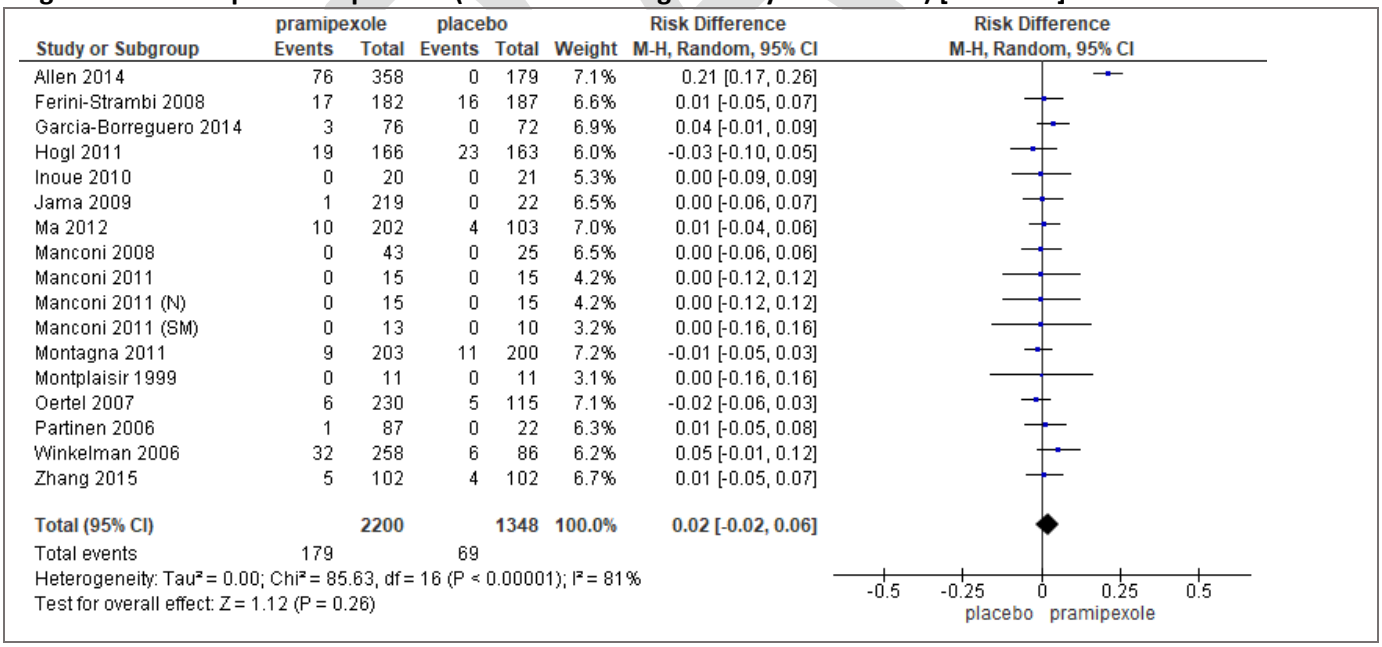
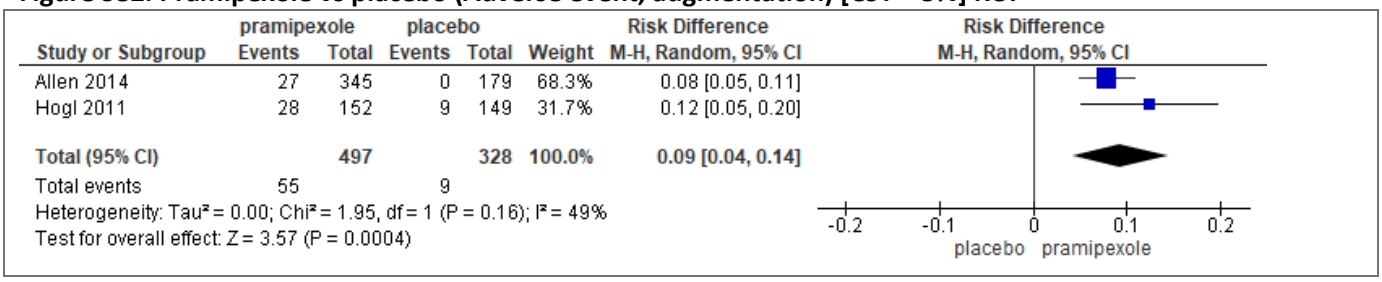


Figure S82. Pramipexole vs placebo (Adverse event, augmentation) [CST = 5%] RCT[1]



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

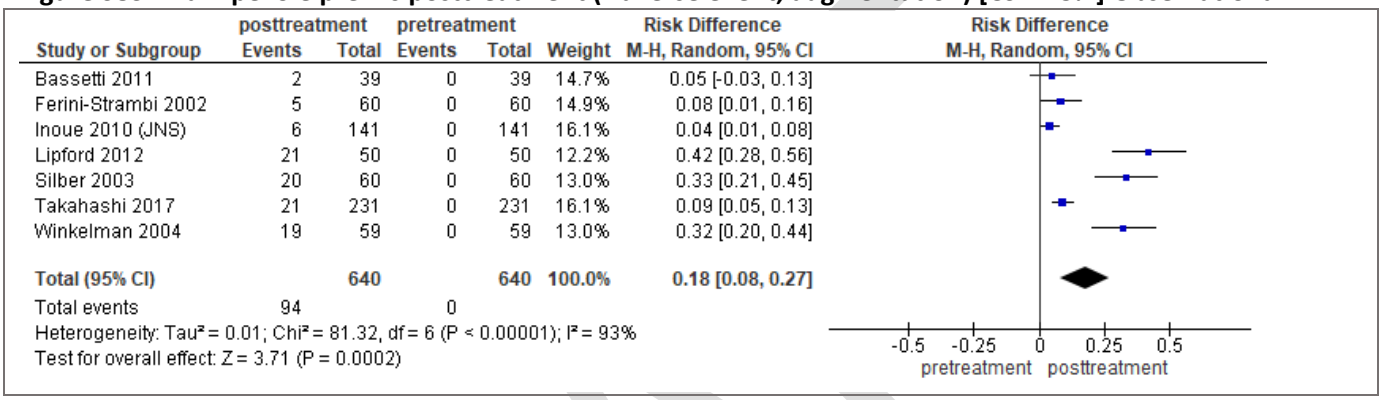


Figure S84. Pramipexole vs placebo (Adverse event, somnolence) [CST = 5%] RCT

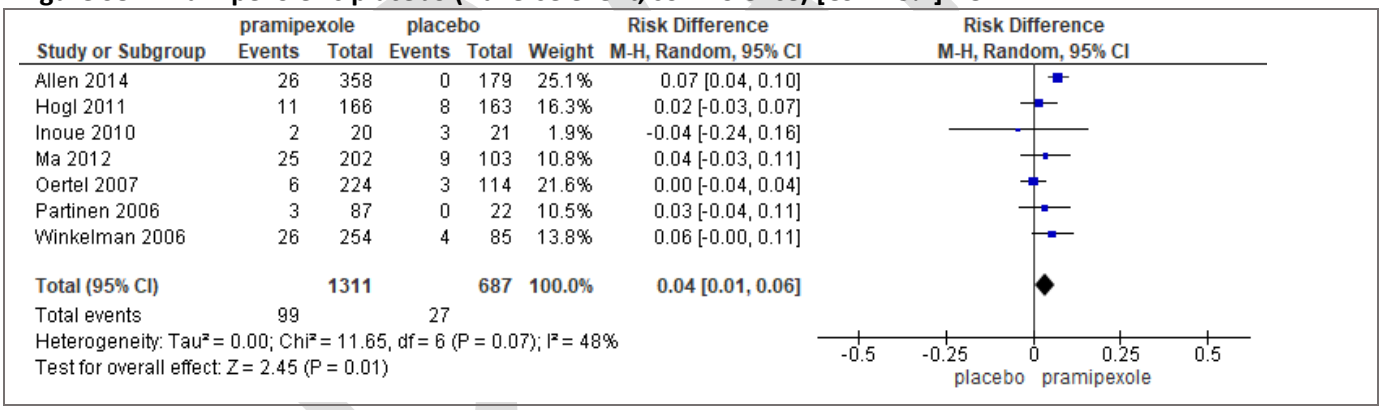


Figure S85. Pramipexole vs placebo (Adverse event, dizziness) [CST = 5%] RCT

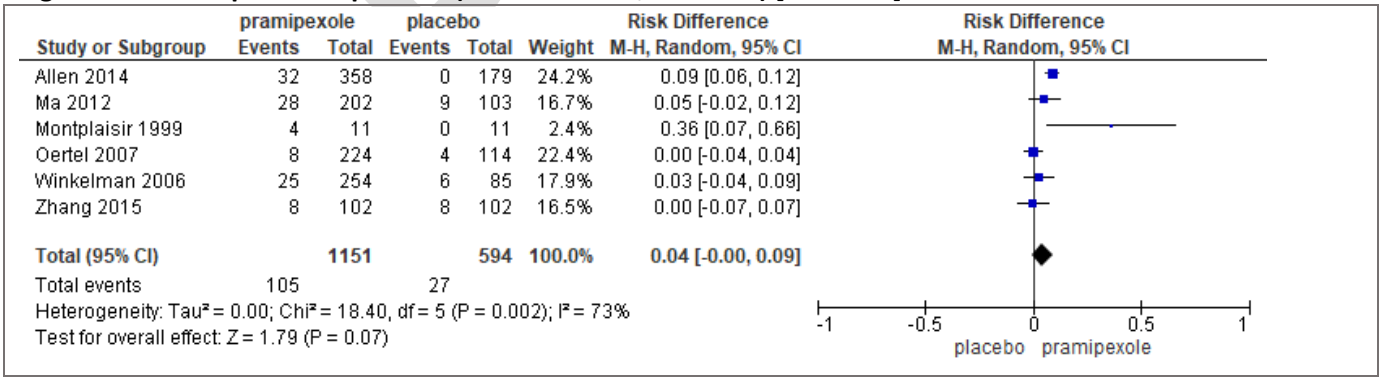
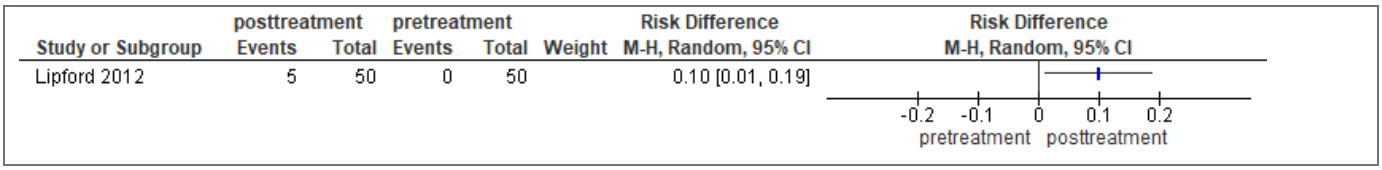


Figure S86. Pramipexole pre- vs posttreatment (Adverse events, impulse control disorder) [CST = 5%] Observational



DRAFT

Rotigotine

Summary of Findings (GRADE)

Table S5 Rotigotine in adults with RLS

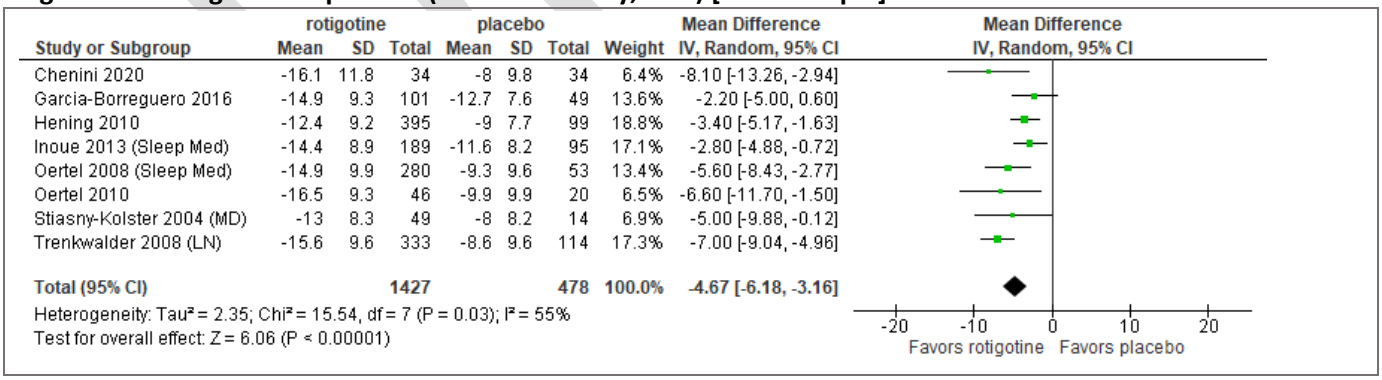
References: Chenini 2020, Garcia-Borreguero 2016, Hening 2010, Inoue 2013 (Sleep Med), Oertel 2008 (Sleep Med), Oertel 2010, Stiasny-Kolster 2004 (MD), Trenkwalder 2008 (LN), Inoue 2013 (PNBP), Oertel 2011, Stiasny-Kolster 2013

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

a. 95% CI of mean difference crossed CST.
b. High I-squared value with unexplained heterogeneity.

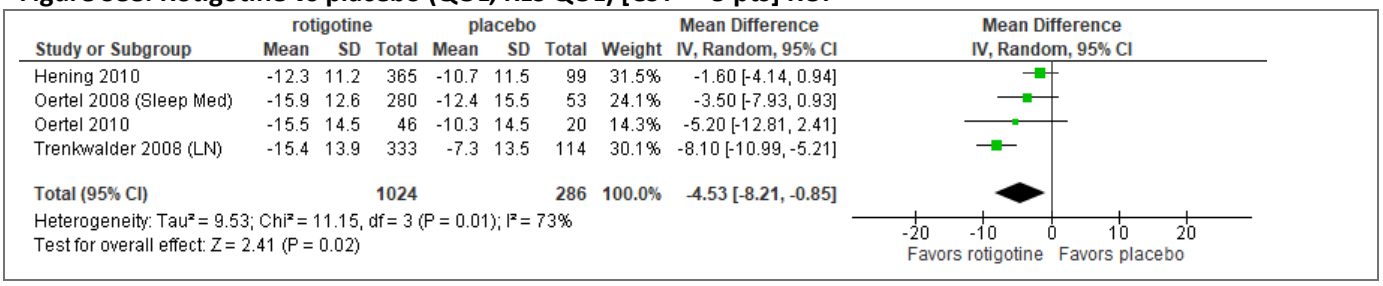
Critical Outcomes

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



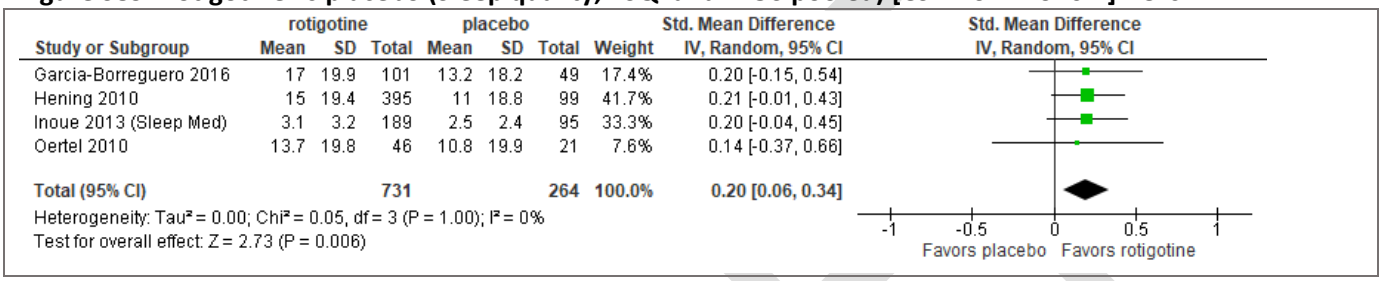
1. Data pooled across different drug dosages for Hening 2010, Inoue 2013, Oertel 2008, Stiasny-Kolster 2004, and Trenkwalder 2008.
2. SEM converted to SD prior to pooling data for Stiasny-Kolster 2004.

Figure S88. Rotigotine vs placebo (QOL, RLS QOL) [CST = -5 pts] RCT[1]



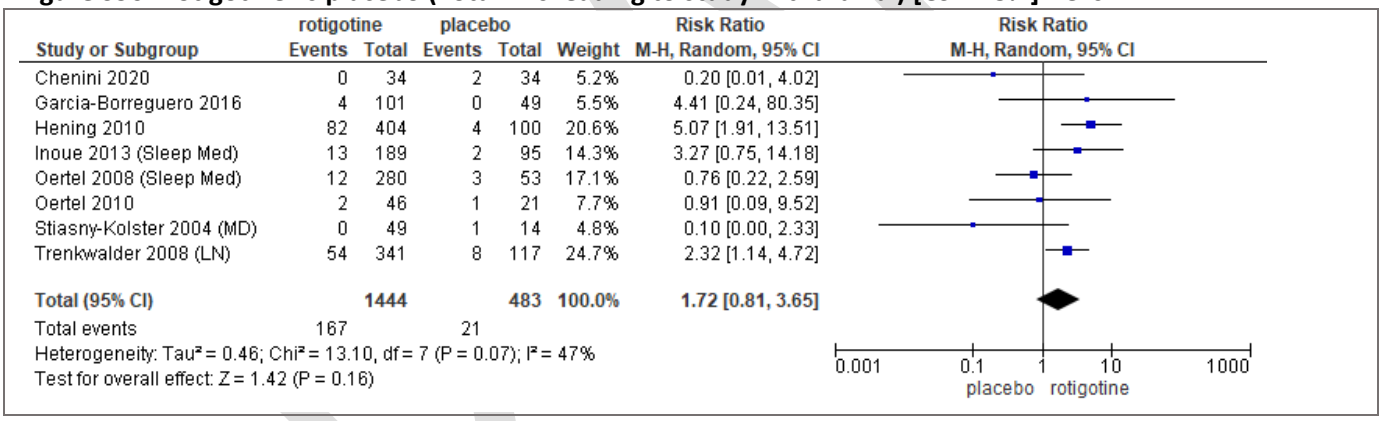
1. Data pooled across different drug dosages for Hening 2010, Oertel 2008, and Trenkwalder 2008.

Figure S89. Rotigotine vs placebo (Sleep quality, PSQI and MOS pooled) [CST = SMD of 0.2] RCTs[1-3]



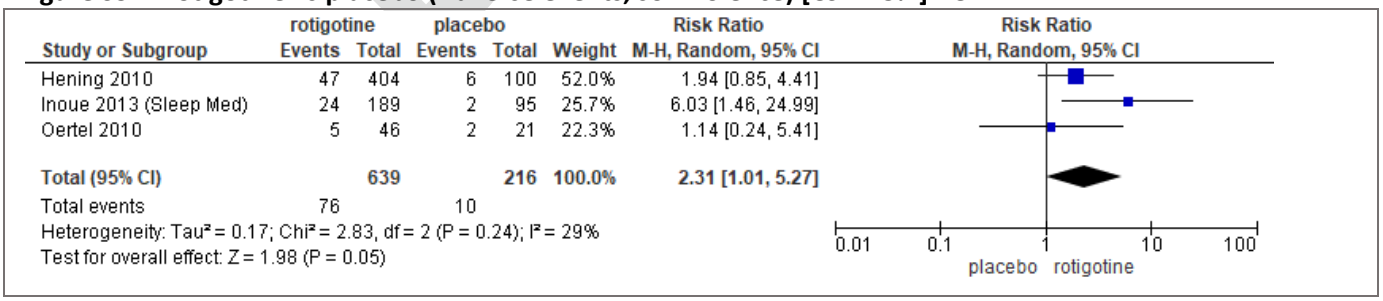
1. Data pooled across different drug dosages for Hening 2010 and Inoue 2013.
2. Inoue 2013 reported the PSQI. All other studies reported on the MOS.
3. Data from the MOS subscales were pooled within studies.

Figure S90. Rotigotine vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs[1]



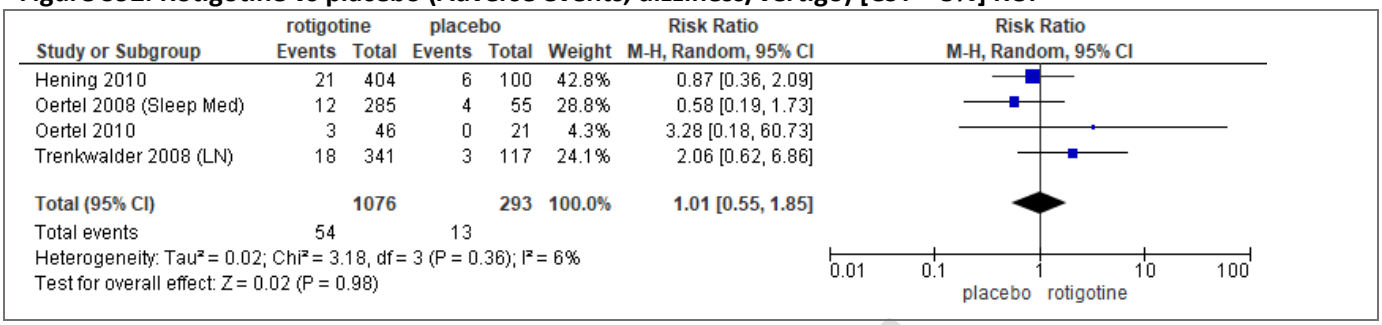
1. Data pooled across different drug dosages for Hening 2010, Inoue 2013, Oertel 2008, Stiasny-Kolster 2004, and Trenkwalder 2008.

Figure S91. Rotigotine vs placebo (Adverse events, somnolence) [CST = 5%] RCT[1]



1. Data pooled across different drug dosages for studies.

Figure S92. Rotigotine vs placebo (Adverse events, dizziness/vertigo) [CST = 5%] RCT[1]



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

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

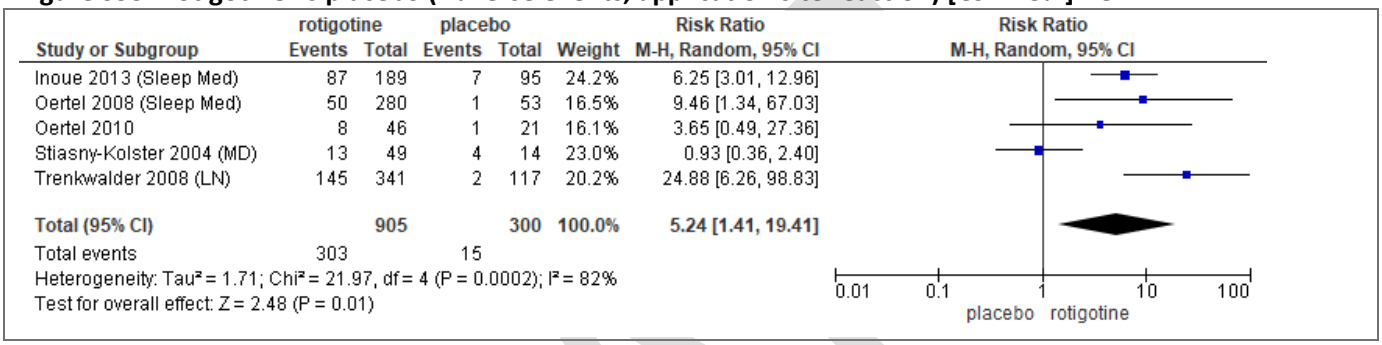
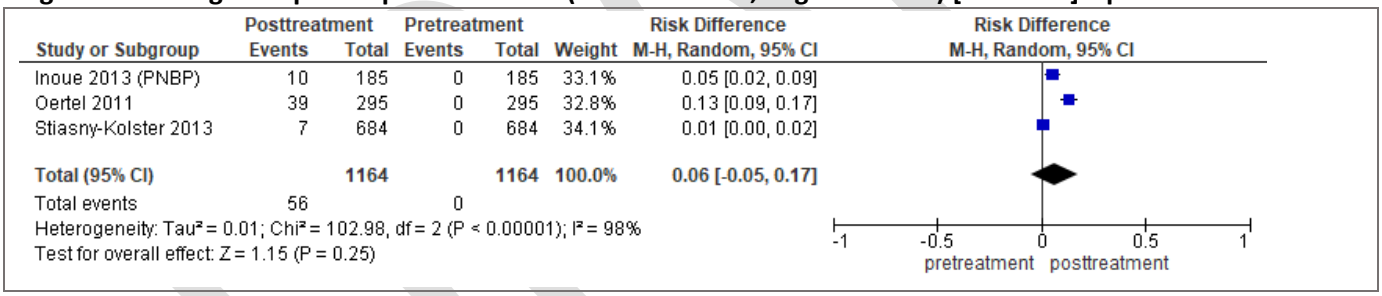


Figure S94. Rotigotine pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Open-label[1-3]



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.

Ropinirole

Summary of Findings (GRADE)

Table S13 Ropinirole in adults with RLS

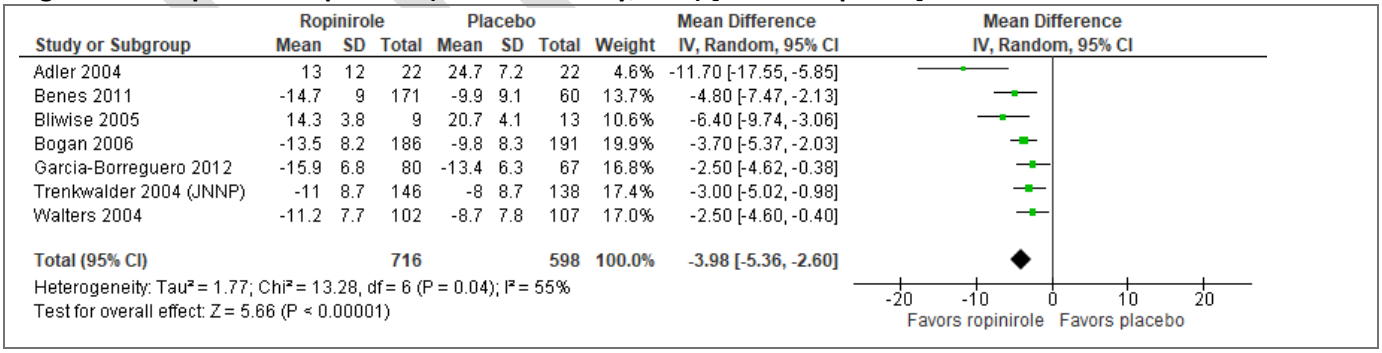
References: Adler 2004, Allen 2004, Beneš 2011, Bliwise 2005, Bogan 2006, Garcı´a-Borreguero 2012, Giorgi 2013, Kushida 2008, Saletu 2000, Saletu 2010, Trenkwalder 2004 (JNNP), Walters 2004, Allen 2011, Giorgi 2013

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

a. 95% CI crosses CST

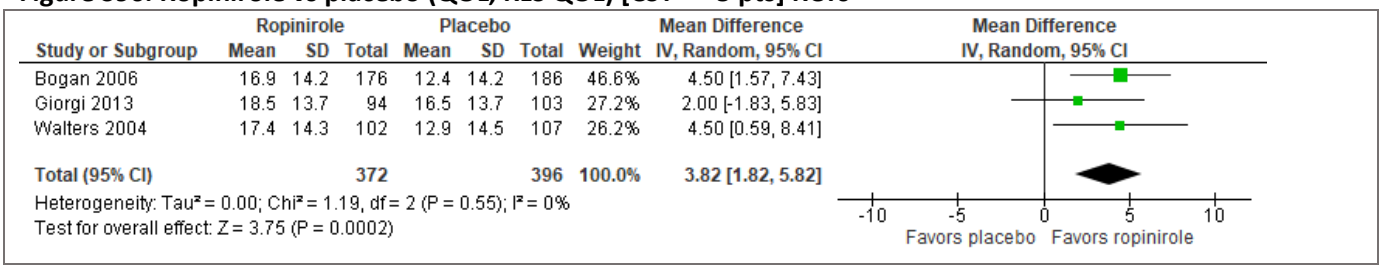
Critical Outcomes

Figure S95. Ropinirole vs placebo (disease severity, IRLS) [CST =-3.0 points] RCTs[1-4]



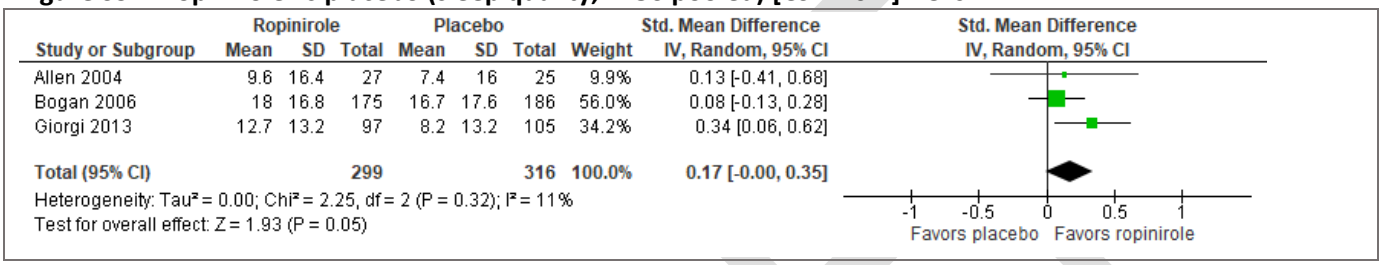
1. Posttreatment values entered for Adler 2004, Garcia-Borreguero 2012, and Bliwise 2005 as change scores were not available.
2. Calculated SDs from 95% CI data reported in Benes 2011.
3. Calculated SDs from 2SE data reported in Bogan 2006.
4. Calculated SDs from SE data reported in Trenkwalder 2004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

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



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]



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

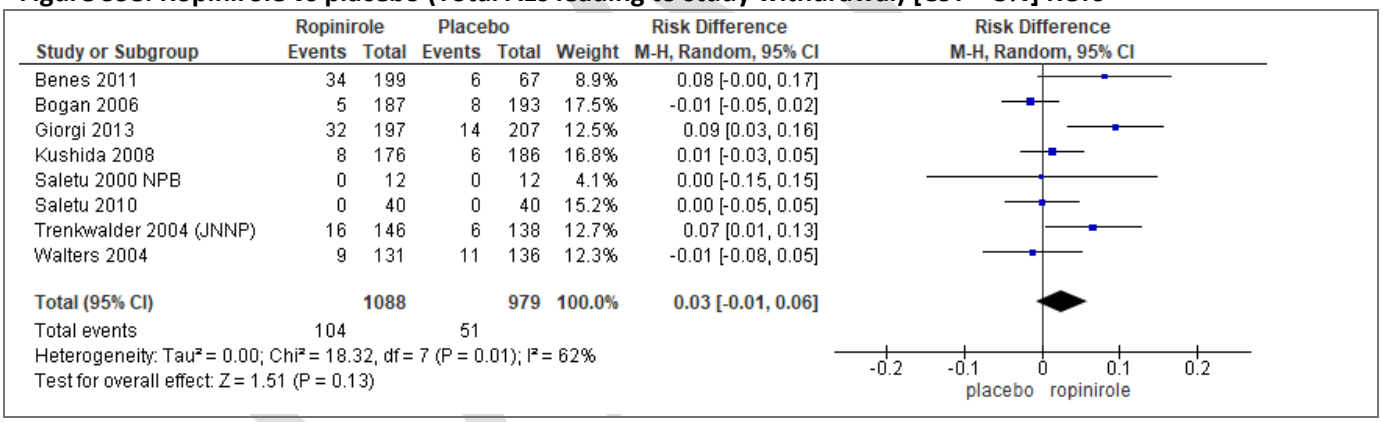
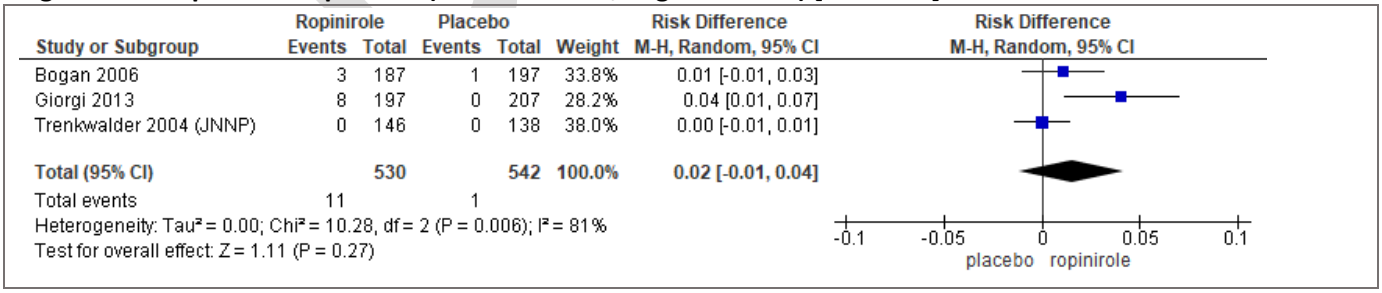
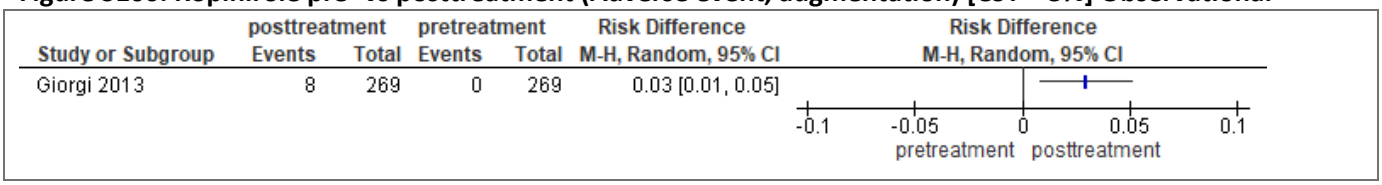


Figure S99. Ropinirole vs placebo (Adverse event, augmentation) [CST = 5%] RCTs[1-3]



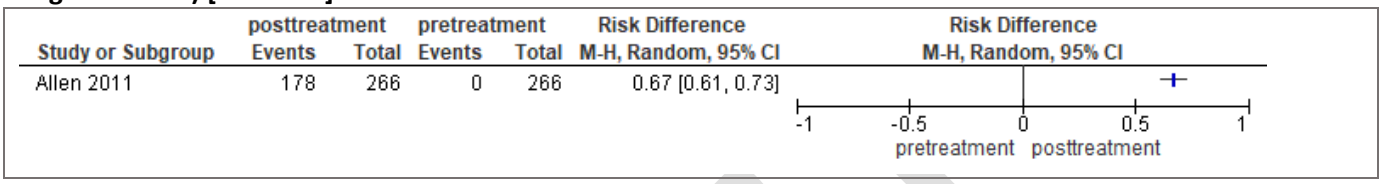
1. Bogan 2006 treatment duration was 12 weeks.
2. Giorgi 2013 treatment duration was 26 weeks.
3. Trenkwalder 2004 treatment duration was 12 weeks.

Figure S100. Ropinirole pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Observational[1]



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%]



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

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

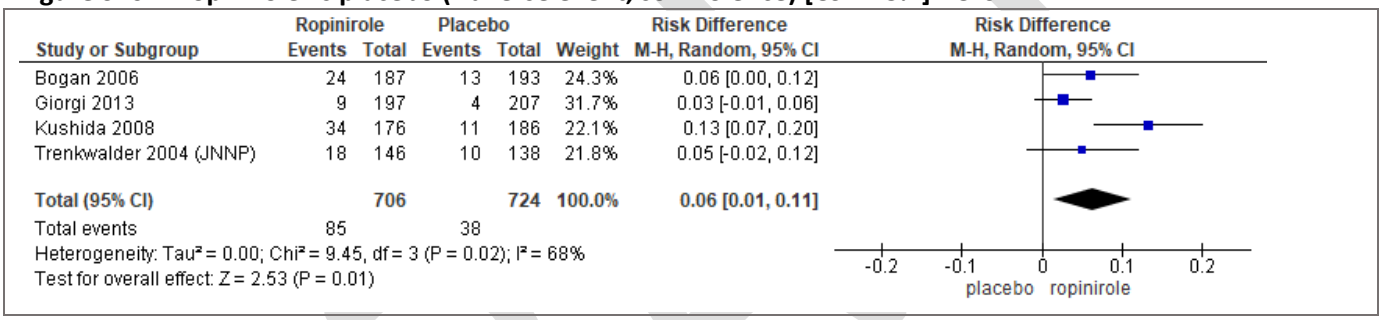
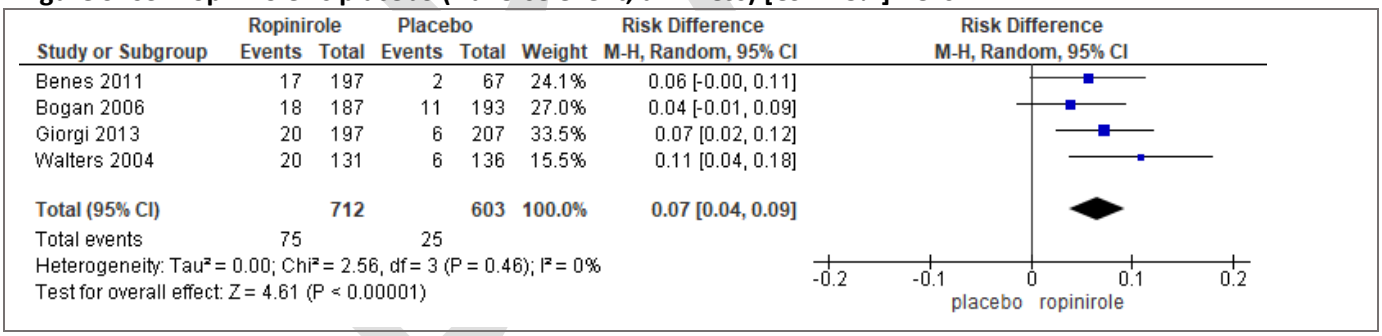


Figure S103. Ropinirole vs placebo (Adverse event, dizziness) [CST = 5%] RCTs



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]	⨁⨁⨁◯ **MODERATE**[a]	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% CI crosses CST.
b. Small sample size.

Critical Outcomes

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

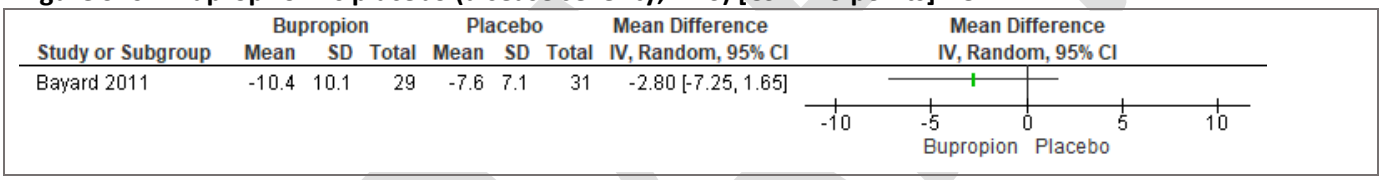
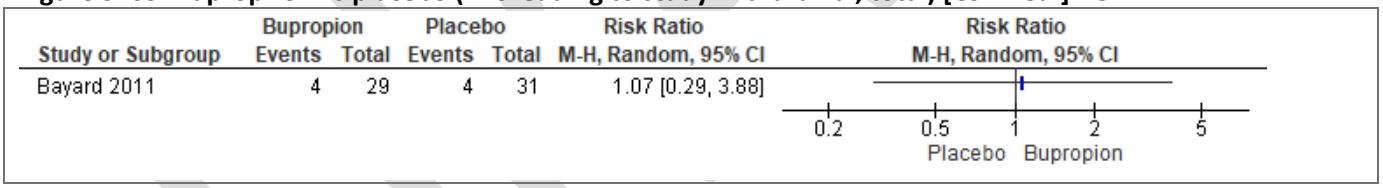


Figure S105. Buproprion vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT



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 (GRADE)	Absolute Difference Carbamazepine vs Placebo or Control	No of Participants (studies)
Disease severity [Subjective frequency of RL sensations]	⨁⨁⨁◯ **MODERATE**[a]	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)

a. Small sample size.
b. 95% CI crosses CST.

Critical Outcomes

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

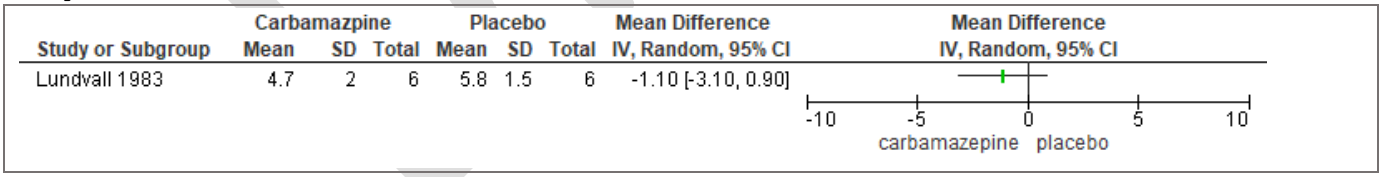


Figure S107. Carbamazepine vs placebo for adults with RLS (Disease severity, subj severity ratings) [No CST] RCT

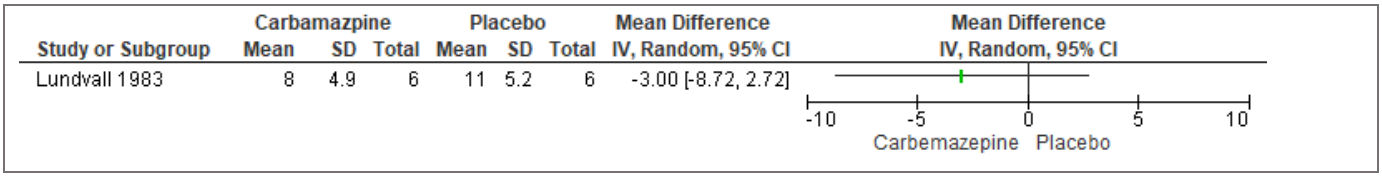


Figure S108. Carbamazepine vs placebo for adults with RLS (AEs leading to study withdrawal, total) [CST = 5%] RCT

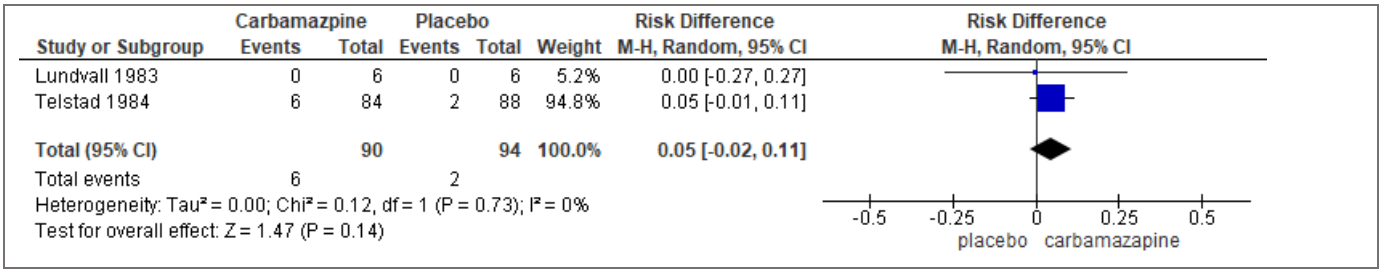


Figure S109. Carbamazepine pre- vs posttreatment for adults with RLS (AEs leading to study withdrawal, total) [CST = 5%] Observational

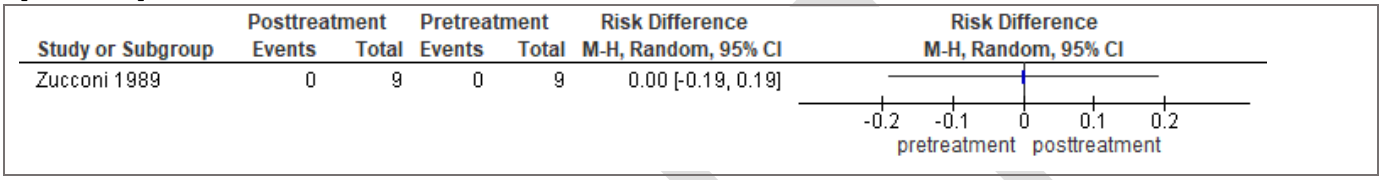
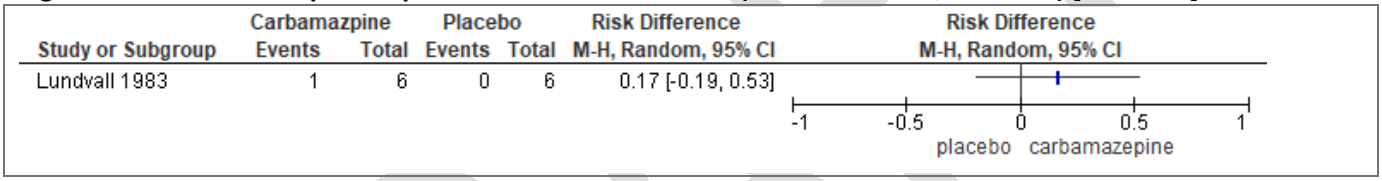
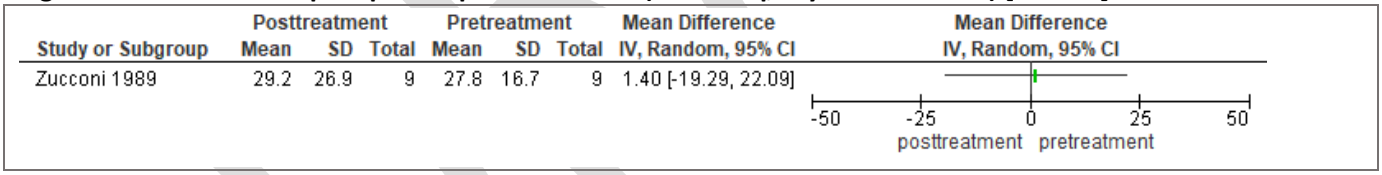


Figure S110. Carbamazepine vs placebo for adults with RLS (Adverse events, dizziness) [CST = 5%] RCT



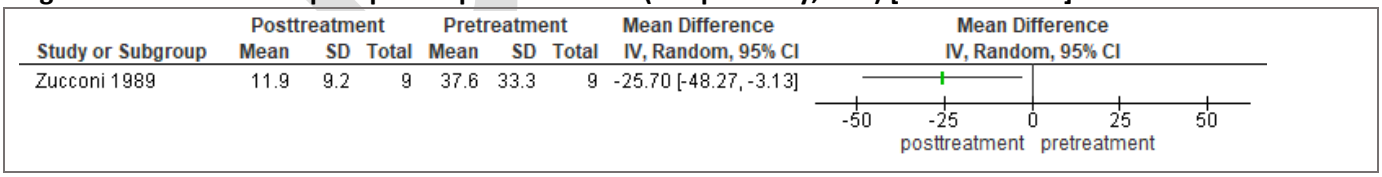
Important Outcomes

Figure S111. Carbamazepine pre- vs posttreatment (PLM Freq, Myoclonus Index) [No CST] Observational[1]



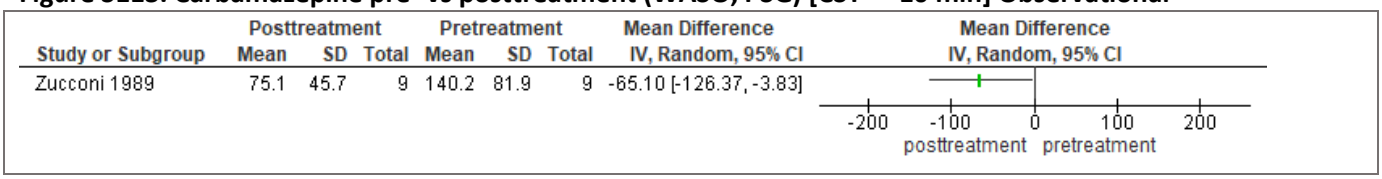
1. Standard deviations were calculated from individual patient data in Zucconi 1989.

Figure S112. Carbamazepine pre- vs posttreatment (sleep latency, PSG) [CST = -10 min] Observational[1]



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

Figure S113. Carbamazepine pre- vs posttreatment (WASO, PSG) [CST = -10 min] Observational[1]



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 [PLMI]	⨁⨁⨁◯ **MODERATE**[a]	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 (1 RCT)
Sleep latency [PSG]	⨁⨁⨁◯ **MODERATE**[a,b]	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 (1 RCT)
WASO [PSG]	⨁⨁⨁◯ **MODERATE**[a]	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 (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)	⨁⨁⨁◯ **MODERATE**[a,c]	**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

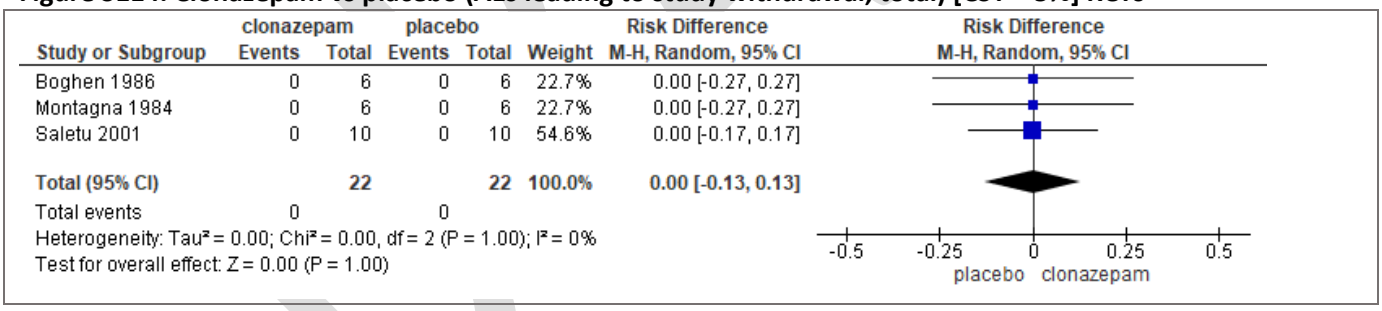
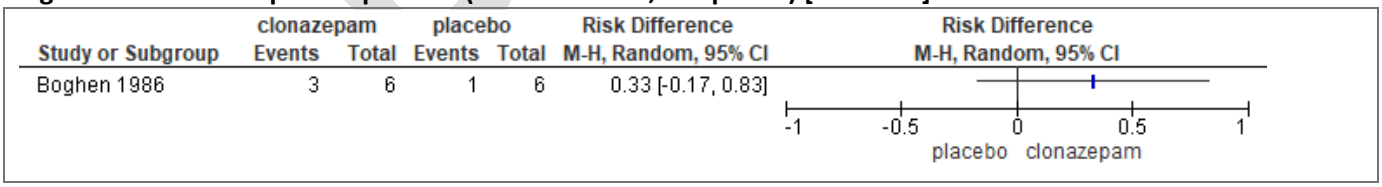


Figure S115. Clonazepam vs placebo (Adverse event, sleepiness) [CST = 5%] RCT



Important Outcomes

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

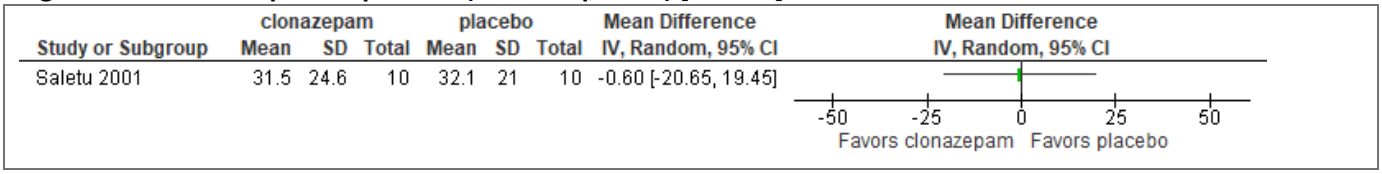


Figure S117. Clonazepam vs placebo (Sleep latency, PSG) [CST = -10 min] RCT

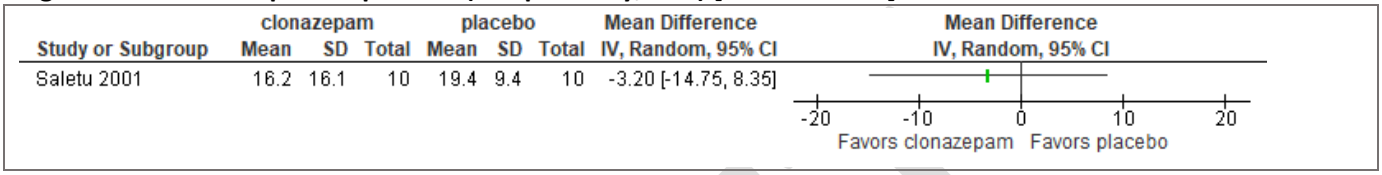
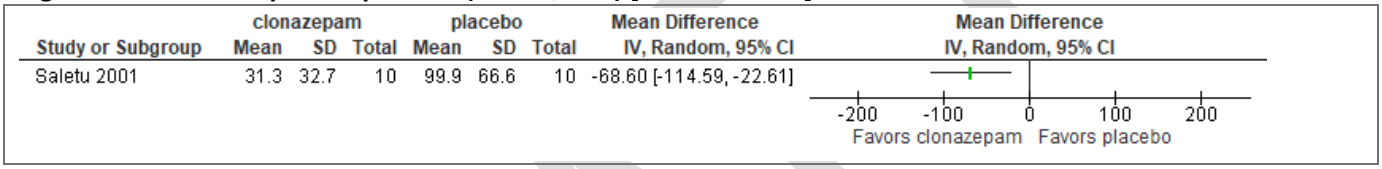


Figure S118. Clonazepam vs placebo (WASO, PSG) [CST = -10 min] RCT



DRAFT

Valerian

Summary of Findings (GRADE)

Table S6 Valerian in adults with RLS

References: Cuellar 2009

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

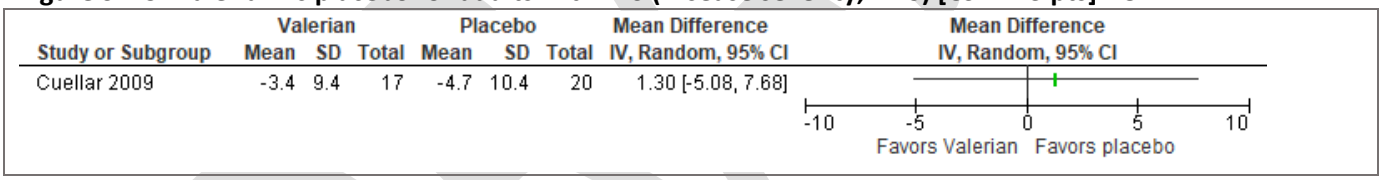


Figure S120. Valerian vs placebo for adults with RLS (Sleep quality, PSQI) [CST = -3 pts] RCT

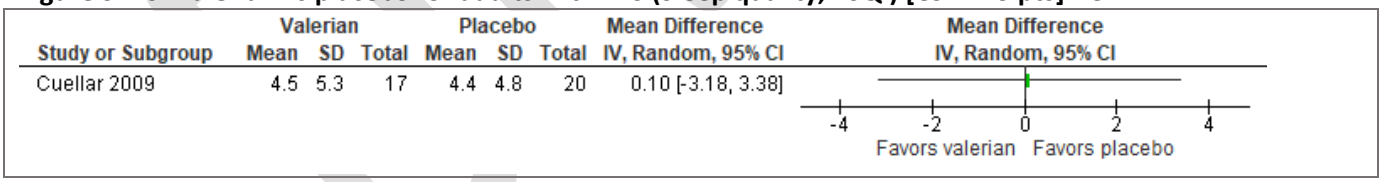


Figure S121. Valerian vs placebo for adults with RLS (AEs leading to study withdrawal, Total) [CST = -5%] RCT

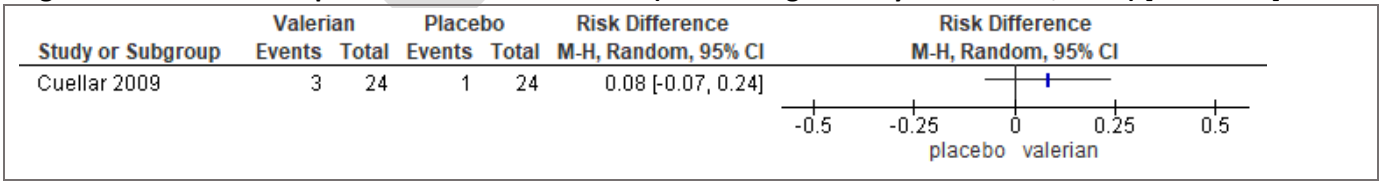
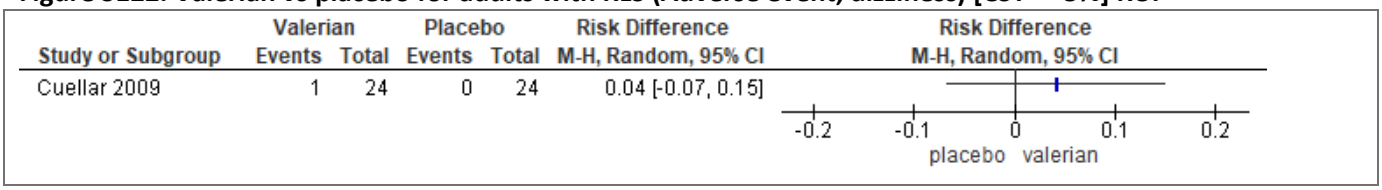


Figure S122. Valerian vs placebo for adults with RLS (Adverse event, dizziness) [CST = -5%] RCT



DRAFT

Valproic Acid

Summary of Findings (GRADE)

Table S7 Valproic Acid in adults with RLS

References: Eisensehr 2004

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Valproic acid vs Placebo or Control	No of Participants (studies)
Disease severity [RLS intensity score, 0-10]	⨁⨁◯◯ **LOW**[a]	The mean difference in the valproic acid group was **1.7 points lower** (3.9 lower to 0.5 higher) compared to control	14 (1 RCT)
Disease severity [RLS duration during 24 hrs]	⨁⨁◯◯ **LOW**[a]	The mean difference in the valproic acid group was **51.5 minutes lower** (292.8 lower to 189.8 higher) compared to control	14 (1 RCT)
PLM Frequency [PLMI]	⨁⨁◯◯ **LOW**[a]	The mean difference in the valproic group was **5.2 PLMs/hr lower** (41.5 PLMs/hr lower to 31.1 PLMs/hr higher) compared to control	14 (1 RCT)
WASO [PSG]	⨁⨁◯◯ **LOW**[a]	The mean difference in the valproic acid group was **3.3 minutes lower** (22.4 lower to 15.8 higher) compared to control	14 (1 RCT)
Adverse events leading to study withdrawal	⨁⨁◯◯ **LOW**[a]	**0 per 1000** in the valproic acid group compared to 0 per 1,000 in the control group	14 (1 RCT)

a. Small sample size.

Critical Outcomes

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

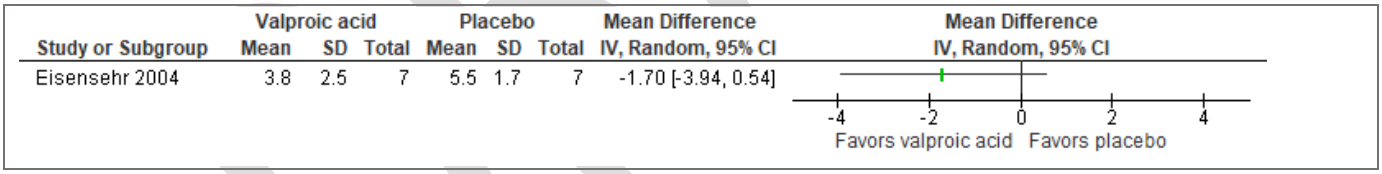


Figure S124. Valproic acid vs placebo for adults with RLS (Disease severity, RLS duration – min. during 24 hrs) [No CST] RCT

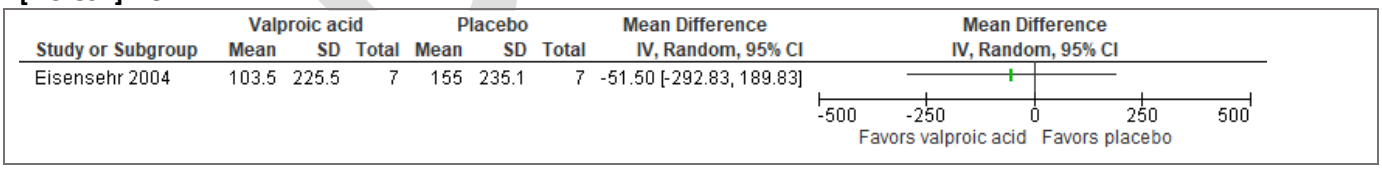
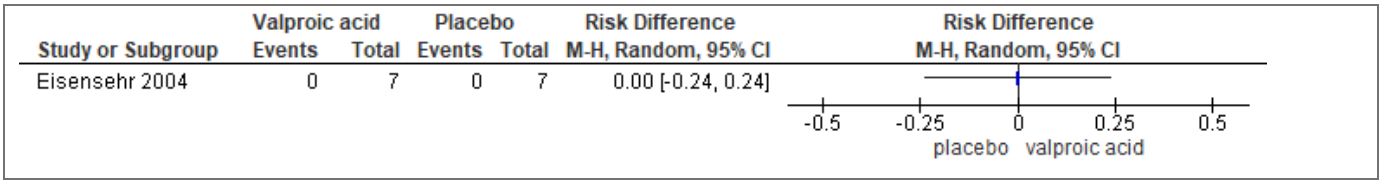


Figure S125. Valproic acid vs placebo for adults with RLS (AEs leading to study withdrawal, Total) [CST = 5%] RCT



Important Outcomes

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

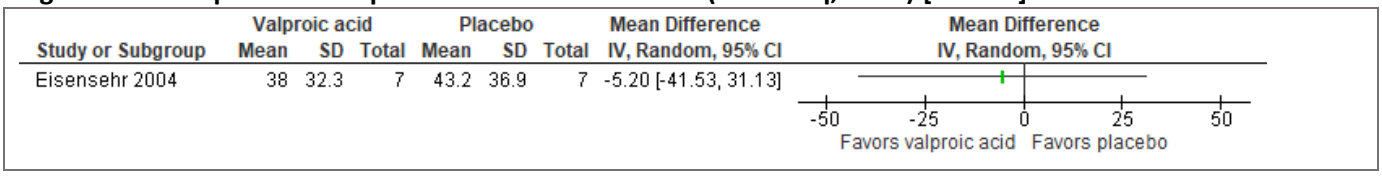
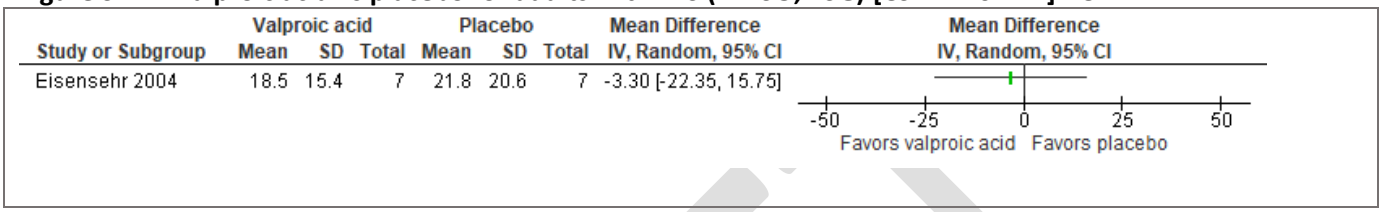


Figure S127. Valproic acid vs placebo for adults with RLS (WASO, PSG) [CST = -10 min] RCT



DRAFT

Cabergoline

Summary of Findings (GRADE)

Table S8 Cabergoline in adults with RLS

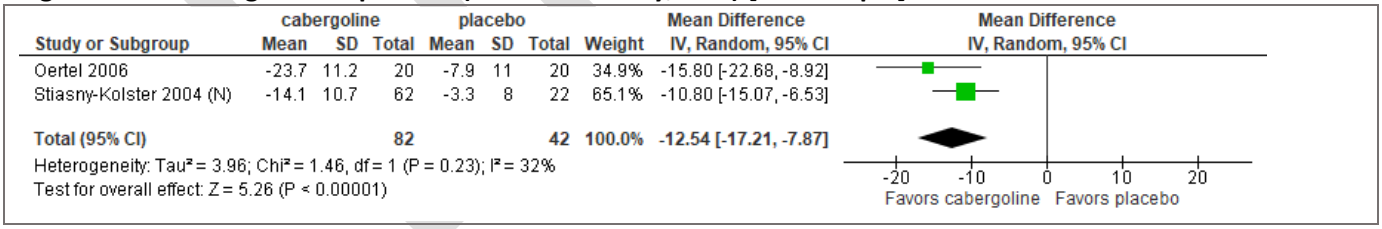
References: Oertel 2006, Stiasny-Kolster 2004, Beneš 2004, Trenkwalder 2007, Zucconi 2003

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



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

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

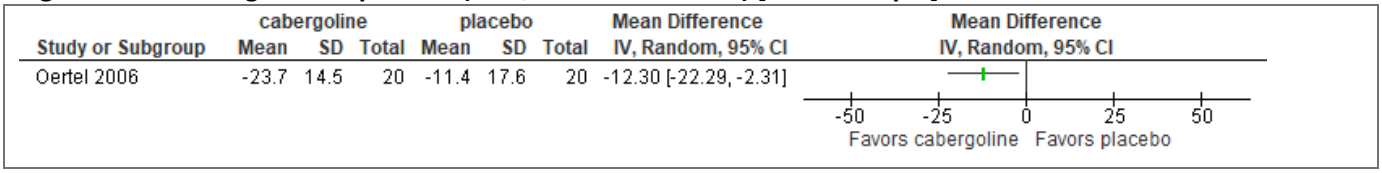


Figure S130. Cabergoline vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCTs

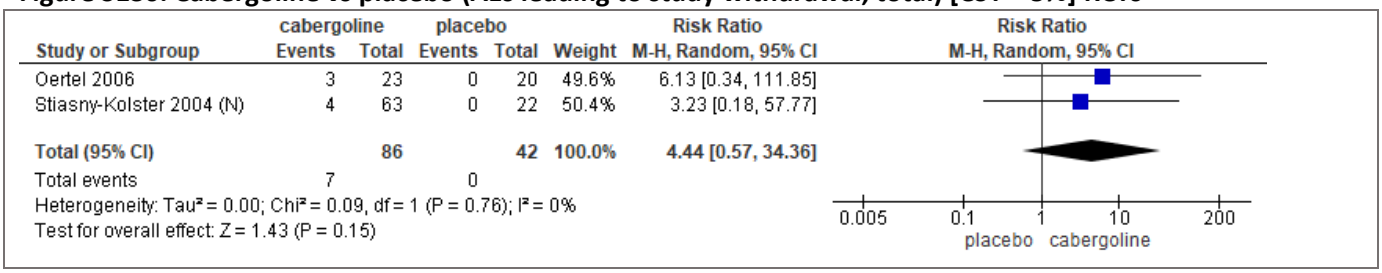
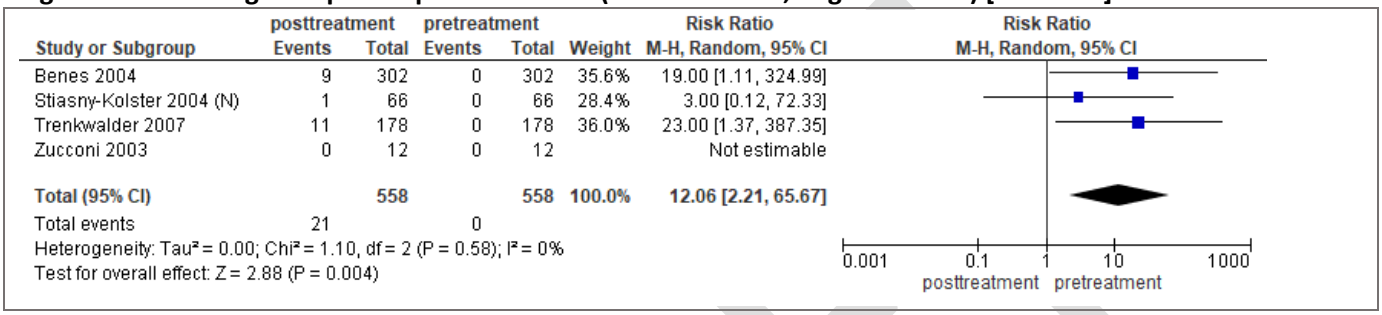
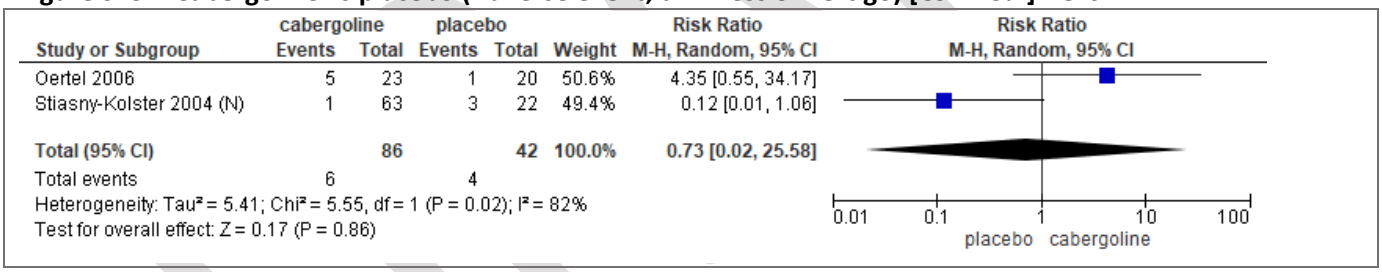


Figure S131. Cabergoline pre- vs posttreatment (Adverse event, augmentation) [CST = 5%] Observational[1]



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



Important Outcomes

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

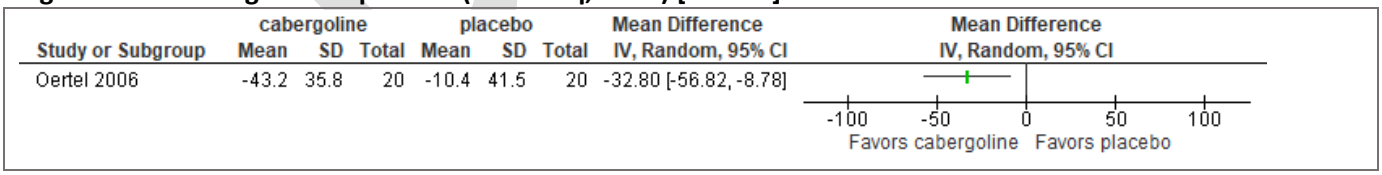
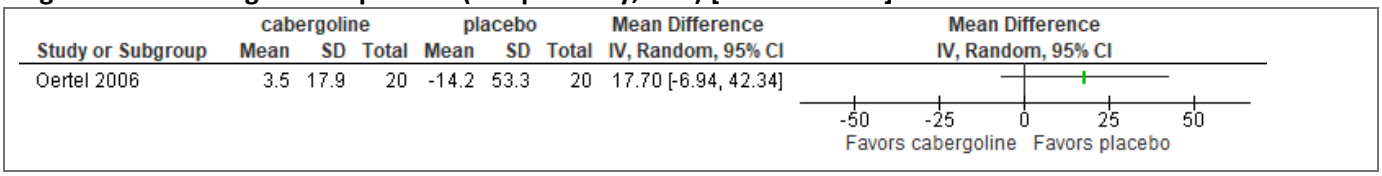


Figure S134. Cabergoline vs placebo (Sleep latency, PSG) [CST = -10 min] RCTs



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 (GRADE)	Absolute Difference Gabapentin vs Placebo or Control	No of Participants (studies)
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

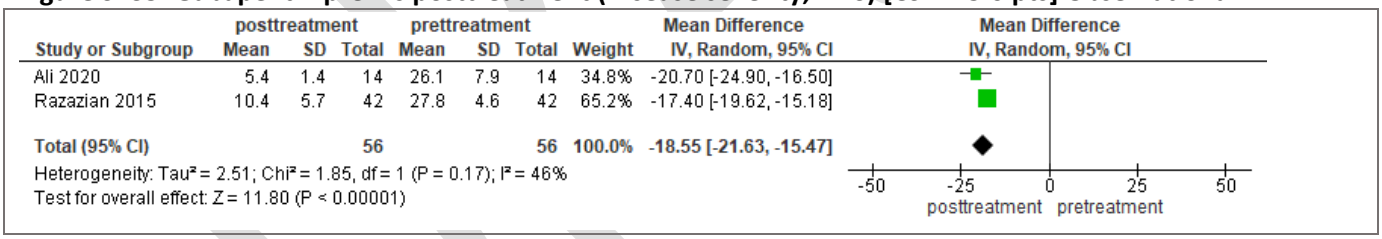


Figure S136. Gabapentin pre- vs posttreatment (Sleep quality, PSQI) [CST =-5.0 pts] Observational

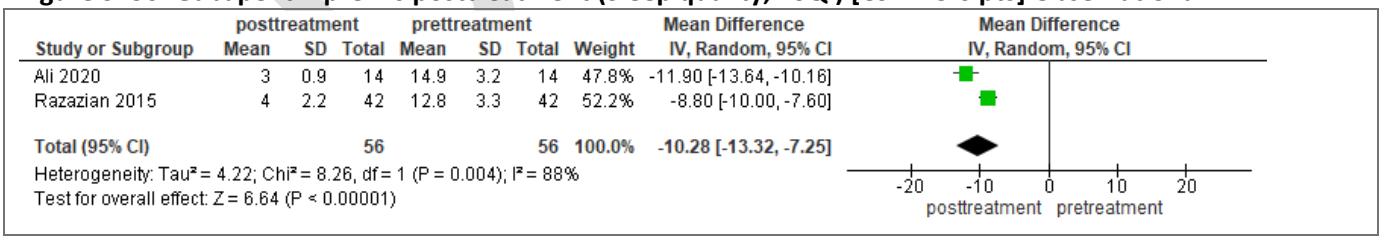


Figure S137. Gabapentin vs placebo (AEs leading to study withdrawal, total) [CST =5%] RCT

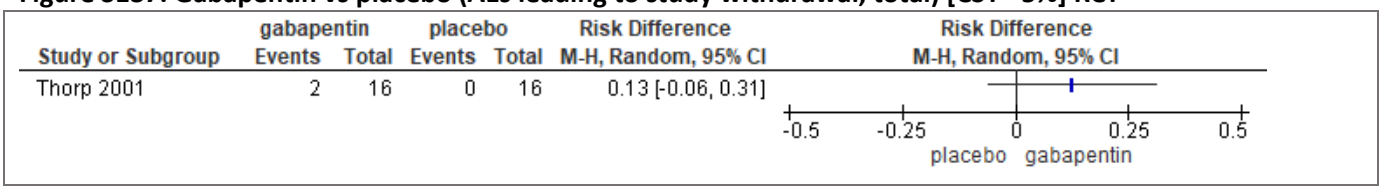


Figure S138. Gabapentin pre- vs posttreatment (AEs leading to study withdrawal, total) [CST =10%] Observational

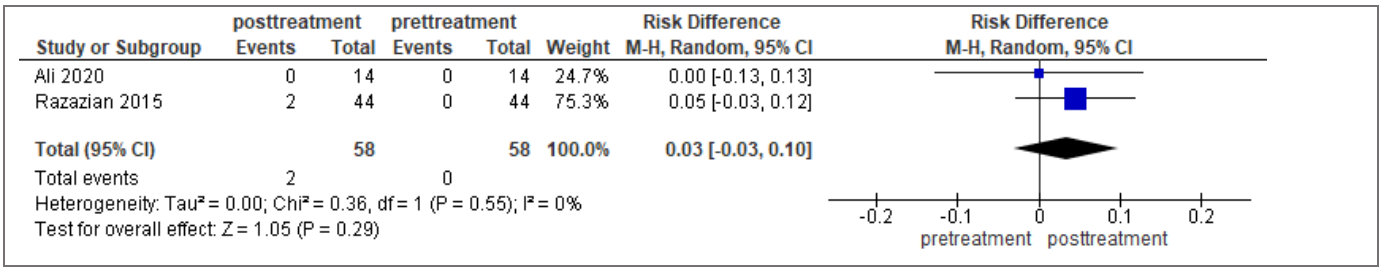


Figure S139. Gabapentin vs placebo (Adverse event, somnolence/lethargy) [CST =5%] RCT

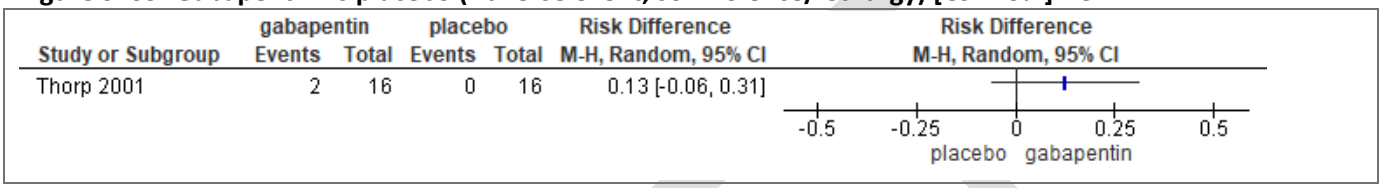
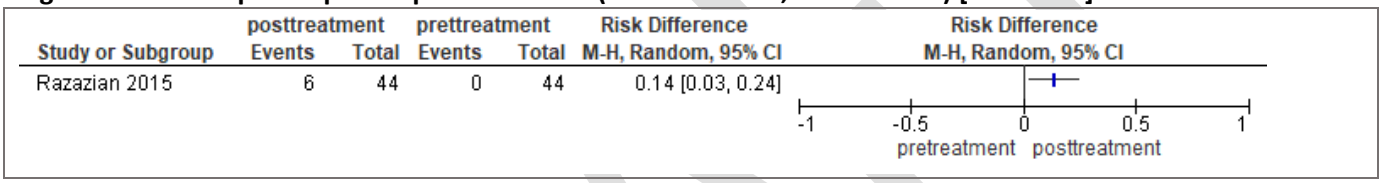


Figure S140. Gabapentin pre- vs posttreatment (Adverse event, somnolence) [CST =10%] Observational



IV iron sucrose in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S21 IV iron sucrose in adults with RLS and ESRD

References: Deng 2017

Outcomes [Tool]	**Certainty of the evidence (GRADE)**	**Absolute Difference** **Gabapentin vs Placebo or Control**	**No of Participants (studies)**
Disease severity [IRLS]	⨁⨁⨁◯ **MODERATE**[a]	The mean difference in the IV iron sucrose group was **6.6 points lower** (8.2 lower to 5.0 lower) compared to control	32 (1 RCT)
Adverse events leading to study withdrawal	⨁⨁⨁◯ **MODERATE**[a]	**0 per 1,000** (110 fewer to 110 more) in the IV iron sucrose group compared to the control group	32 (1 RCT)

a. Small sample size.
b. 95% CI crosses CST

Critical Outcomes

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

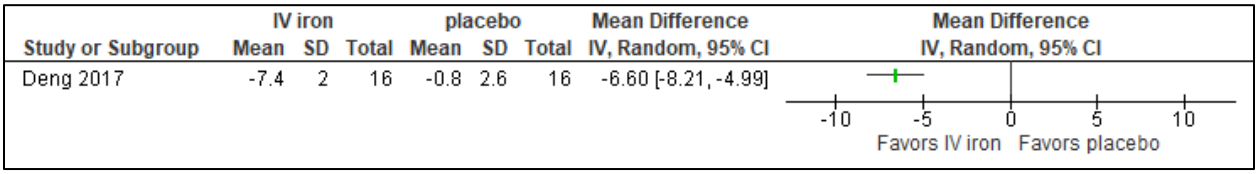
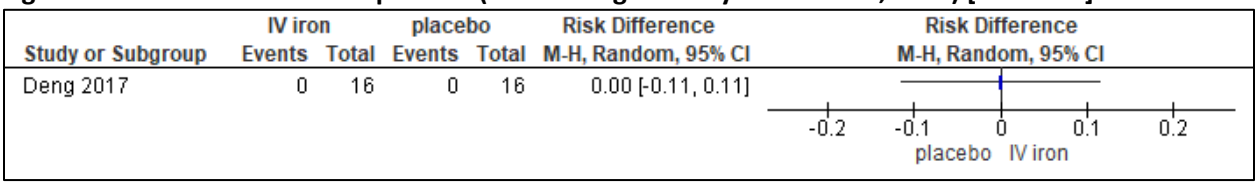


Figure S142. IV Iron sucrose vs placebo (AEs leading to study withdrawal, total) [CST = 5%] RCT



Vitamin C in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S22 Vitamin C in adults with RLS and ESRD

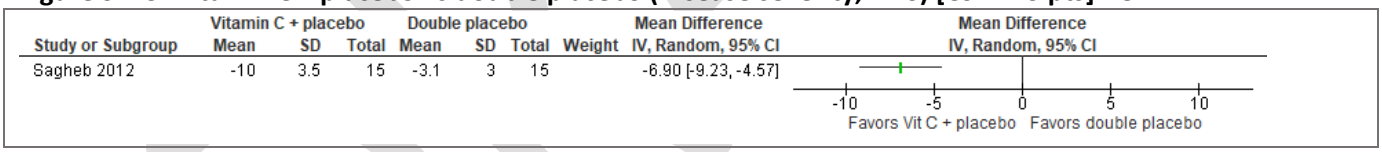
References: Sagheb 2012

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



DRAFT

Levodopa in adults with RLS and ESRD

Summary of Findings (GRADE)

Table S23 Levodopa in adults with RLS and ESRD

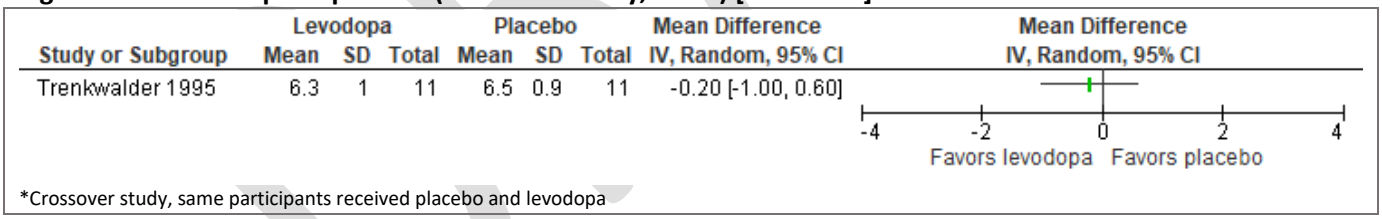
References: Trenkwalder 1995, Ali 2020, Micozkadıoglu 2004, Pellecchia 2004, Razazian 2015

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

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

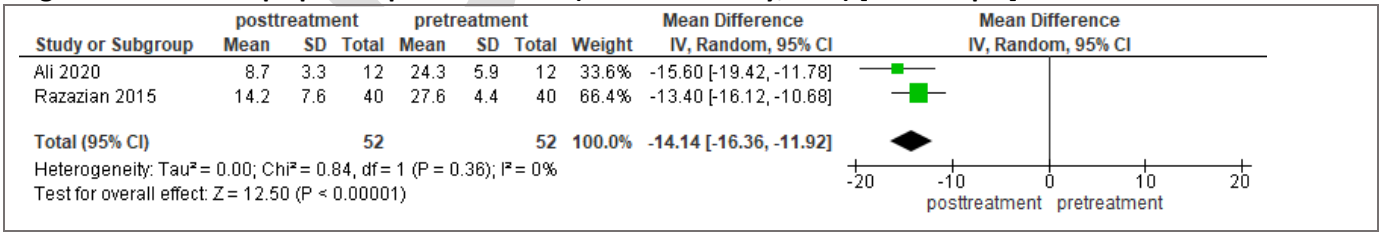
Critical Outcomes

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



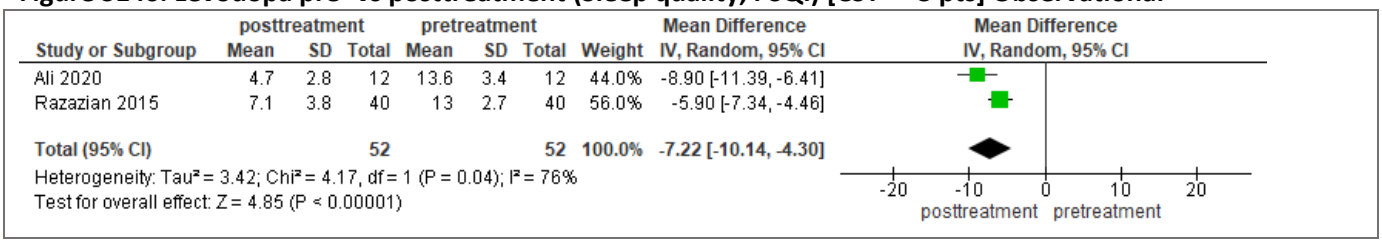
*Crossover study, same participants received placebo and levodopa

Figure S145. Levodopa pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational[1]



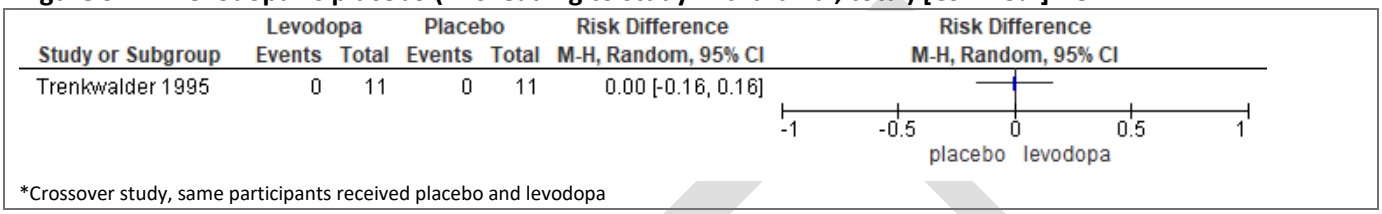
1. Ali 2020 and Razazian 2015 RCTs compared levodopa to gabapentin so pre- vs posttreatment data used for comparison.

Figure S146. Levodopa pre- vs posttreatment (Sleep quality, PSQI) [CST = -3 pts] Observational[1]



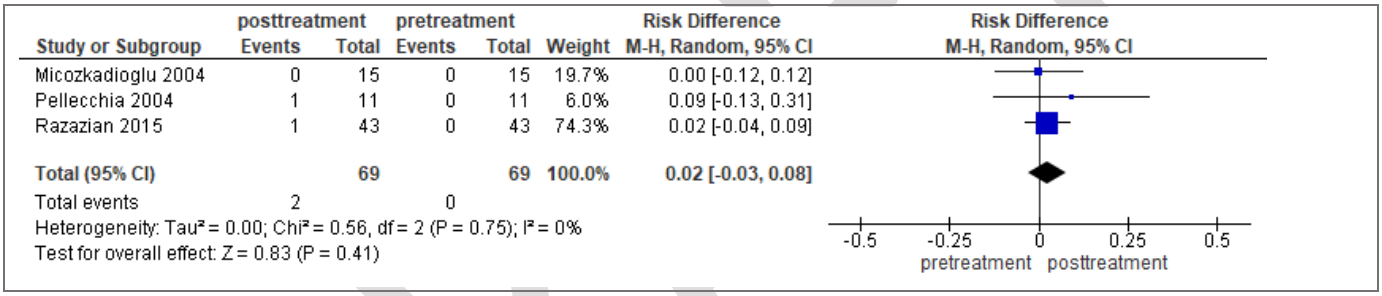
1. Ali 2020 and Razazian 2015 RCTs compared levodopa to gabapentin so pre- vs posttreatment data used for comparison.

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



*Crossover study, same participants received placebo and levodopa

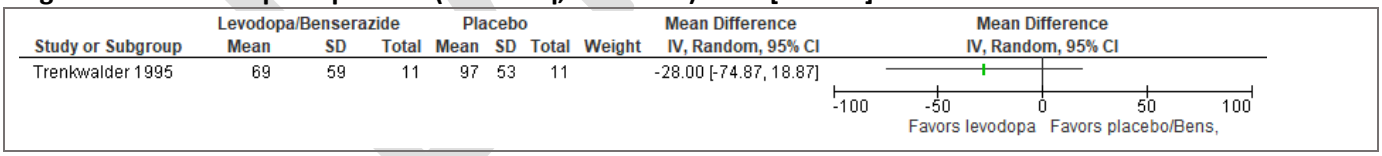
Figure S148. Levodopa pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational[1,2]



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.

Important Outcomes

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

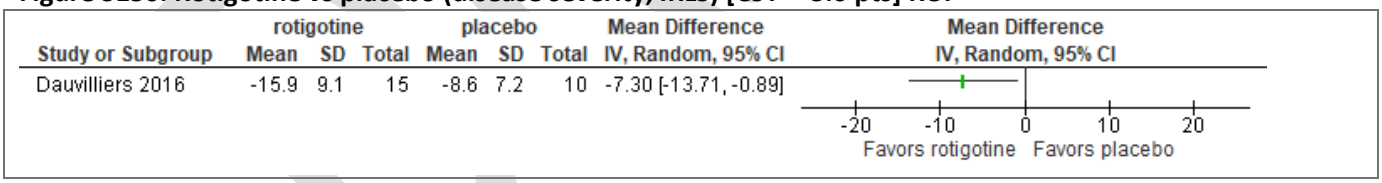


Figure S151. Rotigotine vs placebo (QOL, RLS-QOL Kohnen) [CST = -2.5 pts] RCT

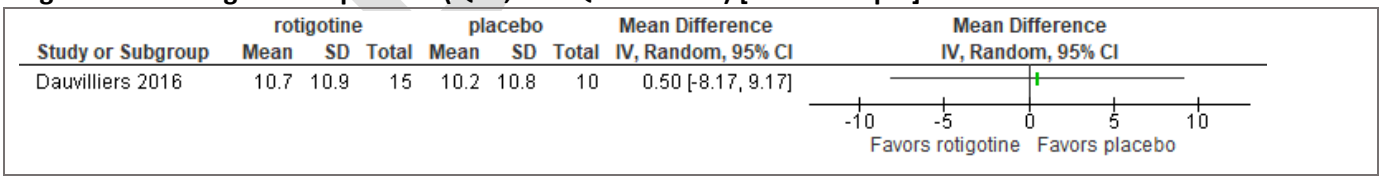
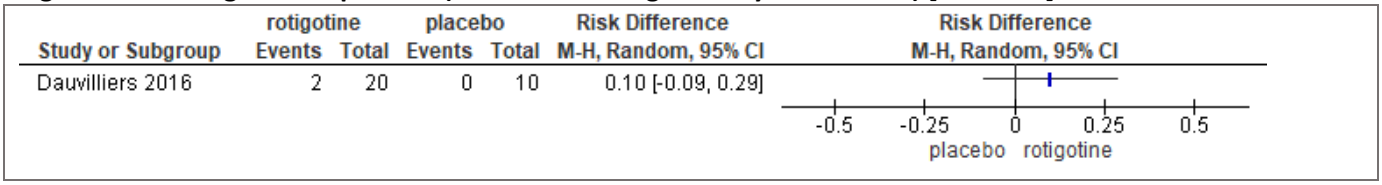


Figure S152. Rotigotine vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCT



Important Outcomes

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

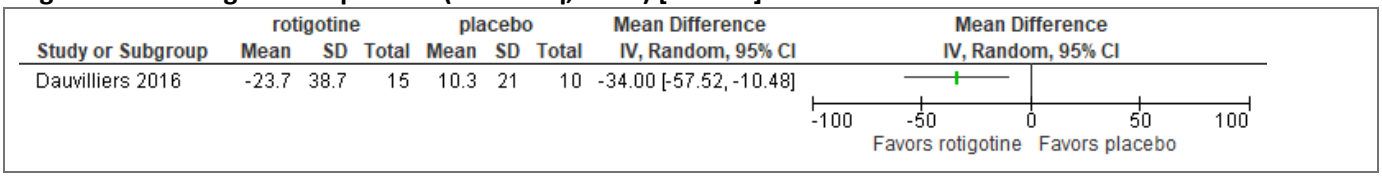


Figure S154. Rotigotine vs placebo (sleep latency, PSG) [CST = -10 min] RCT

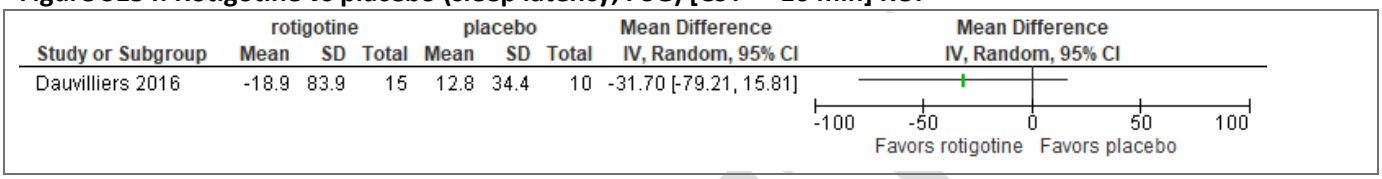
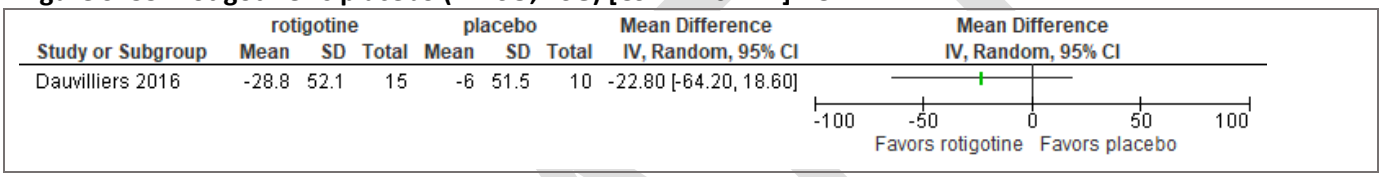


Figure S155. Rotigotine vs placebo (WASO, PSG) [CST = -10 min] RCT



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PICO 3: Adults with PLMD

Triazolam

Summary of Findings (GRADE)

Table S25 Triazolam in adults with PLMD

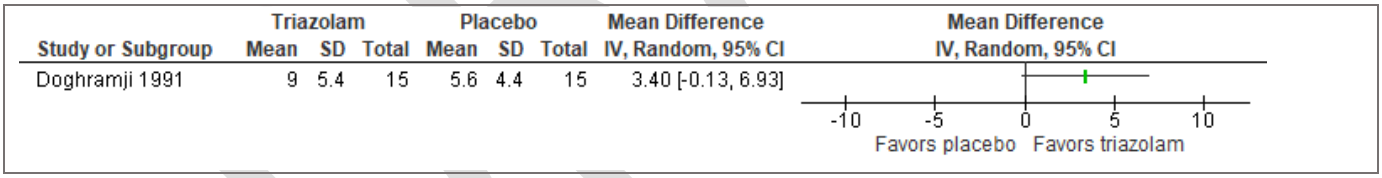
References: Bonnet 1991, Doghramji 1991

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

a. Small sample size
b. 95% CI crosses CST

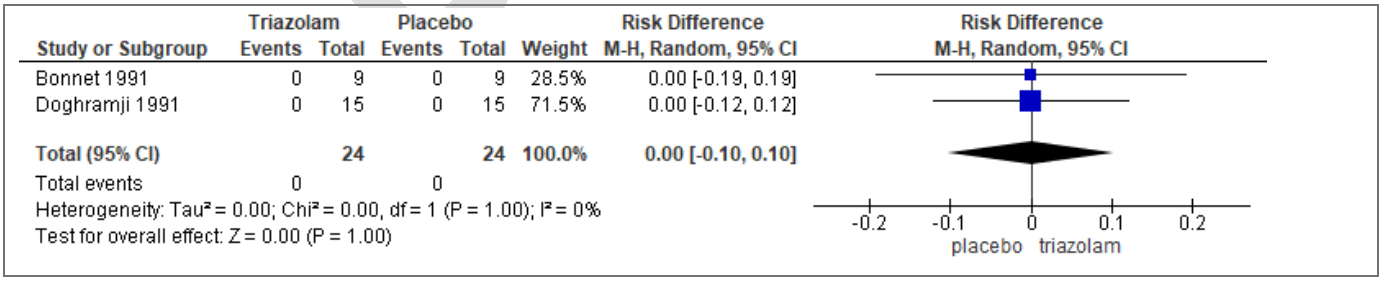
Critical Outcomes

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



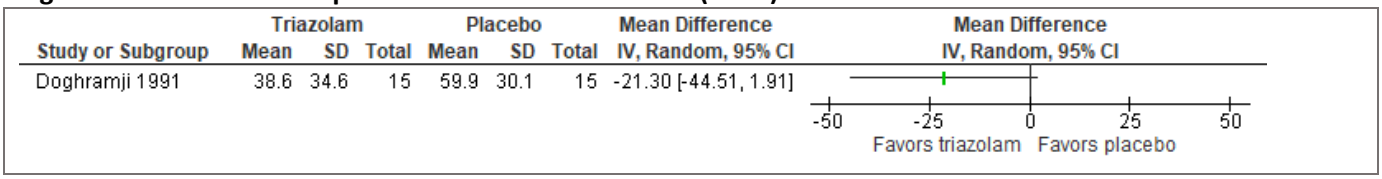
1. Posttreatment data used as change score data were not reported in Doghramji 1991.

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



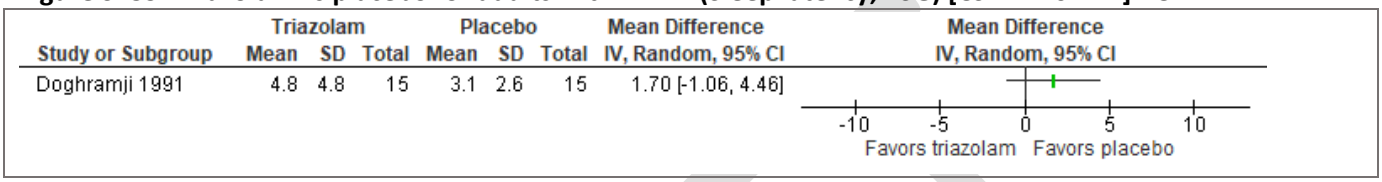
Important Outcomes

Figure S158. Triazolam vs placebo for adults with PLMD (PLMI) RCT[1]



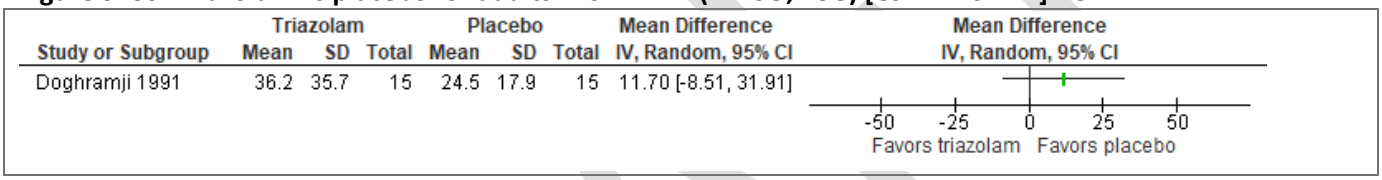
1. Posttreatment data used as change score data were not reported in Doghramji 1991.

Figure S159. Triazolam vs placebo for adults with PLMD (Sleep latency, PSG) [CST = -10 min] RCTl[1]



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] RCT[1]



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

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Valproic Acid

Summary of Findings (GRADE)

Table S26 Valproic Acid in adults with PLMD

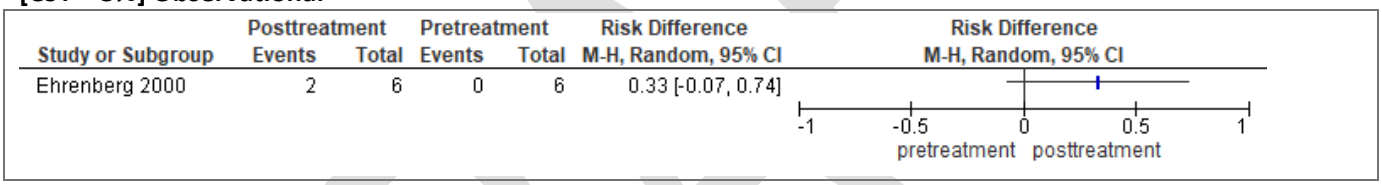
References: Ehrenberg 2000

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Valproic acid vs Placebo or Control	No of Participants (studies)
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)

a. Small sample size.
b. 95% CI crosses CST

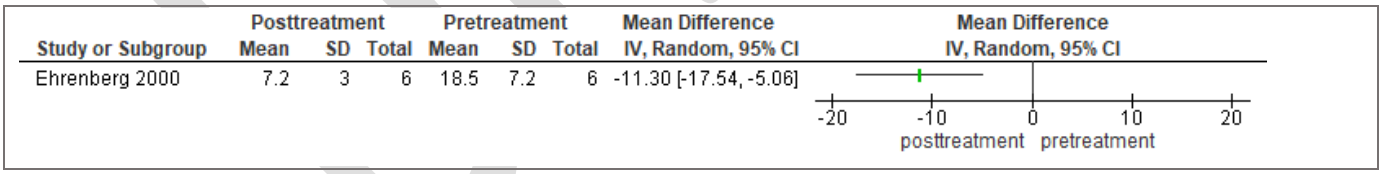
Critical Outcomes

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] Observational[1]



1. Ranges reported in Ehrenberg 2000 were converted to SD.

DRAFT

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 (GRADE)	Absolute Difference Oral iron vs Placebo or Control	No of Participants (studies)
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

Critical Outcomes

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

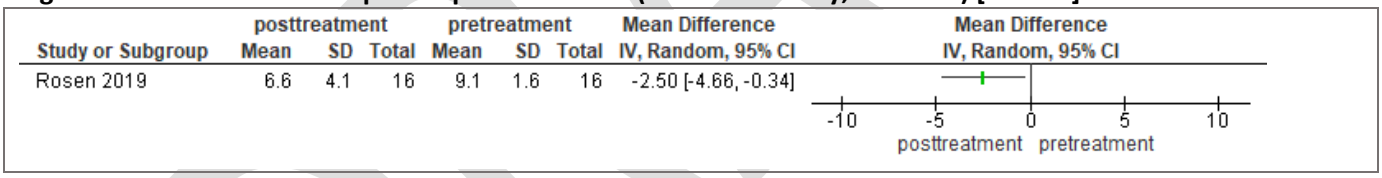


Figure S164. Ferrous sulfate pre- vs posttreatment (Disease severity, IRLS) [CST = -3 pts] Observational

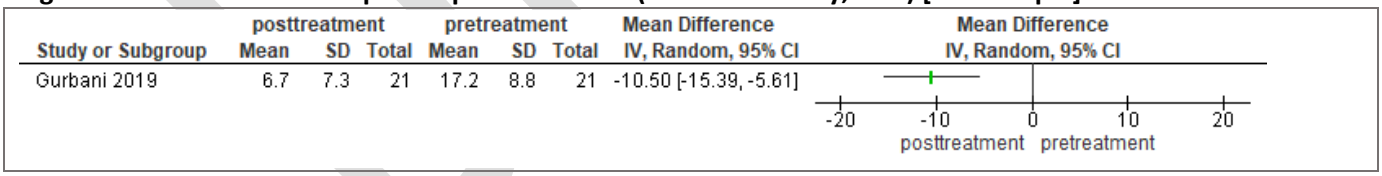


Figure S165. Ferrous sulfate pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

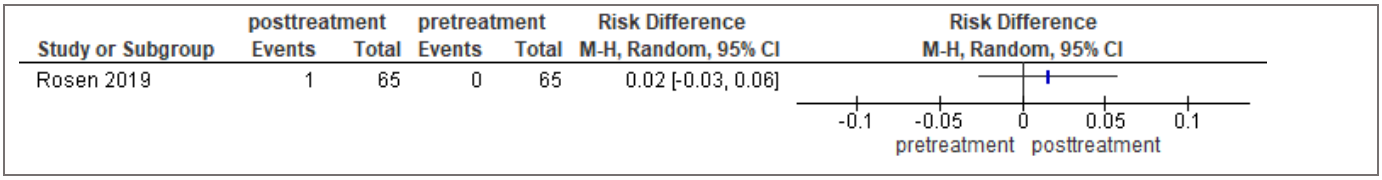
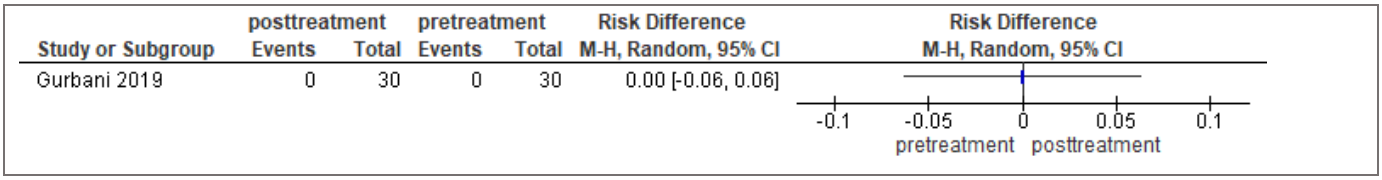
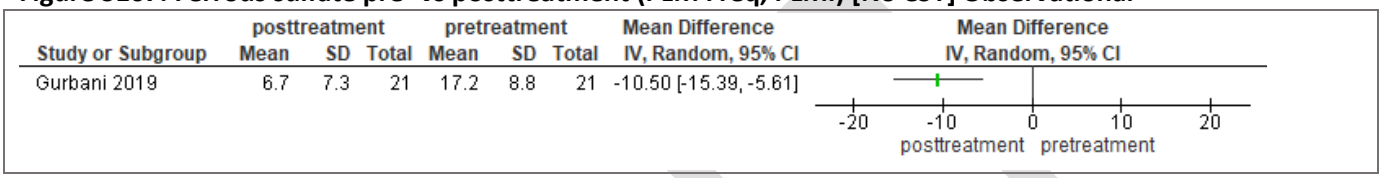


Figure S166. Ferrous sulfate pre- vs posttreatment (adverse event leading to withdrawal, total) [CST = 5%] Observational



Important Outcomes

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



DRAFT

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 (GRADE)**	**Absolute Difference** **IV Iron Sucrose vs Placebo or Control**	**No of Participants (studies)**
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	⨁⨁⨁◯ **MODERATE**[a]	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

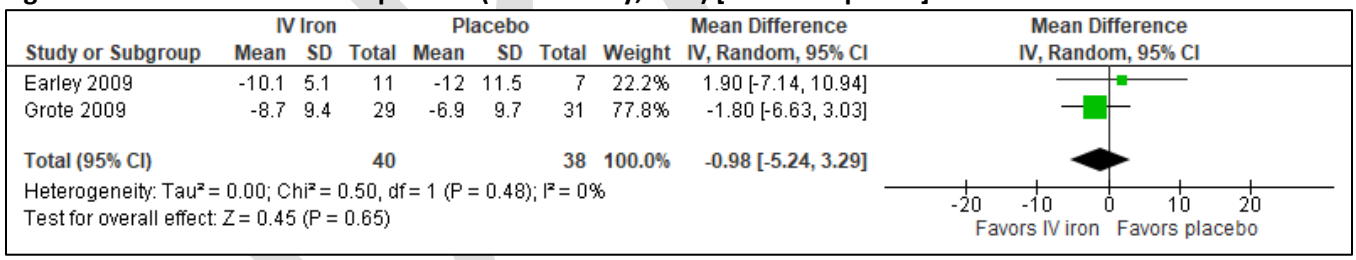
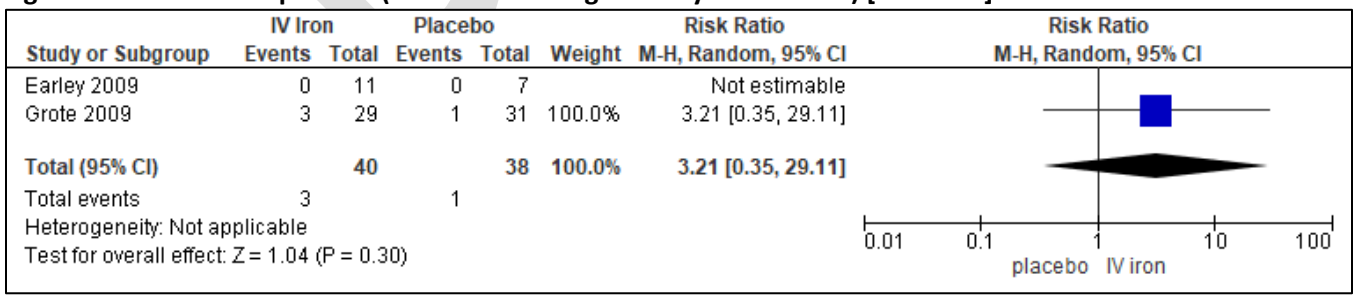


Figure S169. IV Iron vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



Clonidine

Summary of Findings (GRADE)

Table S29 Clonidine in adults with RLS

References: Wagner 1996

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Clonidine vs Placebo or Control	No of Participants (studies)
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	⊕◯◯◯ **LOW**[a,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)

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

Critical Outcomes

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

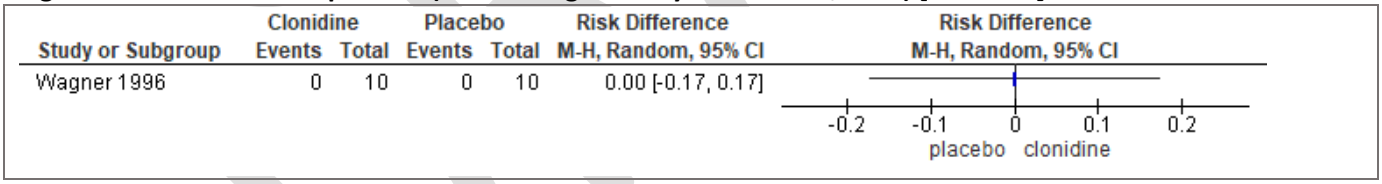


Figure S171. Clonidine vs placebo (Adverse event, sleepiness) [CST = 5%] RCT

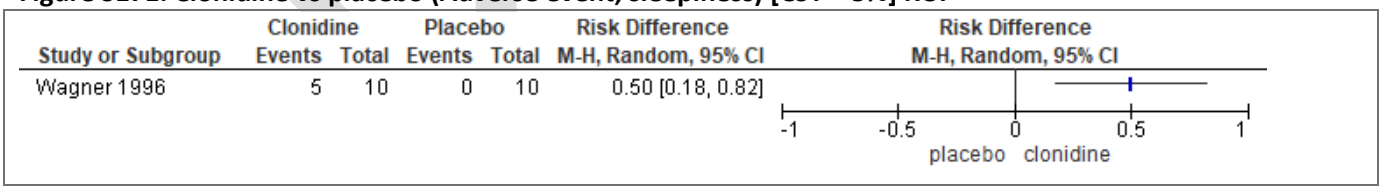
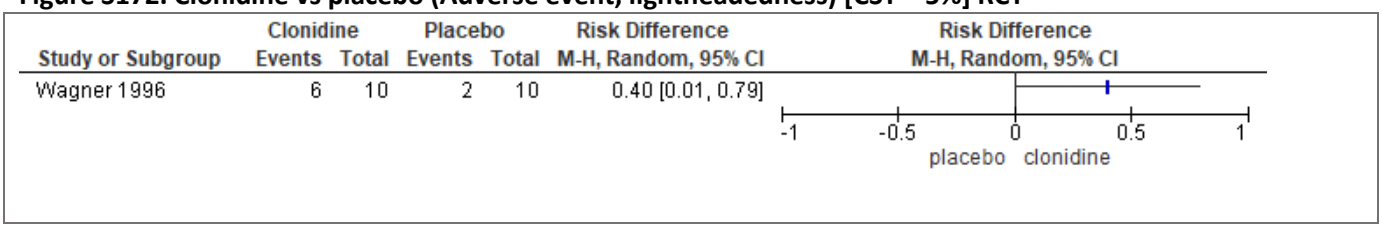


Figure S172. Clonidine vs placebo (Adverse event, lightheadedness) [CST = 5%] RCT



Important Outcomes

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

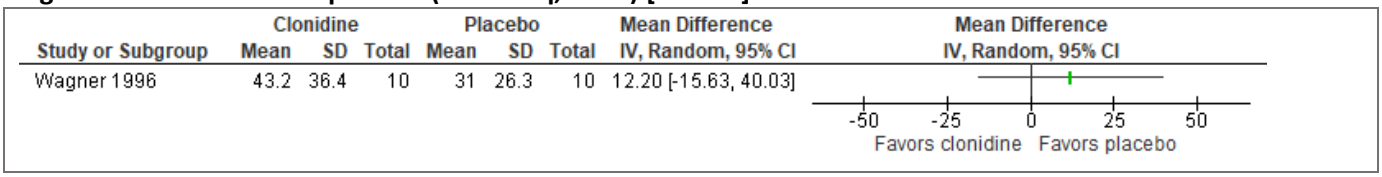
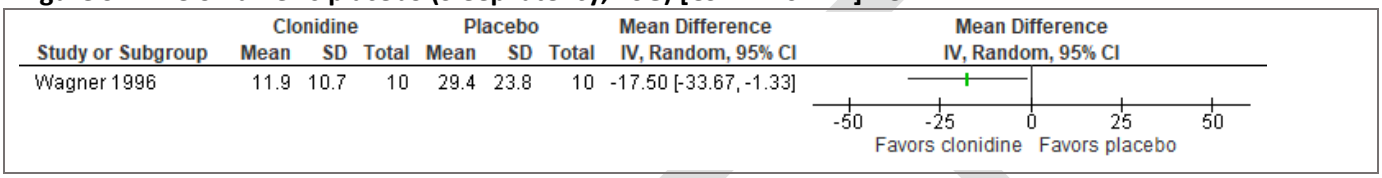


Figure S174. Clonidine vs placebo (Sleep latency, PSG) [CST = -10 min] RCT



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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]	⨁⨁◯◯ **LOW**[a]	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	⨁⨁◯◯ **LOW**[a]	**0 per 1000** in the botulinum group compared to 0 per 1,000 in the control group	60 (2 RCTs)

a. 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

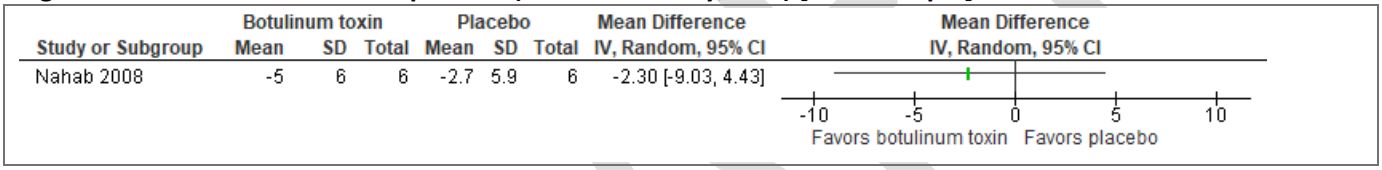
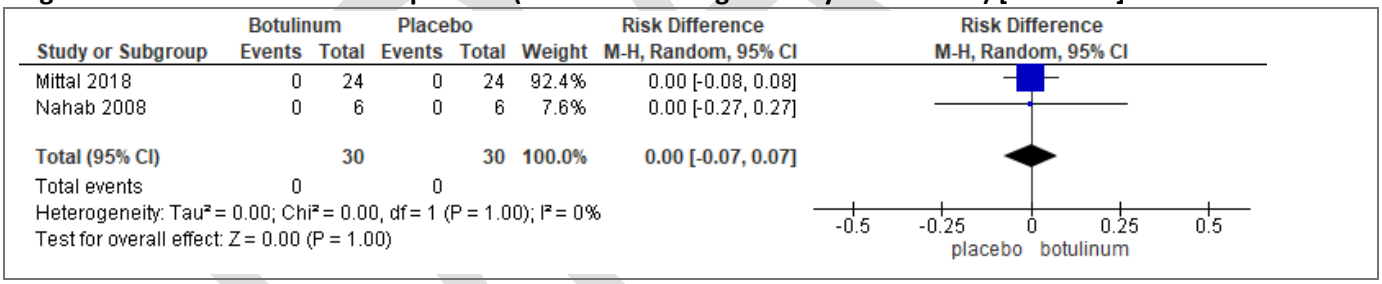


Figure S176. Botulinum toxin vs placebo (Total AEs leading to study withdrawal) [CST = 5%] RCTs



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

a. Small sample size.
b. 95% CI crosses CST.

Critical Outcomes

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

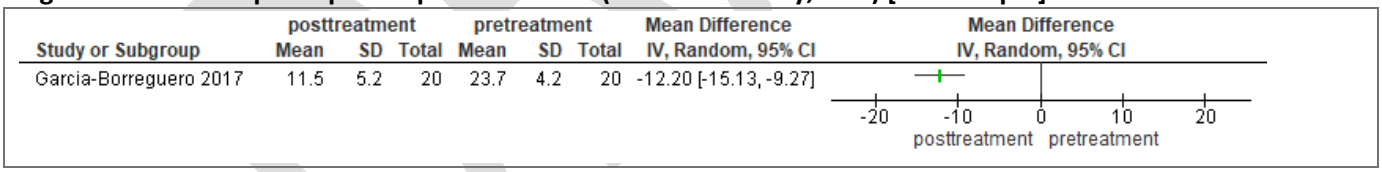


Figure S178. Perampanel pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

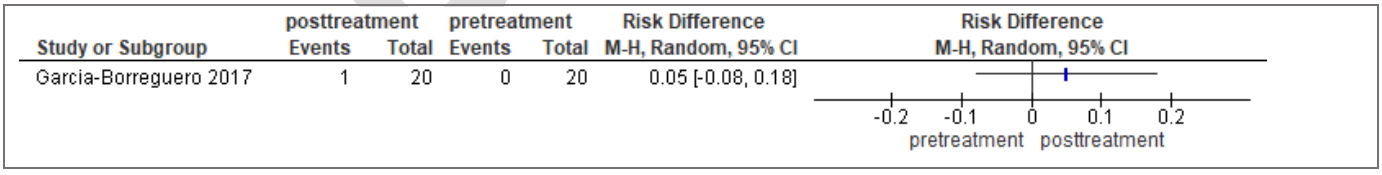


Figure S179. Perampanel pre- vs posttreatment (Adverse event, dizziness) [CST = 5%] Observational

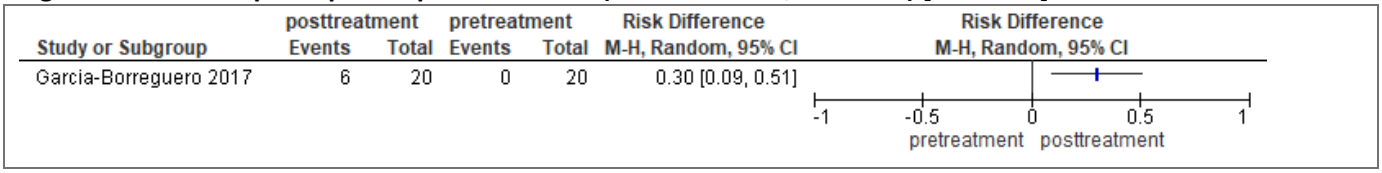
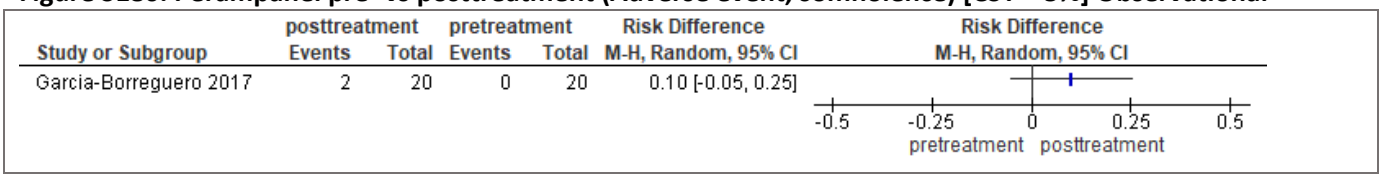


Figure S180. Perampanel pre- vs posttreatment (Adverse event, somnolence) [CST = 5%] Observational



Important Outcomes

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

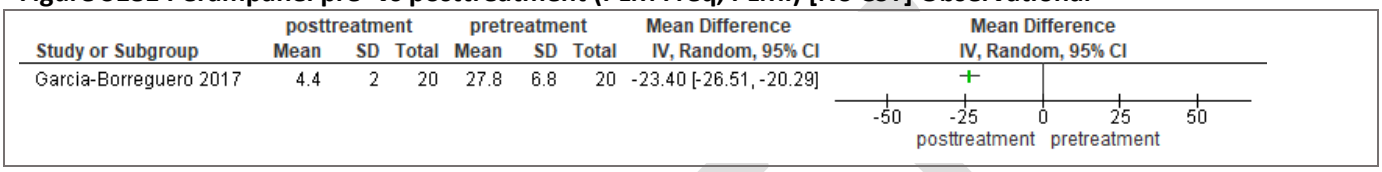


Figure S182. Perampanel pre- vs posttreatment (Sleep latency, PSG) [CST = -10 min] Observational

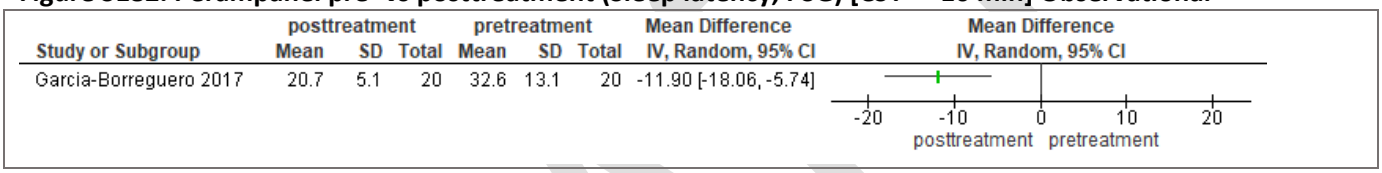
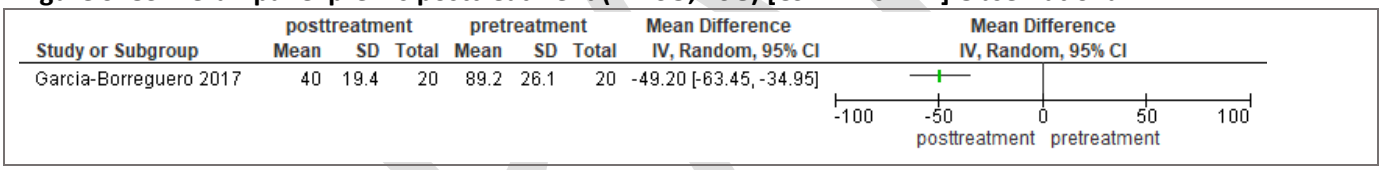


Figure S183. Perampanel pre- vs posttreatment (WASO, PSG) [CST = -10 min] Observational



Vitamin D

Summary of Findings (GRADE)

Table S32 Vitamin D in adults with RLS

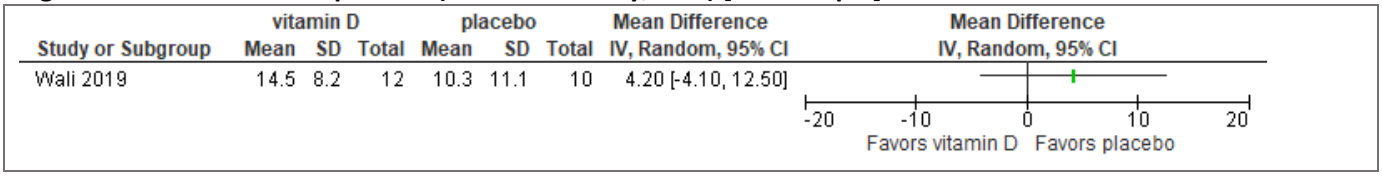
References: Wali 2019, Tutuncu 2020, Wali 2015

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Vitamin D vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⨁⨁◯◯ **LOW**[a]	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]	⨁⨁◯◯ **LOW**[a]	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.

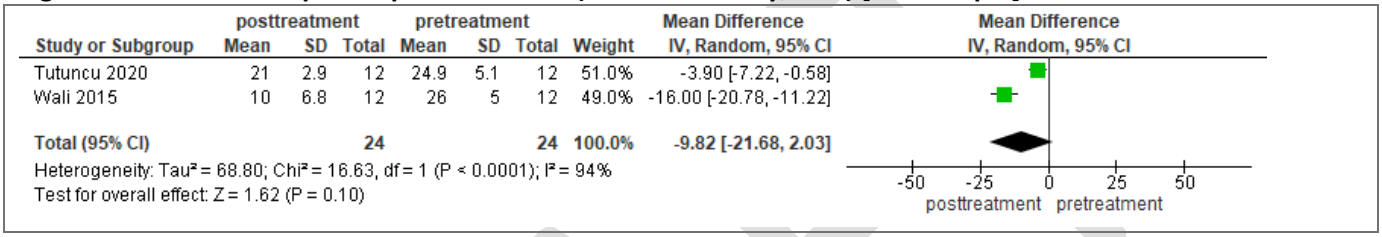
Critical Outcomes

Figure S184. Vitamin D vs placebo (Disease severity, IRLS) [CST = -3 pts] RCT[1]



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] Observational[1]



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

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Yoga

Summary of Findings (GRADE)

Table S33 Yoga in adults with RLS

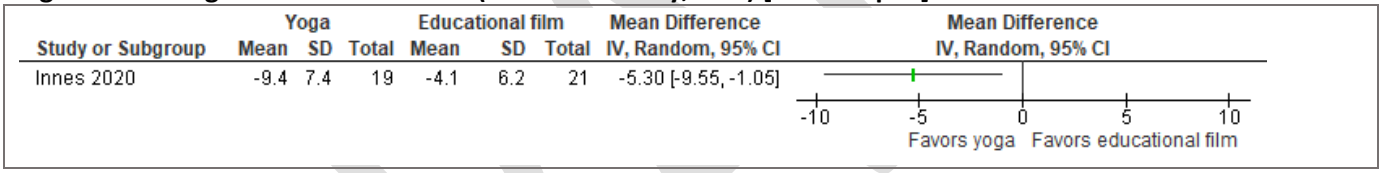
References: Innes 2020, Innes 2013

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** standardized mean difference in the yoga group was **1.1 SD higher** (0.17 higher to 2.1 higher)	20 (1 observational study)

a. Inadequate blinding.
b. Small sample size. 95% CI crosses CST.

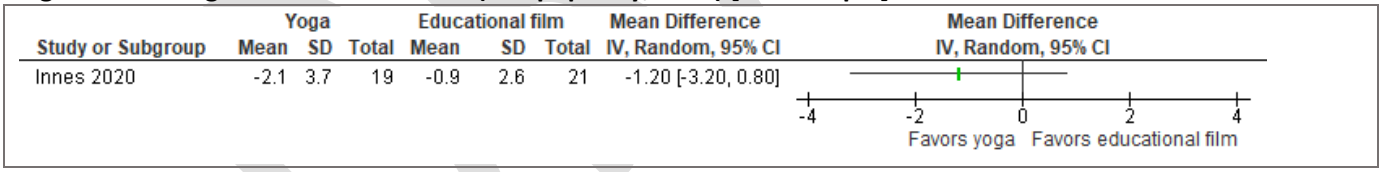
Critical Outcomes

Figure S186. Yoga vs educational film (Disease severity, IRLS) [CST = -3 pts.] RCT[1]



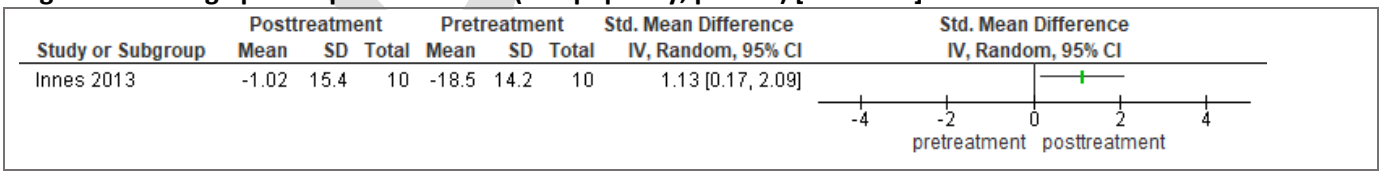
1. SE data were converted to SD.

Figure S187. Yoga vs educational film (Sleep quality, PSQI) [CST = -3 pts] RCT[1]



1. SE data were converted to SD.

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



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)

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

Critical Outcomes

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

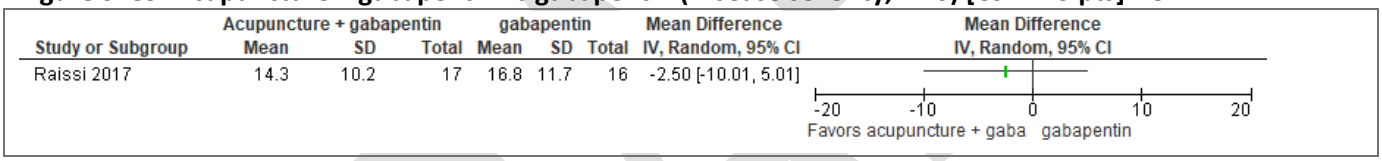
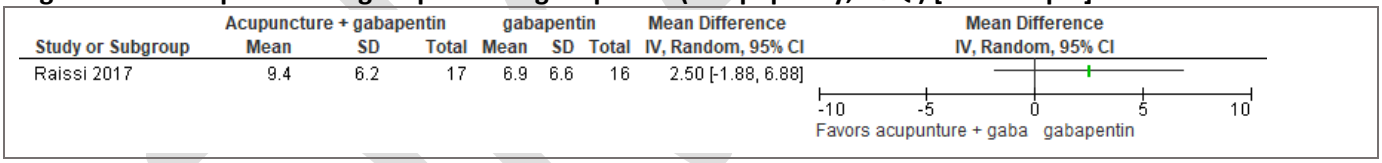


Figure S190. Acupuncture + gabapentin vs gabapentin (Sleep quality, PSQI) [CST = -3 pts] RCT



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 (GRADE)	Absolute Difference CBT vs Placebo or Control	No of Participants (studies)
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

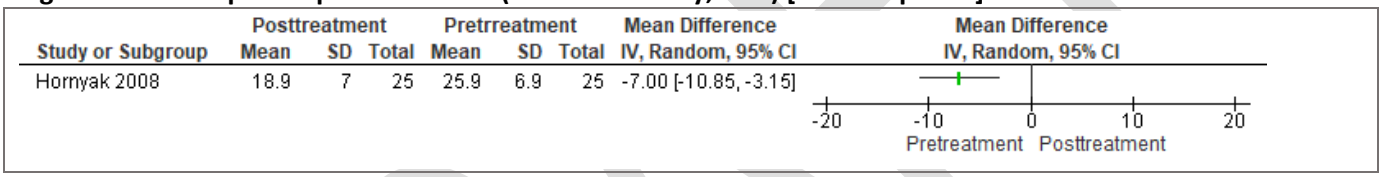
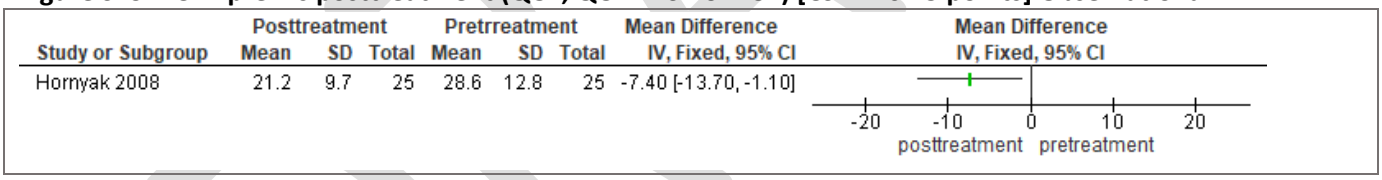


Figure S192. CBT pre- vs posttreatment (QOL, QOL-RLS Kohnen) [CST = -0.25 points] Observational



Near Infrared Light Therapy

Summary of Findings (GRADE)

Table S36 Near infrared light therapy in adults with RLS

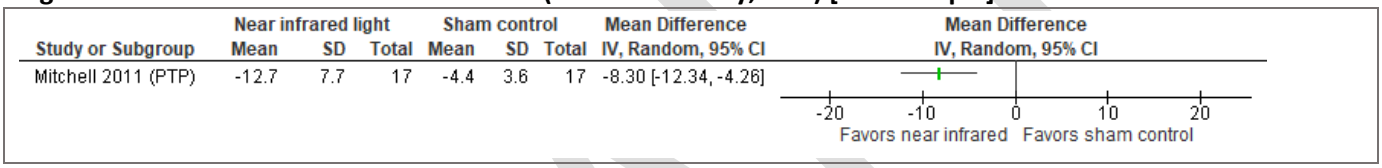
References: Mitchell 2011 (PTP)

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

a. Small sample size.

Critical Outcomes

Figure S193. Near infrared vs sham control (Disease severity, IRLS) [CST = - 3 pts] RCT[1]



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.

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Tramadol

Summary of Findings (GRADE)

Table S37 Tramadol in adults with RLS

References: Lauerma 1999

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

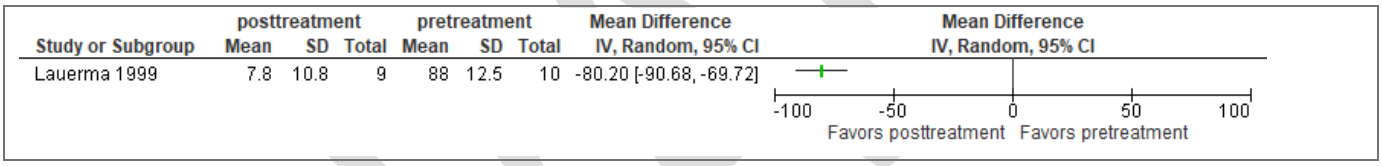


Figure S195. Tramadol pre- vs posttreatment (AEs leading to study withdrawal, total) [CST = 5%] Observational

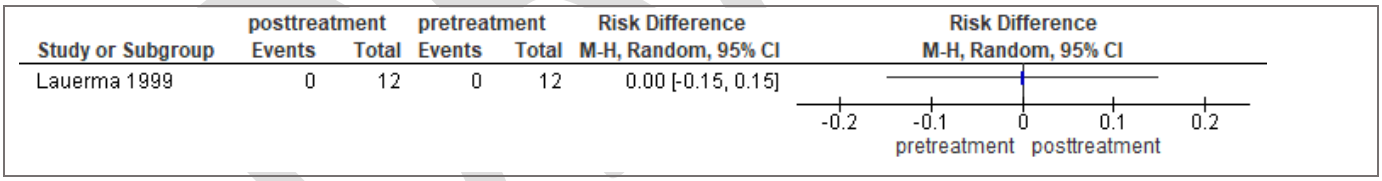
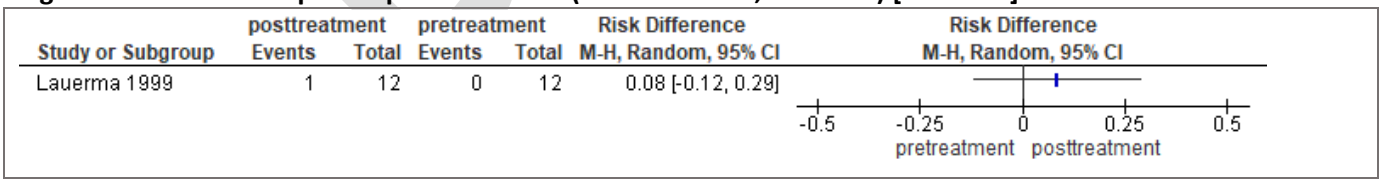


Figure S196. Tramadol pre- vs posttreatment (Adverse event, dizziness) [CST = 5%] Observational



Transcranial Magnetic Stimulation

Summary of Findings (GRADE)

Table S9 Transcranial magnetic stimulation in adults with RLS

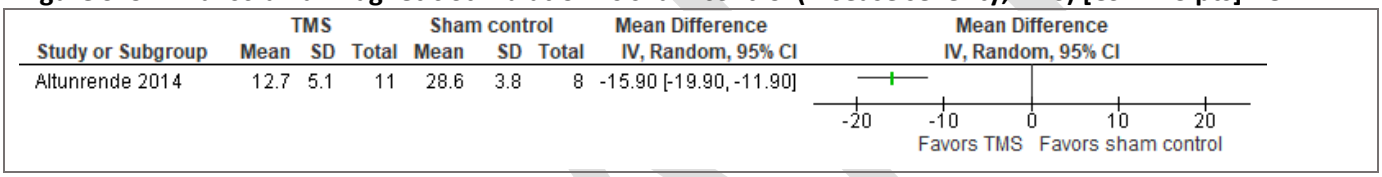
References: Altunrende 2014

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Transcranial magnetic stimulation vs Placebo or Control	No of Participants (studies)
Disease severity [IRLS]	⨁⨁◯◯ **LOW**[a,b]	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.
b. There are concerns regarding the lack of improvement reported in the placebo group.

Critical Outcomes

Figure S197. Transcranial Magnetic Stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT[1]



1. No adverse events were reported.

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Transcutaneous Spinal Direct Current Stimulation

Summary of Findings (GRADE)

Table S39 Transcutaneous spinal DC stimulation in adults with RLS

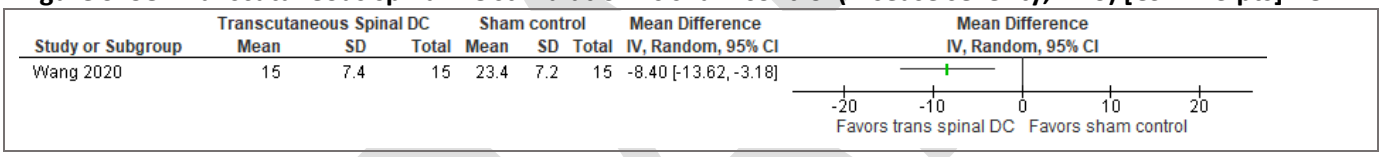
References: Wang 2020

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)

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

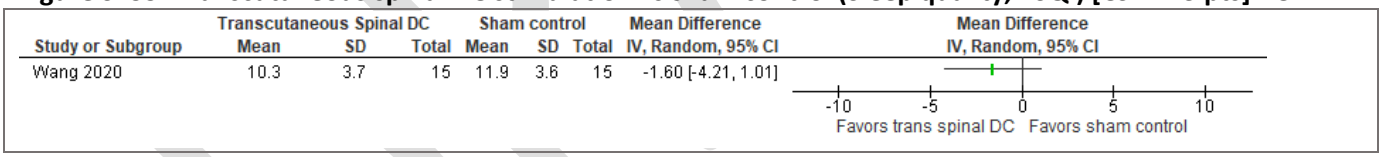
Critical Outcomes

Figure S198. Transcutaneous spinal DC stimulation vs sham control (Disease severity, IRLS) [CST = -3 pts] RCT[1]



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] RCT[1]



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

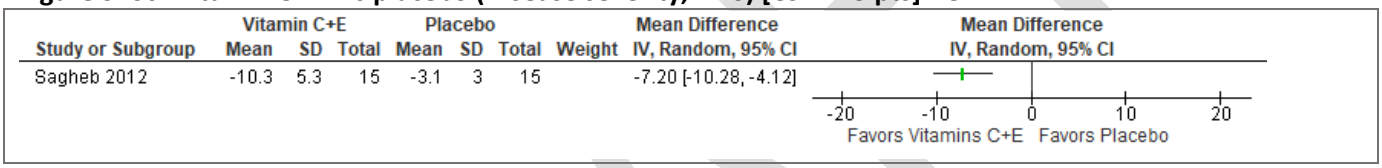
References: Sagheb 2012

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

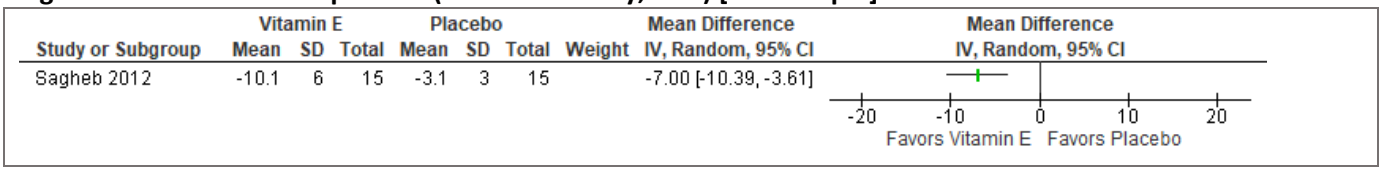
References: Sagheb 2012

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

a. Small sample size.

Critical Outcomes

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



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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
Hydrocortisone
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

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