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European Guideline and Expert Statements on the Management of Narcolepsy in adults and children

A joint European guideline from the European Academy of Neurology (EAN), the European Sleep Research Society (ESRS) and the European Narcolepsy Network (EU-NN)

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Supplement: Methods, Research Strategies, Summary of Findings Tables, Evidence to Decision

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Methods

The work was conducted under the auspices of the the European Academy of Neurology (EAN), the European Sleep Research Society (ESRS) and the European Narcolepsy Network (EUNN). A Task Force (TF) panel of 18 members from 11 European countries was formed with the agreement of the two societies and the network. The document was drafted in line with the 2015 Practical

recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces (Leone 2015). The first face-to-face meeting of the Task Force took place in Lugano, February 9-10th 2017. Two other face-to-face meetings (Bern, April 2019 and Copenhagen, Octorber 2019) and several small-group meetings and tele-conferences were held in order to complete the document.
The panel members - with expertise in neurology, sleep medicine, and a methodological support - were divided in ten working groups each consisting of two panel members. Each working group was responsible for one clinical question.

Topics and questions

Following the first TF meeting, 10 questions (and sub-questions) were elected to be essential for the daily clinical management of patients with narcolepsy. Then an explicit list of outcomes for each question was proposed by the four corresponding authors and circulated to the rest of the working group who were invited to rate their relative importance for clinical decision-making and add new outcomes if needed. The outcome prioritization was performed using a 9-point Likert scale and grouped into three categories (1–3: outcome of low importance; 4–6: outcome important but not critical for decision making and 7–9: outcome critical for decision-making). Not all potential outcomes could have been chosen- only outcomes graded as critical or important according to expert opinion were analysed. Finally, ten questions have been formulated following the Patients–Intervention– Comparator–Outcome (PICO) framework.
These topics have been organized into 5 sections (see below). For the exact wording of the PICO questions please see supplemental data.
The TF developed a document focusing on the following main topics, articulated according to single PICO questions:

Group 1 Question	**Are there disease modifying pharmacological (immune based) or hypocretin transmission or restoring treatments for the improvement or remission of narcolepsy?**
General Topic	**Disease modification**
Population	People with narcolepsy
Age group	All ages
Intervention	1.1: **Hypocretin/Orexin** 1.2: **Immunoglobulins** 1.3: **Plasmapheresis** 1.4: **Steroids** 1.5: **Monoclonal antibodies / Immune modifying therapies**
Comparison	Any (non active and active) comparator
Outcomes	Improvement of orexin levels - important but not critical; Normalization of orexin levels - important but not critical; Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments - Critical; Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments - Critical; Adverse events leading to withdrawal from the drugs - important but not critical; Any adverse event of the drugs - important but not critical.

Group 2 Question	**Can non-pharmacological management programs improve different symptoms of narcolepsy?**
General Topic	**Symptomatic treatment**
Sub- Topic	*Non-pharmacological management*
Population	People with narcolepsy
Age group	All ages
Intervention	2.1: **Scheduled naps** 2.2: **Physical activity** 2.3: **Nutrition, diet** 2.4: **Cognitive therapy** 2.5: **Hypnosis**
Comparison	Any (non active and active) comparator
Outcomes	Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values) - Critical; Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement - Critical; Objective measures: MWT: mean EDS improvement - Critical; Objective measures: MSLT: mean EDS improvement - Important but not critical; Objective measures: SART: mean improvement of n° of errors - Important but not critical; Subjective measures: Sleep diaries: mean reduction of cataplexy – Critical; Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical; Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical;

	Subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical; Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical; Sleep diaries: mean improvement of nighttime disturbed sleep – Critical; Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical; PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical; Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations; percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations; percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical

Group 3 Question	**Can pharmacological management programs improve different symptoms of narcolepsy?**
General Topic	**Symptomatic treatment**
Sub- Topic	*Pharmacological management*
Questions	**3.a**- What is the clinical evidence of pharmacological treatment of excessive daytime sleepiness and expressions of excessive daytime sleepiness?
	3.b- Is there a difference in efficacy between different stimulants/wake promoting drugs?
	4.a- What is the clinical evidence of pharmacological treatment of moderate to severe cataplexy with any kind of anti-cataplectic drugs or antidepressant drugs?
	4.b- Is there a difference in efficacy between different anti-cataplectic drugs?
	5.a- What is the clinical evidence of pharmacological treatment of moderate to severe night time disturbed sleep with any kind of drug?
	5.b- Is there a difference in efficacy between different drugs?
	6.a- What is the clinical evidence of pharmacological treatment of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations with any kind of drug?
	6.b- Is there a difference in efficacy between different drugs?
Population	People with narcolepsy
Age group	Adults
Intervention Questions 3.a/3.b	3.1: **Hypocretin/Orexin** 3.2: **Sodium Oxybate** 3.3: **Amphetamines** 3.4: **Methylphenidate** 3.5: **Solriamfetol** 3.6: **Mazindol** 3.7: **Modafinil** 3.8: **Armodafinil** 3.9: **Pitolisant** 3.10: **Selegiline** 3.11: **Caffeine**
Intervention Questions 4.a/4.b	4.1: **Hypocretin/Orexin** 4.2: **Immunoglobulins** 4.3: **Plasmapheresis** 4.4: **Steroids** 4.5: **Monoclonal antibodies / Immune modifying therapies** 4.6: **Sodium Oxybate** 4.7: **Amphetamines** 4.8: **Methylphenidate** 4.9: **Solriamfetol** 4.10: **Mazindol** 4.11: **Modafinil** 4.12: **Armodafinil** 4.13: **Pitolisant** 4.14: **Selegiline** 4.15: **Tricyclic Antidepressants** 4.16: **SSRI – NSRI - Other Antidepressants** 4.17: **Baclofen**

Intervention Questions 5.a/5.b	5.1: **Hypocretin/Orexin** 5.2: **Sodium Oxybate** 5.3: **Benzodiazepines** 5.4: **Baclofen** 5.5: **Gabapentin** 5.6: **Pregabalin** 5.7: **Melatonin**
Intervention Questions 6.a/6.b	6.1: **Hypocretin/Orexin** 6.2: **Sodium Oxybate** 6.3: **Antidepressants** 6.4: **Benzodiazepines** 6.5: **Baclofen** 6.6: **Gabapentin** 6.7: **Pregabalin** 6.8: **Melatonin**
Comparison	Any (non active and active) comparator
Outcomes Questions 3.a/3.b	Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS; percentage of patients with remission of EDS (according to normative values) - Critical; Subjective measures: Sleep diaries: mean reduction of sleep time - important but not critical; Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement - Critical; Objective measures: MWT: mean EDS improvement - Critical; Objective measures: MSLT: mean EDS improvement - Important but not critical; Objective measures: SART: mean improvement of n° of errors - Important but not critical; Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical
Outcomes Questions 4.a/4.b	Subjective measures: Sleep diaries: mean reduction of cataplexy – Critical; Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical; Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical; Subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical; Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical; Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical
Outcomes Questions 5.a/5.b	Sleep diaries: mean improvement of nighttime disturbed sleep – Critical; Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical; PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical; Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical
Outcomes Questions 6.a/6.b	Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations; percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations; percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical

Group 4 Question	**Can any non- pharmacological and pharmacological management improve co-morbidities and quality of life of patients with narcolepsy?**
General Topic	**Symptomatic treatment**
Sub- Topic	*Co-morbidities and Quality of Life* *Non- pharmacological and pharmacological management*
Question	**7.a**- What is the clinical evidence of any kind of treatment for psychiatric symptoms?
	7.b- Is there a difference in efficacy between different treatments?
	8.a- What is the clinical evidence of any kind of treatment for other sleep disorders (RBD, sleep-disordered breathing, parasomnias, RLS/PLMS)?
	8.b- Is there a difference in efficacy between different treatments?
	9.a- What is the clinical evidence of any kind of treatment for the global improvement of the disease and the prevention of everyday life risks or psychosocial consequences?
	9.b- Is there a difference in efficacy between different treatments?
Population	People with narcolepsy
Age group	All ages
Intervention	**Any**
Comparison	Any (non active and active) comparator
Outcomes	Mood: mean improvement of mood scales – critical

Questions 7.a/7.b	Anxiety scales: mean improvement of anxiety scales - important but not critical Insomnia: mean improvement of insomnia scales - important but not critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical
Outcomes Questions 8.a/8.b	Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values) – Critical Subjective measures: Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement – Critical objective measures: MWT: mean EDS improvement – Critical objective measures: MSLT: mean EDS improvement percentage of patients with remission of EDS (according to normative values) - Important but not Critical Sleep diaries: mean improvement of nighttime disturbed sleep – critical Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Adverse events leading to withdrawal from the intervention - important but not critical Any adverse event of the intervention - important but not critical
Outcomes Questions 9.a/9.b	Global Clinical Impression (overall): mean improvement – Critical Health related QoL: mean improvement of HRQoL according to generic or disease specific scales – Critical Psychosocial implication (school): mean difference of school years loss Psychosocial implication (school): difference of percentage of early school leaving Psychosocial implication (job): difference of percentage of job loss Psychosocial implication (car): difference of percentage of stop driving Psychosocial implication (car): difference of percentage of traffic accidents Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls) - - important but not critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical

PICO Group 5	**Can pharmacological management programs improve different symptoms of narcolepsy?**
General Topic	**Symptomatic treatment**
Sub- Topic	*Pharmacological management*
Question	**10.a**- What is the clinical evidence pharmacological treatment of symptoms of narcolepsy (excessive daytime sleepiness, cataplexy, disturbed sleep, sleep paralysis/sleep-related hallucinations) and metabolic/endocrinological symptoms (obesity, precocious pubertal age) with any kind of drug?
	10.b- Is there a difference in efficacy between different treatments?
Population	People with narcolepsy
Age group	Children
Intervention	10.1: **Sodium Oxybate** 10.2: **Amphetamines** 10.3: **Methylphenidate** 10.4: **Solriamfetol** 10.5: **Modafinil** 10.6: **Armodafinil** 10.7: **Pitolisant** 10.8: **Selegiline** 10.9: **Antidepressants**
Comparison	Any (non active and active) comparator
Outcomes	subjective measures: Pediatric Daytime Sleepiness Scale (PDSS) / ESS-CHADS: mean improvement of EDS – Critical subjective measures: Pediatric Daytime Sleepiness Scale (PDSS) / ESS-CHADS: percentage of patients with remission of EDS (according to normative values) - Critical subjective measures: Global Clinical Impression: mean EDS improvement – Critical subjective measures: percentage of patients with EDS improvement – Critical subjective measures: Sleep diaries: mean reduction of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep – Critical

	Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical

Criteria for considering studies

See above topics and question sections for the detailed inclusion criteria on *target population, interventions, comparator, outcomes.* For the *type of study* inclusion criteria, a hierarchical approach was applied. At first, systematic reviews and randomized controlled trials were searched. Then, in case of absence of those kind of studies, lower quality studies (cohort studies, case-control studies, case series, case reports) were considered. In any case, every study design was considered in the assessment of outcomes on adverse events of treatments.

Search methods for the identification of studies

Published studies were identified from the National Library of Medicine's MEDLINE database, Elsevier's EMBASE database, and the Cochrane Central Register of Controlled Trials by means of specific search strategies using a combination of exploded terms and free text, using_concepts regarding the narcolepsy and treatments for narcolepsy. The strategy used for MEDLINE was translated to other databases. No language or date of publication restrictions were applied. Medication has usually not been studied separately for NT1 / NT2 until recently. If separately studied, it was mentioned in the text.
The detailed search strategies are reported in the next section (see below).

Study selection, data extraction and synthesis

All abstracts or full papers without electronic abstracts were reviewed independently by two reviewers (EB, LV) to identify potentially relevant studies. Disagreement was resolved by discussion. Subsequently, the same reviewers independently assessed those studies considered for inclusion reading the full text, with disagreements resolved by discussion. For each study, task force members extracted the following data: study design, participants (along with inclusion and exclusion criteria); intervention(s) and comparator(s); outcomes; results. For dichotomous outcomes, extracted data consisted of the number of participants with the outcome of interest in each group at each time point. For continuous outcomes, extracted data consisted of the mean and standard deviation (SD) in each group at the last time point. Finally, the data were presented for each PICO and each outcome in Summary of Findings tables.

Assessment of risk of bias of included studies and of overall quality of evidence

Quality of evidence was assessed according to different methods depending on the type of publication. Systematic reviews was assessed for descriptive purposes using the criteria from the AMSTAR checklist (Shea 2007). RCTs were assessed for risk of bias of included RCTs using the risk of bias system proposed by the Cochrane Handbook (Higgins 2011). Overall quality of evidence for each outcome was assessed and synthesized according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g), and presented in Summary of Findings tables (Guyatt 2013a; Guyatt 2013b; Guyatt 2013c).
This approach specifies four levels of quality:

- High: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates;
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low: we are very uncertain about the estimate.

Developing recommendations

The importance of the outcomes of each Review Question was voted by the Task Force members according to the GRADE method (Guyatt 2011a) at the beginning of the guideline development process.
Recommendations were drafted on the basis of the interpretation of the available evidence, according to the GRADE method, i.e. taking into account the balance of benefits and harms regarding the critical and important outcomes (Andrews 2013a; Andrews 2013b). The proposed list of statements and their assigned strength (strong, weak) was initially drafted by WGs and methodologists, who were also in charge of the quality of the evidence analysis. Whole materials were circulated to the whole panel members, who were asked to indicate their agreement with the set of statements by taking into account the available evidence. In the second stage, panellists met during several face-to-face consensus meetings and each statement was presented to all members, together with the additional comments. When evidence were of poor quality, conflicting or absent, the Task Force drafted recommendations based on their expert opinion. The consensus recommendations were done through discussions in the task force. When areas were identified for which good evidence is lacking, the task force considered making recommendations

for future research. Decisions about inclusion were based on factors such as: the importance to patients or the population; potential impact on the European health systems; ethical and technical feasibility.

References

- Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol, 2013a: 66:719-25.
- Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol, 2013b; 66:726-35.
- Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol, 2011; 64:401-6.
- Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol, 2011a; 64:395-400.
- Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol, 2011b; 64:407-15.
- Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol, 2011c; 64:1277-82.
- Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW Jr, Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schünemann HJ. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol, 2011d; 64:1283-93.
- Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group.. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol, 2011e; 64:1294-302.
- Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group.. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol, 2011f;64:1303-10.
- Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, Jaeschke R, Rind D, Dahm P, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Murad MH, Schünemann HJ; GRADE Working Group.. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol, 2011g; 64:1311-6.
- Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol; 2013a; 66:151-7.
- Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol, 2013b; 66:158-72.
- Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, Johnston BC, Karanicolas P, Akl EA, Vist G, Kunz R, Brozek J, Kupper LL, Martin SL, Meerpohl JJ, Alonso-Coello P, Christensen R, Schunemann HJ. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol, 2013c; 66:173-83.
- Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies . In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. Eur J Neurol 2015;22:1505-10.
- Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007 Feb 15; 7:10

Results of the systematic search

The literature search was performed between July and October 2018. An updated search was performed in October 2019. Finally, in July 2020 an ultimate search was launched including only RCTs. Results of the search are reported in **Table e1** by search strategy and detailed in the following pages. A summary of the included evidence by Group of questions is reported in **Table e2**.

Table e1. Results of the search reported by single question and by step/

Search strategy	***Records screened***	***Full text assessed***	***Studies included***
Hypocretin/Orexin: PICOs 1.1; 3.1; 4.1; 5.1; 6.1	886	9	2
Immunoglobulins: PICOs 1.2; 4.2	143	16	11
Plasmapheresis: PICOs 1.3; 4.3	30	1	1
Steroids: PICOs 1.4; 4.4	69	4	4
Immune modifying therapies / Monoclonal antibodies: PICOs 1.5; 4.5	74	2	2
Scheduled naps: PICO 2.1	342	7	6
Physical activity: PICO 2.2	115	1	0
Nutrition / diet: PICO 2.3	336	3	1
Cognitive therapy: PICO 2.4	201	3	0
Hypnosis: PICO 2.5	35	4	0
Sodium Oxybate: PICOs 3.2; 4.6; 5.2; 6.2	697	39	25
Amphetamines: PICOs 3.3; 4.7	590	6	6
Methylphenidate: PICOs 3.4; 4.8	553	5	2
Solriamfetol: PICOs 3.5; 4.9	70	8	5
Mazindol: PICOs 3.6; 4.10	59	9	5
Modafinil: PICOs 3.7; 4.11	903	29	15
Armodafinil: PICOs 3.8; 4.12	176	4	3
Pitolisant: PICOs 3.9; 4.13	135	4	3
Selegiline: PICOs 3.10; 4.14	66	4	3
Caffeine: PICOs 3.11	57	2	1
Antidepressants: PICOs 4.15; 4.16; 6.3	637	31	1
Baclofen: PICOs 4.17; 5.4; 6.5	44	3	2
Benzodiazepines: PICOs 5.3; 6.4	385	4	1
Gabapentin: PICOs 5.5; 6.6	63	0	0
Pregabalin: PICOs 5.6; 6.7	20	0	0
Melatonin: PICOs 5.7; 6.8	153	0	0
Psychiatric symptoms (insomnia scales improvement): PICO 7	150	1	0
Psychiatric symptoms (anxiety and mood scales): PICO 7	156	8	2
Sleep disordered breathing: PICO 8.1	169	8	2
RBD: PICO 8.2	393	6	3
RLS/PLMS: PICO 8.3	710	6	6
Global improvement of the disease: PICO 9	92	21	25
Health-related quality of life: PICO 9	432	18	
Everyday life risks or psychosocial consequences: PICO 9	733	21	
Children: PICO 10	573	21	18
total	10247	308	155

Table e2. Synoptic view of literature search results and included papers by single Group.

Group	***Age***	***PICO and included studies***
1. Are there disease modifying pharmacological (immune based) or hypocretin transmission or restoring treatments for the improvement or remission of narcolepsy?	All ages	1.1 (Hypocretin/Orexin) = 0 1.2 (Immunoglobulins) = 12 1.3 (Plasmapheresis) = 1 1.4 (Steroids) = 4 1.5 (Monoclonal antibodies / Immune modifying therapies)= 2
2. Can non-pharmacological management programs improve different symptoms of narcolepsy?	All ages (data only on adults)	2.1 (Scheduled naps) = 6 2.2 (Physical activity) = 0 2.3 (Nutrition, diet) = 1 2.4 (Cognitive therapy) = 0 2.5 (Hypnosis) = 0
3. Can pharmacological management programs improve different symptoms of narcolepsy?	Adults	<u>Excessive daytime sleepiness</u> 3.1 (Hypocretin/Orexin) = 1 3.2 (Sodium Oxybate) = 22 3.3 (Amphetamines) = 6 3.4 (Methylphenidate) = 2 3.5 (Solriamfetol) = 5 3.6 (Mazindol) = 5 3.7 (Modafinil) = 15 3.8 (Armodafinil) = 3 3.9 (Pitolisant) = 3 3.10 (Selegiline) = 3 3.11 (Caffeine) = 1
		<u>Cataplexy</u> 4.1 (Hypocretin/Orexin) = 0 4.2 (Immunoglobulins) = 10 4.3 (Plasmapheresis) = 1 4.4 (Steroids) = 3 4.5 (Monoclonal antibodies / Immune modifying therapies)= 2 4.6 (Sodium Oxybate) = 20 4.7 (Amphetamines) = 6 4.8 (Methylphenidate) = 0 4.9 (Solriamfetol) = 5 4.10 (Mazindol) = 5 4.11 (Modafinil) = 15 4.12 (Armodafinil) = 3 4.13 (Pitolisant) = 3 4.14 (Selegiline) = 3 4.15 (Tricyclic Antidepressants) = 6 4.16 (SSRI – NSRI - Other Antidepressants) = 8 4.17 (Baclofen) = 2
		<u>night-time disturbed sleep</u> 5.1 (Hypocretin/Orexin) = 2 5.2 (Sodium Oxybate) = 25 5.3 (Benzodiazepines) = 1 5.4 (Baclofen) = 0 5.5 (Gabapentin) = 0 5.6 (Pregabalin) = 0 5.7 (Melatonin) = 0
		<u>sleep paralysis/sleep-related hallucinations</u> 6.1 (Hypocretin/Orexin) = 0 6.2 (Sodium Oxybate) = 21 6.3 (Antidepressants) = 5 6.4 (Benzodiazepines) = 0 6.5 (Baclofen) = 0 6.6 (Gabapentin) = 0 6.7 (Pregabalin) = 0 6.8 (Melatonin) = 0
4. Can any non- pharmacological and pharmacological management improve co-morbidities and quality of life of patients with narcolepsy?	All ages	7 (psychiatric symptoms) = 2 8.1 (SDB) = 2 8.2 (RBD) = 3 8.3 (RLS/PLM) = 6 9 (CGI; QoL; prevention of everyday life risks) = 24
5. Can pharmacological management programs improve different symptoms of narcolepsy?	Children	10.1 (Sodium Oxybate) = 7 10.2 (Amphetamines) = 0

		10.3 (Methylphenidate) = 1 10.4 (Solriamfetol) = 0 10.5 (Modafinil) = 6 10.6 (Armodafinil) = 0 10.7 (Pitolisant) = 1 10.8 (Selegiline) = 0 10.9 (Any Antidepressant Drug) = 3

Search strategies and Flow-charts by single search

Search strategy: Hypocretin/Orexin

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	Therapy/Broad[filter] AND (Hypocretin*[Title/Abstract] OR Orexin*[Title/Abstract] OR "Orexins"[Mesh])	1055
3	1 AND 2	164

PUBMED IN PROCESS

#	Search	Results
1	Hypocretin*[Title/Abstract] OR Orexin*[Title/Abstract]	4600
2	(narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract]	4554
3	inprocess[sb] or publisher[sb]	176192
4	1 AND 2 AND 3	45

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Orexins] explode all tree	17
5	orexin*:ti,ab,kw OR hypocretin:ti,ab,kw	186
6	4 OR 5	186
7	3 AND 6	34

EMBASE

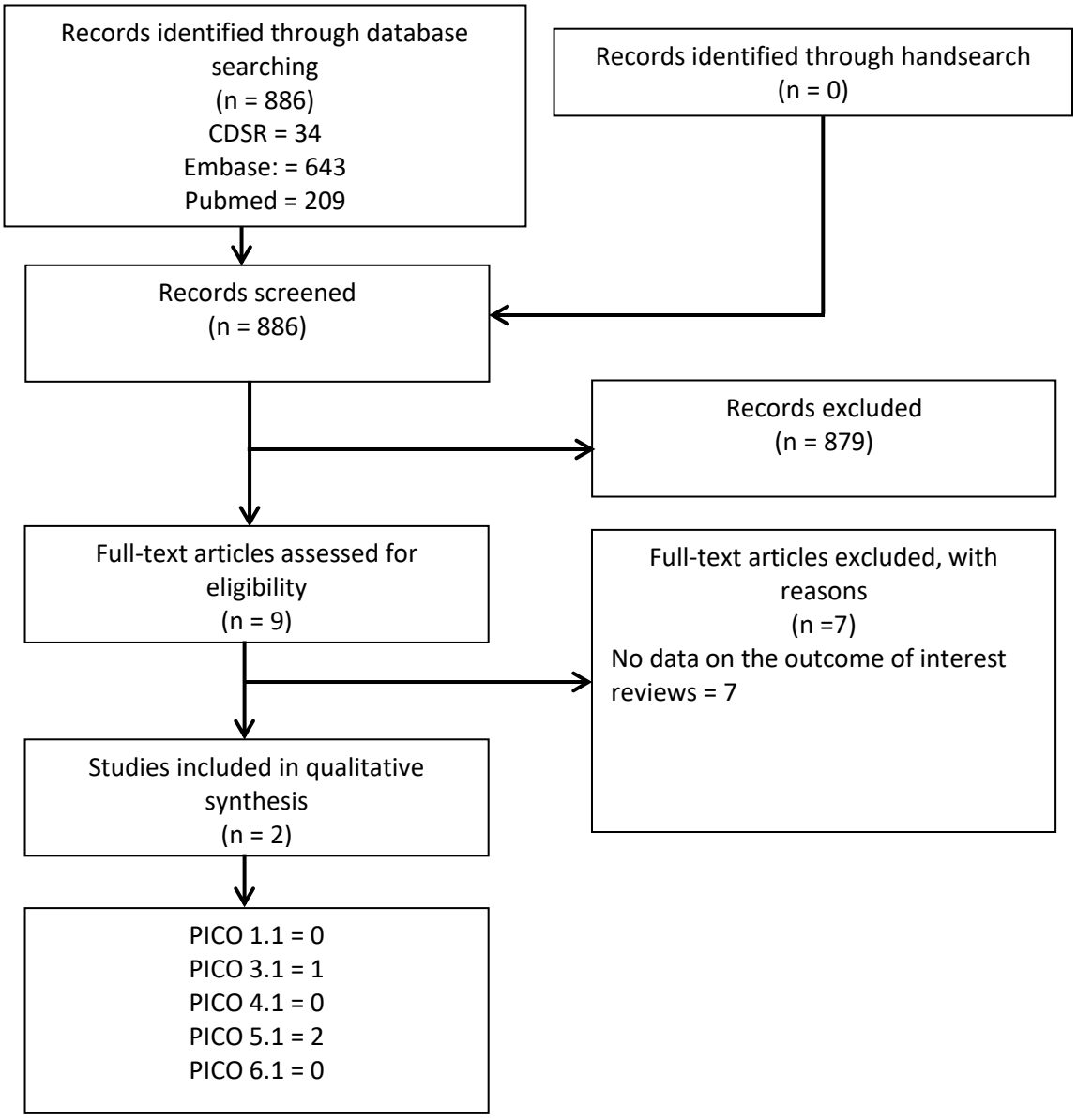
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9499
4	'orexin'/exp/dd_dt	147
5	'hypocretin':ti,ab,kw OR orexin*:ti,ab,kw	6436
6	4 OR 5	6481
7	3 AND 6	1892
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	816
9	8 AND [humans]/lim	643

Flow-chart of studies: Hypocretin/Orexin

PICOs

1.1: Hypocretin/Orexin for the improvement or remission of narcolepsy, all ages
3.1: Hypocretin/Orexin for improvement of excessive daytime sleepiness, adults
4.1: Hypocretin/Orexin for improvement of moderate to severe cataplexy, adults
5.1: Hypocretin/Orexin for improvement of moderate to severe night time disturbed sleep, adults
6.1: Hypocretin/Orexin for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e1: July 2018 run (October 2019 update).



Search strategy: Immunoglobulins

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"Intravenous IG"[Title/Abstract] OR Intravenous Antibod*[Title/Abstract] OR Intravenous Immune Globulin*[Title/Abstract] OR Intravenous Immunoglobulin*[Title/Abstract] OR IV Immunoglobulin*[Title/Abstract] OR IVIG[Title/Abstract] OR "Immunoglobulins IV"[Title/Abstract] OR Flebogamma[Title/Abstract] OR Gamimune[Title/Abstract] OR Gamimmune[Title/Abstract] OR Gammagard[Title/Abstract] OR Iveegam[Title/Abstract] OR Gammonativ[Title/Abstract] OR Gamunex[Title/Abstract] OR Globulin[Title/Abstract] OR GlobulinN[Title/Abstract] OR Intraglobin[Title/Abstract] OR "Modified Immune Globulin"[Title/Abstract] OR Privigen[Title/Abstract] OR Venimmune[Title/Abstract] OR Sandoglobulin[Title/Abstract] OR Venoglobulin[Title/Abstract] OR Alphaglobin[Title/Abstract] OR Endobulin[Title/Abstract] OR "Immunoglobulins, Intravenous"[Mesh] OR (Immune Globulin*[Title/Abstract] and Intravenous[Title/Abstract]	56105
3	1 AND 2	24

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Immunoglobulins, Intravenous] explode all tree	843
5	IV Immunoglobulin* OR IVIG OR "Immunoglobulins IV" OR Flebogamma:ti,ab,kw OR Gamimune:ti,ab,kw OR Gamimmune:ti,ab,kw OR Gammagard:ti,ab,kw OR Iveegam:ti,ab,kw OR Gammonativ:ti,ab,kw OR Gamunex:ti,ab,kw OR Globulin:ti,ab,kw OR GlobulinN:ti,ab,kw OR Intraglobin:ti,ab,kw OR "Modified Immune Globulin":ti,ab,kw OR Privigen:ti,ab,kw OR Venimmune:ti,ab,kw OR Sandoglobulin:ti,ab,kw OR Venoglobulin:ti,ab,kw OR Alphaglobin:ti,ab,kw OR Endobulin:ti,ab,kw	4929
6	"Intravenous IG":ti,ab,kw OR “Intravenous Antibody”:ti,ab,kw OR “Intravenous Antibodies”:ti,ab,kw OR “Intravenous Immune Globulin”:ti,ab,kw OR “Intravenous Immune Globulins”:ti,ab,kw OR “Intravenous Immunoglobulin”:ti,ab,kw OR “Intravenous Immunoglobulins”:ti,ab,kw	4120
7	Immune Globulin* near/2 Intravenous	184
8	4 OR 5 OR 6 OR 7	8182
9	3 AND 8	0

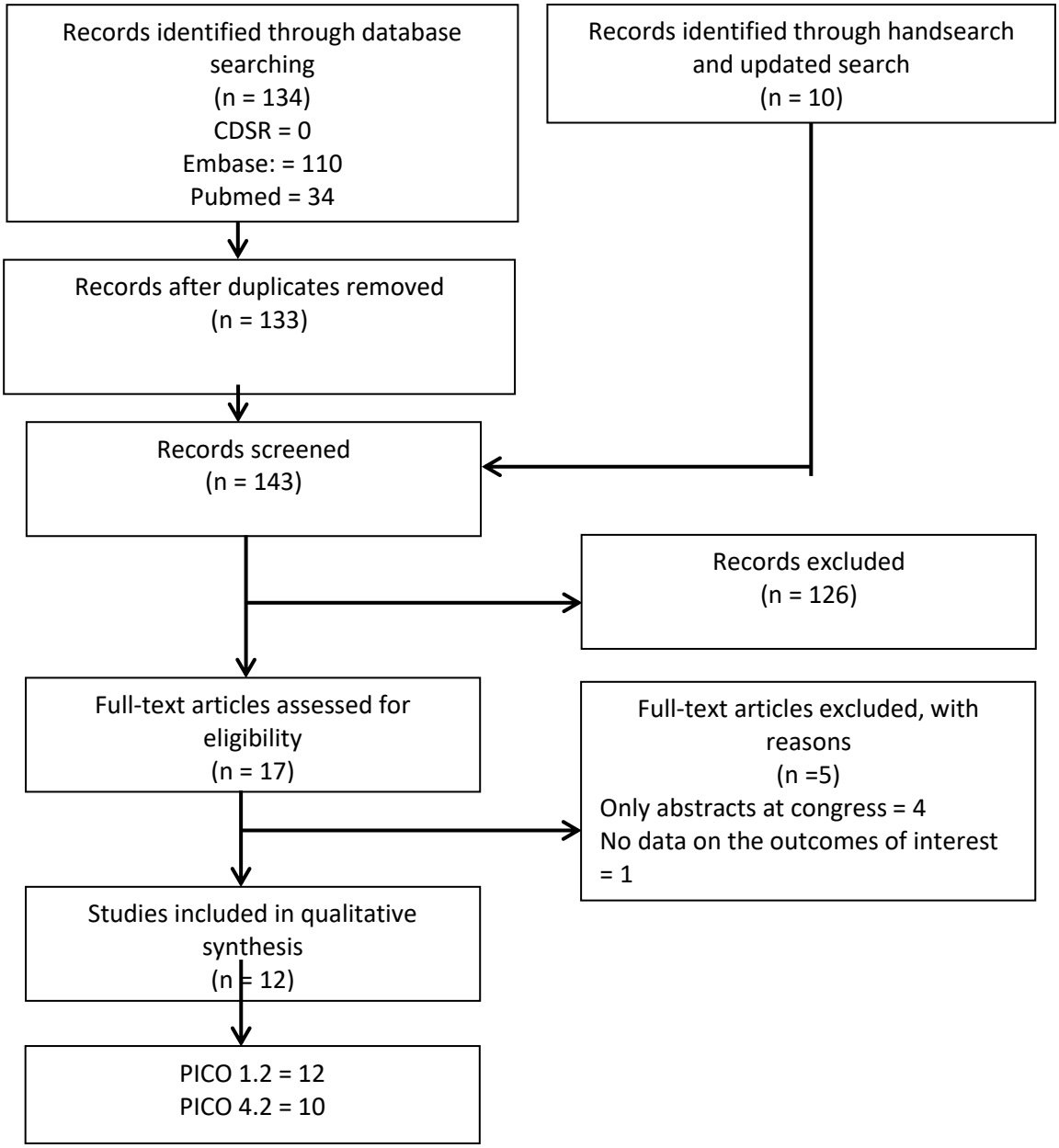
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9497
4	('immune globulin*' NEAR/1 'intravenous'):ti,ab,kw OR (immunoglobulin*' NEAR/1 'intravenous'):ti,ab,kw	18880
5	'iv immunoglobulin*':ti,ab,kw OR 'ivig':ti,ab,kw OR 'immunoglobulins iv':ti,ab,kw OR 'flebogamma':ti,ab,kw OR 'gamimune':ti,ab,kw OR 'gamimmune':ti,ab,kw OR 'gammagard':ti,ab,kw OR 'iveegam':ti,ab,kw OR 'gammonativ':ti,ab,kw OR 'gamunex':ti,ab,kw OR 'globulin':ti,ab,kw OR 'globulinn':ti,ab,kw OR 'intraglobin':ti,ab,kw OR 'modified immune globulin':ti,ab,kw OR 'privigen':ti,ab,kw OR venimmune':ti,ab,kw OR 'sandoglobulin':ti,ab,kw OR 'venoglobulin':ti,ab,kw OR 'alphaglobin':ti,ab,kw OR 'endobulin':ti,ab,kw	59580
6	'intravenous ig':ti,ab,kw OR ('intravenous' NEAR/1 'antibod*'):ti,ab,kw OR ('intravenous' NEAR/1 'immune globulin*'):ti,ab,kw)OR ('intravenous' NEAR/1 'immunoglobulin*'):ti,ab,kw	19088
7	'immunoglobulin'/exp/dd_iv	31478
8	4/7 OR	91023
9	3 AND 8	110

Flow-chart of studies: Immunoglobulins

PICOs
1.2: Immunoglobulins for the improvement or remission of narcolepsy, all ages
4.2: Immunoglobulins for improvement of cataplexy, adults

Figure e2: July 2018 run (October 2019 update).



Search strategy: Plasmapheresis

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5292
2	"plasma exchange"[Title/Abstract] OR Plasmapheres*[Title/Abstract] OR "Plasmapheresis"[Mesh]	17943
3	1 AND 2	3

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Plasmapheresis] explode all tree	187
5	"plasma exchange":ti,ab,kw	637
6	Plasmapheres*:ti,ab,kw	615
7	4 OR 5 OR 6	1077
8	3 AND 7	0

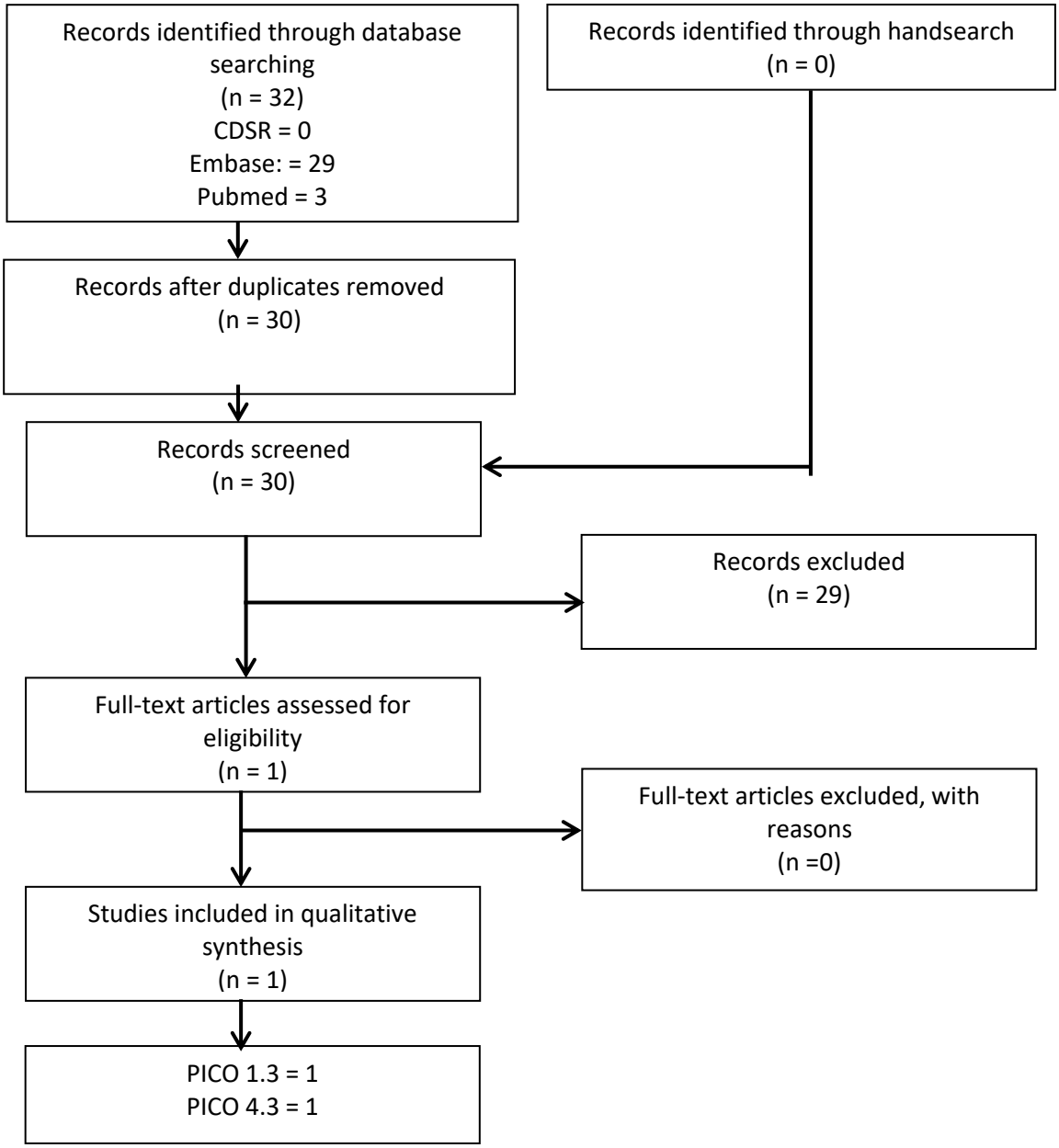
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9495
4	'plasmapheres*':ti,ab,kw	13863
5	'plasmapheresis'/exp	33872
6	'plasma exchange':ti,ab,kw	11601
7	4 OR 5 OR 6	38348
8	3 AND 7	29

Flow-chart of studies: Plasmapherisis

PICOs
1.3: Plasmapherisis for the improvement or remission of narcolepsy, all ages
4.3: Plasmapherisis for improvement of cataplexy, adults

Figure e3: July 2018 run (October 2019 update).



Search strategy: Steroids

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	Steroid*[title7abstract] or (Predate[Title/Abstract] OR Predonine[Title/Abstract] OR "Di-Adreson-F"[Title/Abstract] OR DiAdresonF[Title/Abstract] OR Metipred[Title/Abstract] OR 6-Methylprednisolone[Title/Abstract] OR Urbason[Title/Abstract] OR Medrol[Title/Abstract] OR NSC-134087[Title/Abstract] OR Stereocyt[Title/Abstract] OR Sterecyt[Title/Abstract] OR Leo-1031[Title/Abstract] OR Prednisolone[Title/Abstract] OR Fluprednisolone[Title/Abstract] OR Methylprednisolone[Title/Abstract] OR Prednimustine[Title/Abstract] OR Clobetasol[Title/Abstract] OR Dexamethasone[Title/Abstract] OR Desoximetasone[Title/Abstract] OR Dexamethasone Isonicotinate[Title/Abstract] OR Flumethasone[Title/Abstract] OR "Fluocinolone aceetonide"[Title/Abstract] OR Fluocinonide[Title/Abstract] OR Fluocortolone[Title/Abstract] OR Diflucortolone[Title/Abstract] OR Fluorometholone[Title/Abstract] OR Fluoxymesterone[Title/Abstract] OR Fluprednisolone[Title/Abstract] OR Flurandrenolone[Title/Abstract] OR Flurogestone Acetate[Title/Abstract] OR Paramethasone[Title/Abstract] OR Triamcinolone[Title/Abstract] OR Flubenisolone[Title/Abstract] OR Celestona[Title/Abstract] OR Cellestoderm[Title/Abstract] OR Celestone[Title/Abstract] OR Clofenazon[Title/Abstract] OR Clobetasol[Title/Abstract] OR Olux[Title/Abstract] OR Dermovate[Title/Abstract] OR Embeline[Title/Abstract] OR Temovate[Title/Abstract] OR Methylfluorprednisolone[Title/Abstract] OR Decameth[Title/Abstract] OR Dexasone[Title/Abstract] OR Maxidex[Title/Abstract] OR Millicorten[Title/Abstract] OR Oradexon[Title/Abstract] OR Hexadrol[Title/Abstract] OR fluorodexamethasone[Title/Abstract] OR Fluocinolone[Title/Abstract] OR Fluortriamcinolone[Title/Abstract] OR Jellin[Title/Abstract] OR Jellisoft[Title/Abstract] OR Synalar[Title/Abstract] OR Co-Fluocin[Title/Abstract] OR "Co Fluocin"[Title/Abstract] OR Flucinar[Title/Abstract] OR Fluodermo[Title/Abstract] OR Fluotrex[Title/Abstract] OR Flusolgen[Title/Abstract] OR Gelidina[Title/Abstract] OR Fluocortolone[Title/Abstract] OR Ultralan[Title/Abstract] OR Fluorometholone[Title/Abstract] OR Cortisdin[Title/Abstract] OR Efflumidex[Title/Abstract] OR Flucon[Title/Abstract] OR Fluor-Op[Title/Abstract] OR "Fluor Op"[Title/Abstract] OR Fluoro-Ophtal[Title/Abstract] OR "Fluoro Ophtal"[Title/Abstract] OR Fluoropos[Title/Abstract] OR Fluoximesteron[Title/Abstract] OR Halotestin[Title/Abstract] OR Fluoxymesterone[Title/Abstract] OR Android-F[Title/Abstract] OR "Android F"[Title/Abstract] OR Flurandrenolide[Title/Abstract] OR Cordran[Title/Abstract] OR Haelan[Title/Abstract] OR Cronolone[Title/Abstract] OR Flurogestone[Title/Abstract] OR Flugestone[Title/Abstract] OR Volon[Title/Abstract] OR Aristocort[Title/Abstract] OR Beclometasone[Title/Abstract] OR Asmabec[Title/Abstract] OR Ascocortonyl[Title/Abstract] OR Beclamet[Title/Abstract] OR Beclo[Title/Abstract] OR Beclocort[Title/Abstract] OR Beclomet[Title/Abstract] OR Bemedrex[Title/Abstract] OR Beclomethasone[Title/Abstract] OR Beclorhinol[Title/Abstract] OR Becloturmant[Title/Abstract] OR Sanasthmax[Title/Abstract] OR Beconase[Title/Abstract] OR Becodisk[Title/Abstract] OR Sanasthmyl[Title/Abstract] OR Becodisks[Title/Abstract] OR Propaderm[Title/Abstract] OR Becotide[Title/Abstract] OR Becloforte[Title/Abstract] OR Bronchocort[Title/Abstract] OR Ventolair[Title/Abstract] OR AeroBec[Title/Abstract] OR Nasobec[Title/Abstract] OR Ecobec[Title/Abstract] OR Beclazone[Title/Abstract] OR Respocort[Title/Abstract] OR Prolair[Title/Abstract] OR Filair[Title/Abstract] OR Vancenase[Title/Abstract] OR Vanceril[Title/Abstract] OR Aldecin[Title/Abstract] OR Viarin[Title/Abstract] OR Ecobec[Title/Abstract] OR Beclazon[Title/Abstract] OR "Chlormadinone Acetate"[Title/Abstract] OR "Neo Eunomin"[Title/Abstract] OR NeoEunomin[Title/Abstract] OR Chlormadinone[Title/Abstract] OR Cyproterone[Title/Abstract] OR heterocyclic steroid*[Title/Abstract] OR chlorinated steroid*[Title/Abstract] OR fluorinated steroid*[Title/Abstract] OR "Steroids, Fluorinated"[Mesh] OR "Steroids, Brominated"[Mesh] OR "Steroids, Chlorinated"[Mesh] OR "Steroids, Heterocyclic"[Mesh] or "Prednisolone"[Mesh] OR Steroids, Fluorinated"[Mesh] OR "Steroids, Brominated"[Mesh] OR "Steroids, Chlorinated"[Mesh] OR "Steroids, Heterocyclic"[Mesh]	351584
3	1 AND 2	18

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	(steroid* Predate OR Predonine OR "Di-Adreson-F" OR DiAdresonF OR Metipred OR 6-Methylprednisolone OR Urbason OR Medrol OR NSC-134087 OR Stereocyt OR Sterecyt OR Leo-1031 OR Prednisolone OR Fluprednisolone OR Methylprednisolone OR Prednimustine OR Clobetasol OR Dexamethasone OR Desoximetasone OR Dexamethasone Isonicotinate OR Flumethasone OR "Fluocinolone aceetonide" OR Fluocinonide OR Fluocortolone OR Diflucortolone OR Fluorometholone OR Fluoxymesterone OR Fluprednisolone OR Flurandrenolone OR Flurogestone Acetate OR Paramethasone OR Triamcinolone OR Flubenisolone OR Celestona OR Cellestoderm OR Celestone OR Clofenazon OR Clobetasol OR Olux OR Dermovate OR Embeline OR Temovate OR Methylfluorprednisolone OR Decameth OR Dexasone OR Maxidex OR Millicorten OR Oradexon OR Hexadrol OR fluorodexamethasone OR Fluocinolone OR Fluortriamcinolone OR Jellin OR Jellisoft OR Synalar OR Co-Fluocin OR "Co Fluocin" OR Flucinar OR Fluodermo OR Fluotrex OR Flusolgen OR Gelidina OR Fluocortolone OR Ultralan OR Fluorometholone OR Cortisdin OR Efflumidex OR Flucon OR Fluor-Op OR "FluOR Op" OR Fluoro-Ophtal OR "Fluoro Ophtal" OR Fluoropos OR Fluoximesteron OR Halotestin OR Fluoxymesterone OR Android-F OR "Android F" OR Flurandrenolide OR Cordran OR Haelan OR Cronolone OR Flurogestone OR Flugestone OR Volon OR Aristocort OR Beclometasone OR Asmabec OR Ascocortonyl OR Beclamet OR Beclo OR Beclocort OR Beclomet OR Bemedrex OR Beclomethasone OR Beclorhinol OR Becloturmant OR Sanasthmax OR Beconase OR Becodisk OR Sanasthmyl OR Becodisks OR Propaderm OR Becotide OR Becloforte OR Bronchocort OR Ventolair OR AeroBec OR Nasobec OR Ecobec OR Beclazone OR Respocort OR Prolair OR Filair OR Vancenase OR Vanceril OR Aldecin OR Viarin OR Ecobec OR Beclazon OR "Chlormadinone Acetate" OR "Neo Eunomin" OR NeoEunomin OR Chlormadinone OR Cyproterone OR heterocyclic steroid* OR chlorinated steroid* OR fluorinated steroid*):ti,ab,kw	44127
5	MeSH descriptor: [Steroids, Fluorinated] explode all trees	6494
6	MeSH descriptor: [Steroids, Brominated] explode all trees	0
7	MeSH descriptor: [Steroids, Chlorinated] explode all trees	1466
8	MeSH descriptor: [Steroids, Heterocyclic] explode all trees	521
9	MeSH descriptor: [Prednisolone] explode all trees	4321
10	4 OR 5 OR 5 OR 7 OR 8 OR 9	45148
11	3 AND 10	0

EMBASE

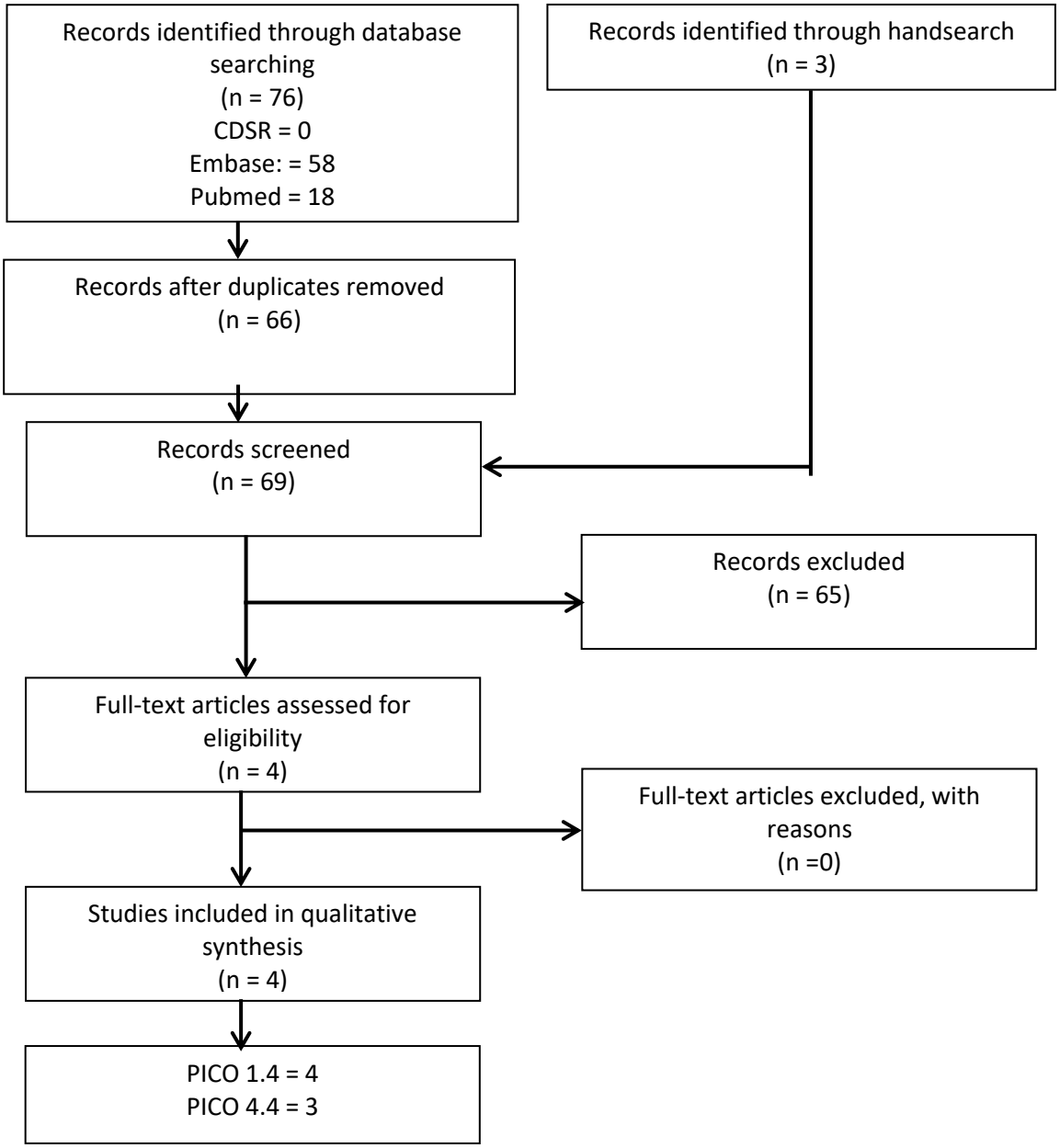
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9499
4	steroid*: ti,ab,kw or 'predate':ti,ab,kw OR 'predonine':ti,ab,kw OR 'di-adreson-f':ti,ab,kw OR 'diadresonf':ti,ab,kw OR 'metipred':ti,ab,kw OR '6-methylprednisolone':ti,ab,kw OR 'urbason':ti,ab,kw OR 'medrol':ti,ab,kw OR 'nsc-134087':ti,ab,kw OR 'stereocyt':ti,ab,kw OR 'sterecyt':ti,ab,kw OR 'leo-1031':ti,ab,kw OR 'prednisolone':ti,ab,kw OR 'methylprednisolone':ti,ab,kw OR 'prednimustine':ti,ab,kw OR 'dexamethasone':ti,ab,kw OR 'desoximetasone':ti,ab,kw OR 'dexamethasone isonicotinate':ti,ab,kw OR 'flumethasone':ti,ab,kw OR 'fluocinolone aceetonide':ti,ab,kw OR 'fluocinonide':ti,ab,kw OR 'diflucortolone':ti,ab,kw OR 'fluprednisolone':ti,ab,kw OR 'flurandrenolone':ti,ab,kw OR 'flurogestone acetate':ti,ab,kw OR 'parametha sone':ti,ab,kw OR 'triamcinolone':ti,ab,kw OR 'flubenisolone':ti,ab,kw OR 'celestona':ti,ab,kw OR 'cellestoderm':ti,ab,kw OR 'celestone':ti,ab,kw OR 'clofenazon':ti,ab,kw OR 'clobetasol':ti,ab,kw OR 'olux':ti,ab,kw OR 'dermovate':ti,ab,kw OR 'embeline':ti,ab,kw OR 'temovate':ti,ab,kw OR 'methylfluorprednisolone':ti,ab,kw OR 'decameth':ti,ab,kw OR 'dexasone':ti,ab,kw OR 'maxidex':ti,ab,kw OR 'millicorten':ti,ab,kw OR 'oradexon':ti,ab,kw OR 'hexadrol':ti,ab,kw OR 'fluorodexamethasone':ti,ab,kw OR 'fluocinolone':ti,ab,kw OR 'fluortriamcinolone':ti,ab,kw OR 'jellin':ti,ab,kw OR 'jellisoft':ti,ab,kw OR 'synalar':ti,ab,kw OR 'co-fluocin':ti,ab,kw OR 'co fluocin':ti,ab,kw OR 'flucinar':ti,ab,kw OR 'fluodermo':ti,ab,kw OR 'fluotrex':ti,ab,kw OR 'flusolgen':ti,ab,kw OR 'gelidina':ti,ab,kw OR 'fluocortolone':ti,ab,kw OR 'ultralan':ti,ab,kw OR 'fluorometholone':ti,ab,kw OR 'cortisdin':ti,ab,kw OR 'efflumidex':ti,ab,kw OR 'flucon':ti,ab,kw OR 'fluor-op':ti,ab,kw OR 'fluor op':ti,ab,kw OR 'fluoro-ophtal':ti,ab,kw	425808

	OR 'fluoro ophtal':ti,ab,kw OR 'fluoropos':ti,ab,kw OR 'fluoximesteron':ti,ab,kw OR 'halotestin':ti,ab,kw OR 'fluoxymesterone':ti,ab,kw OR 'android-f':ti,ab,kw OR 'android f':ti,ab,kw OR 'flurandrenolide':ti,ab,kw OR 'cordran':ti,ab,kw OR 'haelan':ti,ab,kw OR 'cronolone':ti,ab,kw OR 'flurogestone':ti,ab,kw OR 'flugestone':ti,ab,kw OR 'volon':ti,ab,kw OR 'aristocort':ti,ab,kw OR 'beclometasone':ti,ab,kw OR 'asmabec':ti,ab,kw OR 'ascocortonyl':ti,ab,kw OR 'beclamet':ti,ab,kw OR 'beclo':ti,ab,kw OR 'beclocort':ti,ab,kw OR 'beclomet':ti,ab,kw OR 'bemedrex':ti,ab,kw OR 'beclomethasone':ti,ab,kw OR 'beclorhinol':ti,ab,kw OR 'becloturmant':ti,ab,kw OR 'sanasthmax':ti,ab,kw OR 'beconase':ti,ab,kw OR 'becodisk':ti,ab,kw OR 'sanasthmyl':ti,ab,kw OR 'becodisks':ti,ab,kw OR 'propaderm':ti,ab,kw OR 'becotide':ti,ab,kw OR 'becloforte':ti,ab,kw OR 'bronchocort':ti,ab,kw OR 'ventolair':ti,ab,kw OR 'aerobec':ti,ab,kw OR 'nasobec':ti,ab,kw OR 'beclazone':ti,ab,kw OR 'respocort':ti,ab,kw OR 'prolair':ti,ab,kw OR 'filair':ti,ab,kw OR 'vancenase':ti,ab,kw OR 'vanceril':ti,ab,kw OR 'aldecin':ti,ab,kw OR 'viarin':ti,ab,kw OR 'ecobec':ti,ab,kw OR 'beclazon':ti,ab,kw OR 'chlormadinone acetate':ti,ab,kw OR 'neo eunomin':ti,ab,kw OR 'neoeunomin':ti,ab,kw OR 'chlormadinone':ti,ab,kw OR 'cyproterone':ti,ab,kw	
5	('steroid*' NEAR/1 'heterocyclic'):ti,ab,kw OR ('steroid*' NEAR/1 'fluorinated'):ti,ab,kw OR (('steroid*' NEAR/1 'chlorinated'):ti,ab,kw	218
6	'fluorinated steroid'/exp	123
7	'heterocyclic steroid'/exp	354
8	'prednisolone'/exp	119132
9	4 OR 5 OR 6 OR 7 OR 8	504443
10	3 AND 9	58

Flow-chart of studies: Steroids

PICOs
1.4: Steroids for the improvement or remission of narcolepsy, all ages
4.4: Steroids for improvement of cataplexy, adults

Figure e4: July 2018 run (October 2019 update).



Search strategy: Immune modifying therapies

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5293
2	(immune modifying therap* OR immune modifying treat* OR disease modifying treat* OR disease modifying therap*)	4024
3	1 AND 2	1

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	"immune modifying therapies":ti,ab,kw OR "immune modifying therapy":ti,ab,kw OR "immune modifying treatment":ti,ab,kw OR "disease modifying therapies":ti,ab,kw OR "disease modifying therapy":ti,ab,kw OR "disease modifying treatment":ti,ab,kw OR "disease modifying treatments":ti,ab,kw (Word variations have been searched)	589
5	3 AND 4	0

EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9498
4	'disease modifying' NEAR/1 'therap*':ti,ab,kw 'disease modifying' NEAR/1 'treat*':ti,ab,kw 'immune modifying' NEAR/1 'treat*':ti,ab,kw 'immune modifying' NEAR/1 'therap*':ti,ab,kw 'disease modifying therapy'/exp	8084
5	3 AND 4	**7**

Search strategy: Monoclonal antibodies

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5292
2	dalimumab[Title/Abstract] OR evacizumab[Title/Abstract] OR Cetuximab[Title/Abstract] OR Denosumab[Title/Abstract] OR Natalizumab[Title/Abstract] OR Omalizumab[Title/Abstract] OR Palivizumab[Title/Abstract] OR Ranibizumab[Title/Abstract] OR Trastuzumab[Title/Abstract] OR Ustekinumab OR monoclonal antibod*[Title/Abstract] OR "Antibodies, Monoclonal"[Mesh] OR "alemtuzumab"[Supplementary Concept] OR Alemtuzumab[Title/Abstract]	255878
3	1 AND 2	9

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Antibodies, Monoclonal]	9251
5	dalimumab ti,ab,kw OR evacizumab ti,ab,kw OR Cetuximab ti,ab,kw OR Denosumab ti,ab,kw OR Natalizumab ti,ab,kw OR Omalizumab ti,ab,kw OR Palivizumab ti,ab,kw OR Ranibizumab ti,ab,kw OR Trastuzumab ti,ab,kw OR Ustekinumab ti,ab,kw OR Alemtuzumab:ti,ab,kw	6203
6	monoclonal near/1 antibod*:ti,ab,kw	10280
7	4 OR 5 OR 6	19801
8	3 AND 7	0

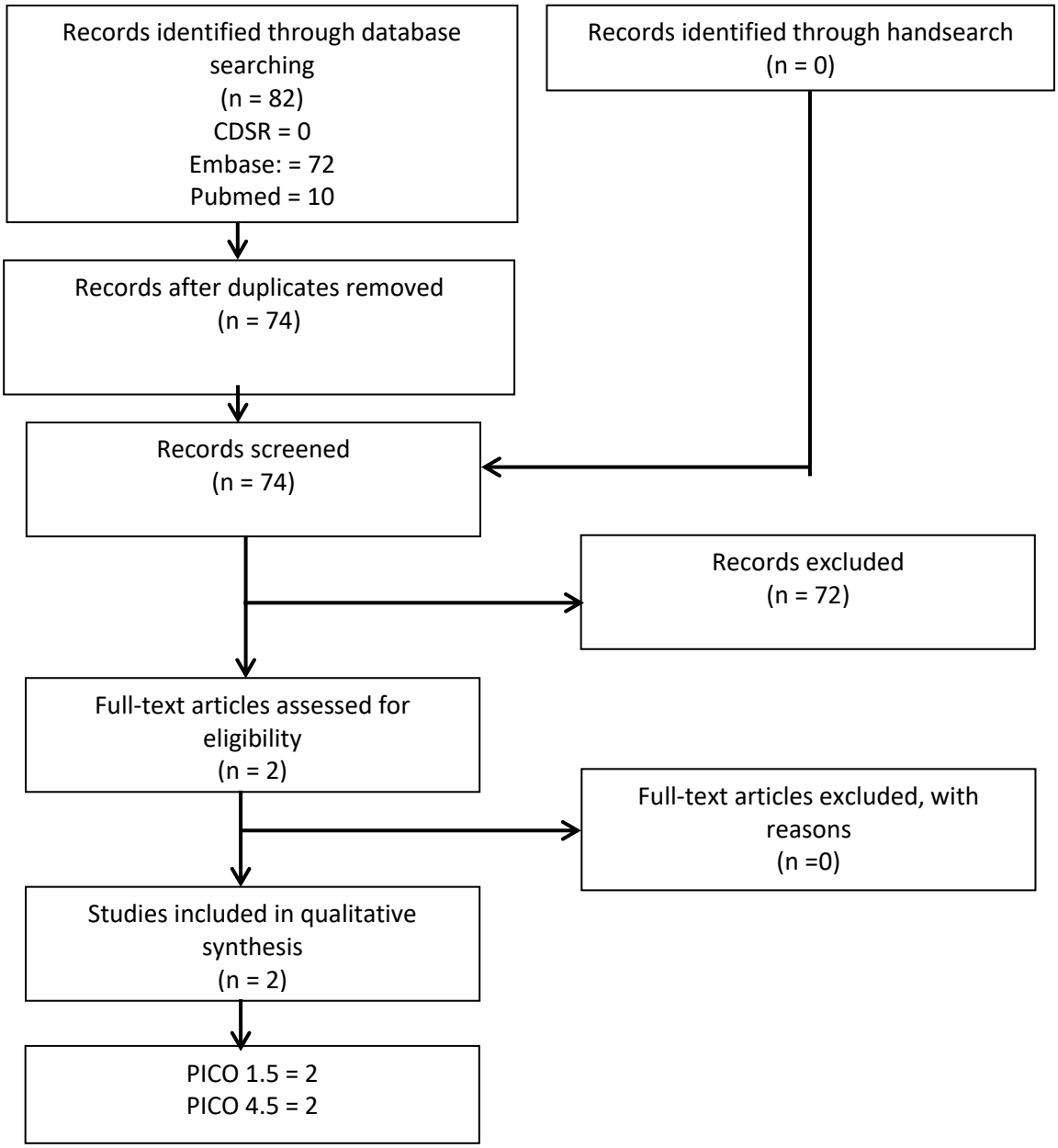
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7187
3	1 OR 2	9495
4	'monoclonal antibody'/exp	482340
5	'dalimumab':ti,ab,kw OR 'evacizumab':ti,ab,kw OR 'cetuximab':ti,ab,kw OR 'denosumab':ti,ab,kw OR natalizumab':ti,ab,kw	8425
6	4 OR 5	484773
7	3 AND 6	65

Flow-chart of studies: Monoclonal antibodies / Immune modifying therapies

PICOs
1.5: Monoclonal antibodies / Immune modifying therapies for the improvement or remission of narcolepsy, all ages
4.5: Monoclonal antibodies / Immune modifying therapies for improvement of cataplexy, adults

Figure e5: July 2018 run (October 2019 update).



Search strategy: Scheduled naps

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5314
2	nap*[Title/Abstract] OR napping[Title/Abstract] OR scheduled sleep*[Title/Abstract] OR "Sleep Hygiene"[Mesh] OR "sleep hygiene"[Title/Abstract]	24902
3	1 AND 2	114

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	"MeSH descriptor: [Sleep Hygiene] explode all trees	10
5	nap*:ti,ab,kw or napping*:ti,ab,kw OR "scheduled sleep":ti,ab,kw OR "sleep hygiene":ti,ab,kw	5863
6	4 OR 5	5863
7	3 AND 6	27

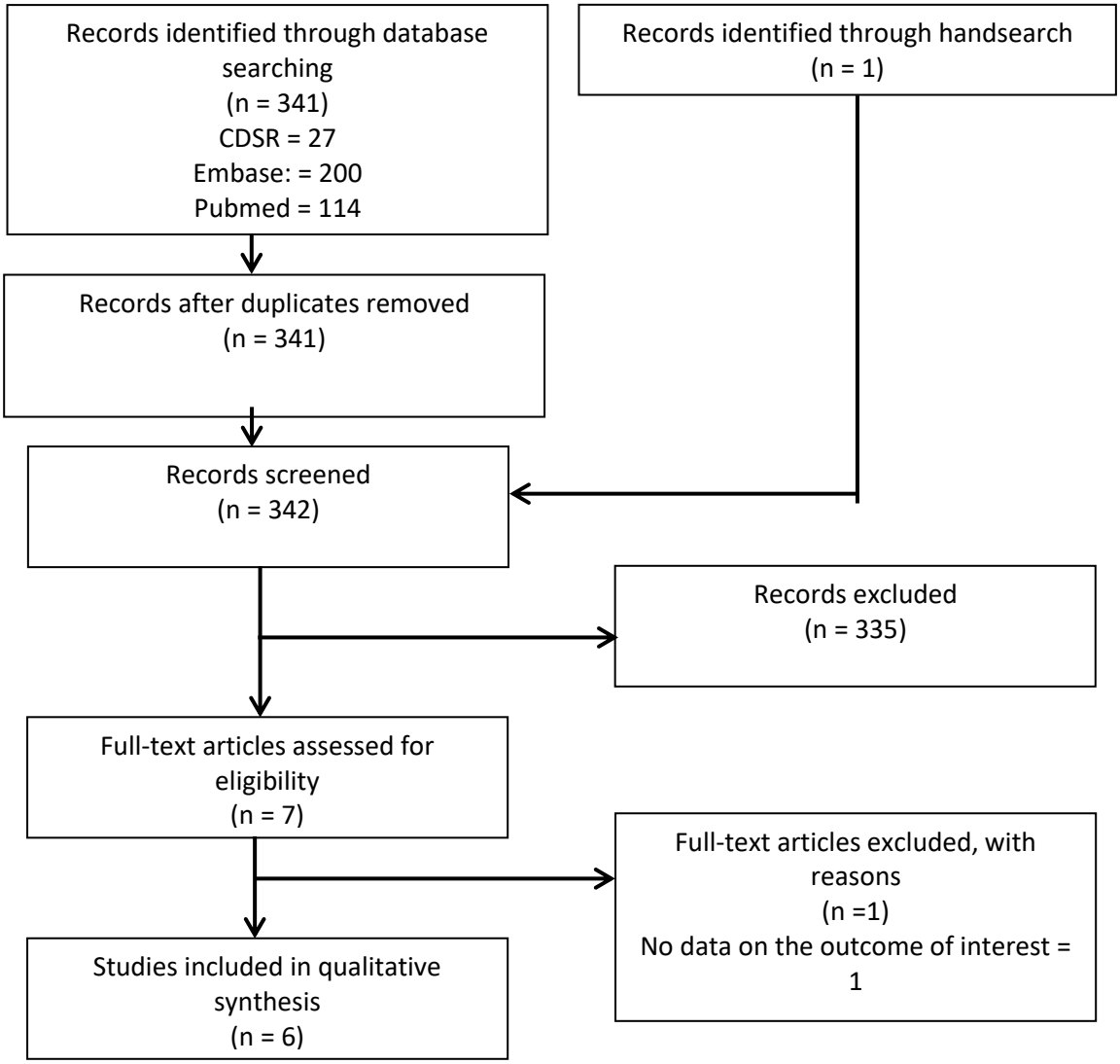
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'sleep hygiene'/exp	101
5	'nap*':ti,ab,kw OR 'napping*':ti,ab,kw OR 'sleep hygiene':ti,ab,kw OR ('scheduled' NEAR/2 'sleep'):ti,ab,kw	88481
6	4 OR 5	88787
7	3 AND 6	395
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	200

Flow-chart of studies: Scheduled naps

PICO
2.1: Scheduled naps for the improvement of different symptoms of narcolepsy, all ages

Figure e6: August 2018 run (October 2019 update).



Search strategy: Physical activity

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"Exercise"[Mesh] OR Physical Activit*[title/abstract] OR Exercis*[title/abstract]	402008
3	1 AND 2	34

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Exercise] explode all tree	21610
5	“Physical Activity”:ti,ab,kw OR “Physical Activities”:ti,ab,kw OR Exercis*:ti,ab,kw	82560
6	4 OR 5	84982
7	3 AND 6	3

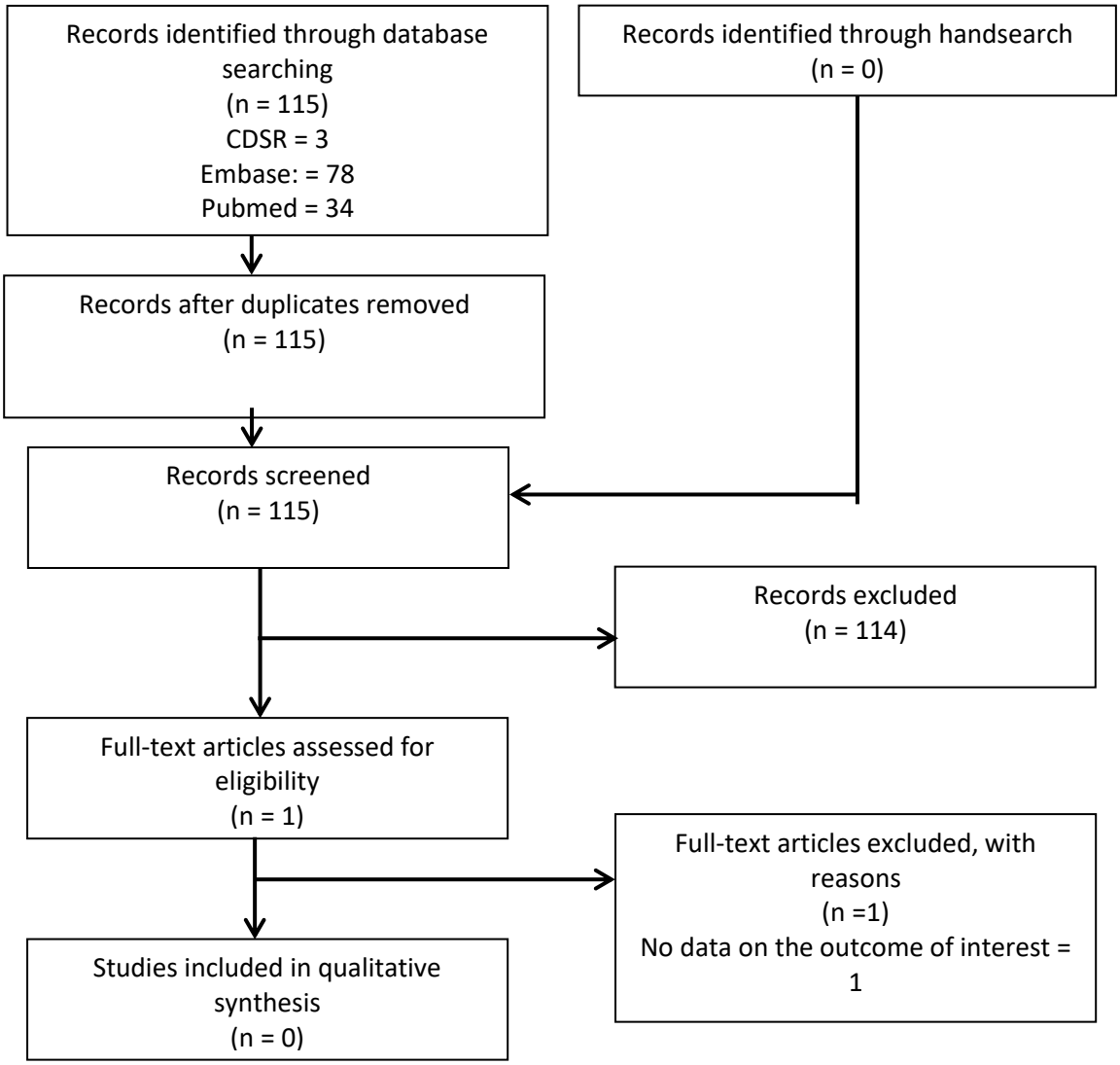
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'physical activity'/exp	352889
5	'exercis*':ti,ab,kw OR 'physical' NEAR/2 'activit*':ti,ab,kw	450781
6	4 OR 5	679114
7	3 AND 6	618
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	78

Flow-chart of studies: Physical activity

PICO
2.2: Physical activity for the improvement of different symptoms of narcolepsy, all ages

Figure e7: August 2018 run (October 2019 update).



Search strategy: Nutrition, diet

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5310
2	diet[title/abstract] OR diets[title/abstract] OR dietary[title/abstract] OR "Diet, Food, and Nutrition"[Mesh] OR nutrition*[Title/Abstract]	1288249
3	1 AND 2	114

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	"MeSH descriptor: [Diet, Food, and Nutrition] explode all tree	49024
5	diet:ti,ab,kw OR diets:ti,ab,kw OR dietary OR nutrition:ti,ab,kw	76220
6	4 OR 5	9207
7	3 AND 6	10

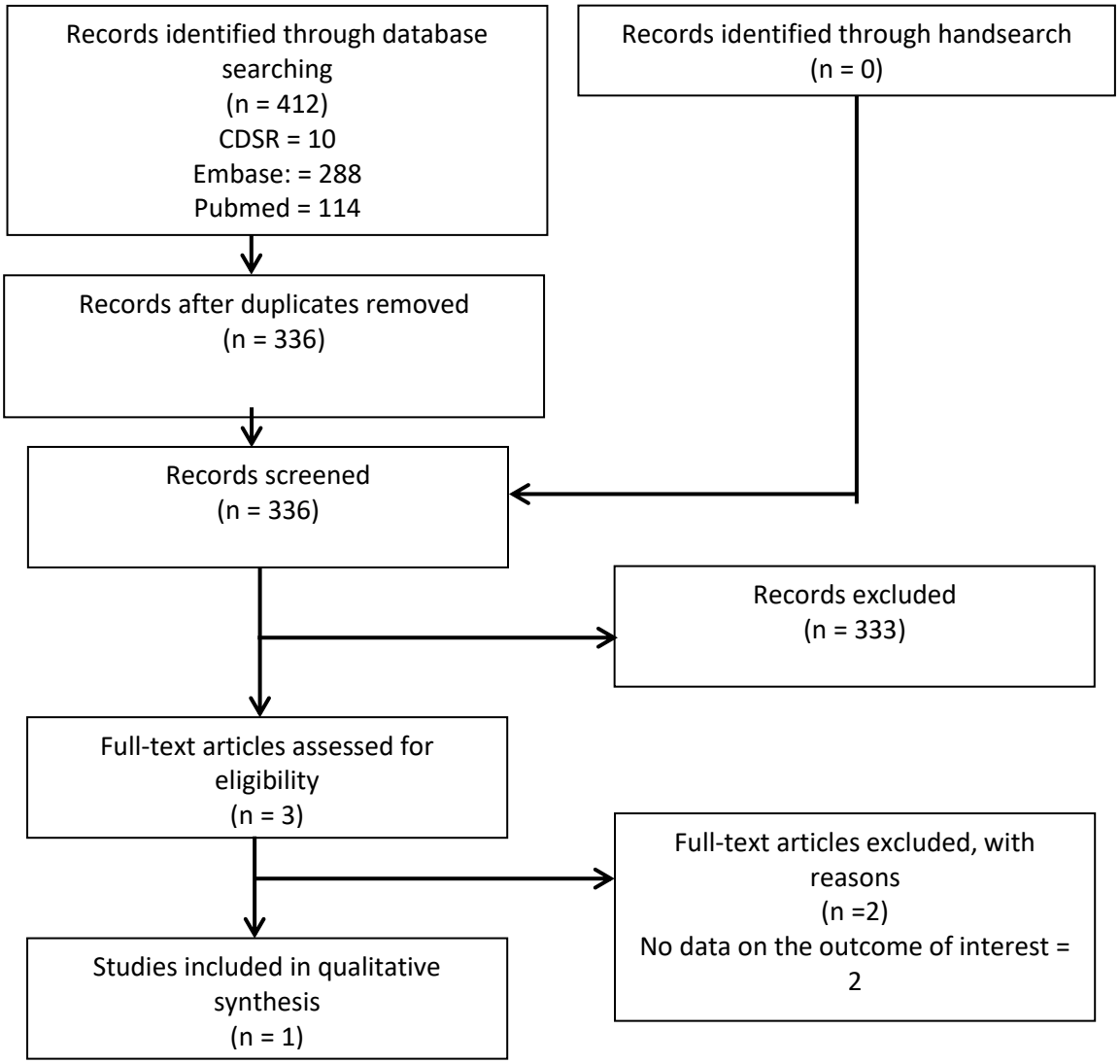
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9256
4	'nutrition'/exp OR 'diet'/exp	1987956
5	'diet':ti,ab,kw OR 'diets':ti,ab,kw OR 'dietary':ti,ab,kw OR 'nutrition':ti,ab,kw	717585
6	4 OR 5	2173465
7	3 AND 6	618
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'human'/de	288

Flow-chart of studies: Nutrition, diet

PICO
2.3: Nutrition, diet for the improvement of different symptoms of narcolepsy, all ages

Figure e8: August 2018 run (October 2019 update).



Search strategy: Cognitive therapy

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	Cognitive Therap*[title/abstract] OR Cognitive Treatment*[title/abstract] OR Behavioral Therap*[title/abstract] OR behavioral treatment*[title/abstract] OR BehaviOR Therap*[title/abstract] OR BehaviOR Treatment*[title/abstract] OR Behavioural Therap*[title/abstract] OR behavioural treatment*[title/abstract] OR Behaviour Therap*[title/abstract] OR Behaviour Treatment*[title/abstract] OR Psychotherap*[title/abstract] OR cognition therap*[title/abstract] OR cognition treatment*[title/abstract] OR "Psychotherapy"[Mesh:NoExp] OR "BehaviOR Therapy"[Mesh] OR "Cognitive Therapy"[Mesh]	140339
3	1 AND 2	59

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	MeSH descriptor: [Psychotherapy] explode all tree	20667
5	MeSH descriptor: [BehaviOR Therapy] explode all tree	14289
6	MeSH descriptor: [Cognitive Therapy] explode all tree	7500
7	cognitive NEAR/2 therap*	15100
8	cognitive NEAR/2 treatment*	2572
9	behav* NEAR/2 therap*	17217
10	behav* NEAR/2 treatment*	4090
11	cognition NEAR/2 therap*	1036
12	cognition NEAR/2 treatment*	177
13	4/13 OR	35976
14	3 AND 4	9

EMBASE

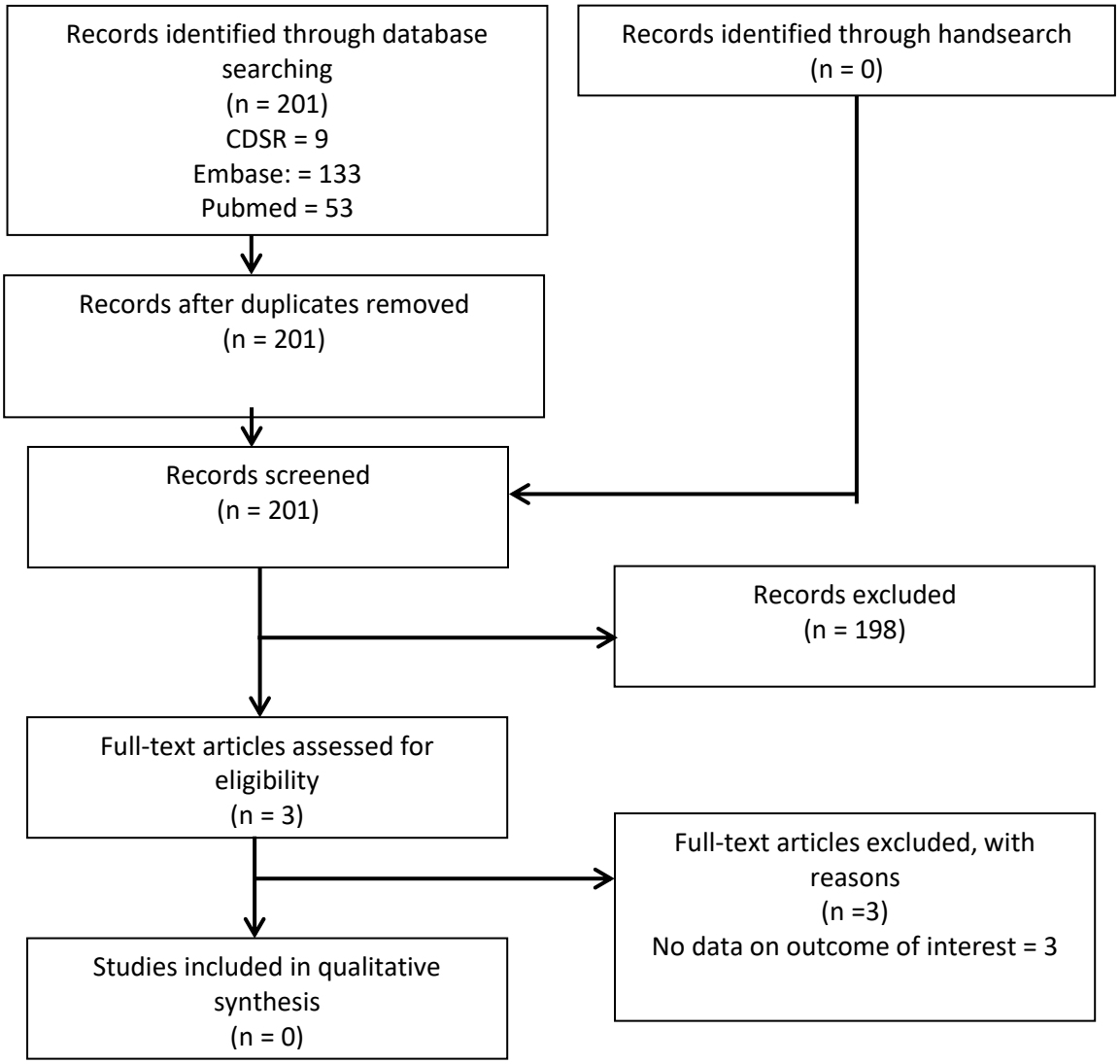
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'psychotherapy'/de OR 'behaviOR therapy'/exp OR 'cognitive therapy'/exp OR 'cognitive behavioral therapy'/exp	160319
5	('cognitive' NEAR/2 'therap*'):ti,ab,kw OR ('cognitive' NEAR/2 'treatment*'):ti,ab,kw OR ('cognition' NEAR/2 'treatment*'):ti,ab,kw OR ('cognition' NEAR/2 'therap*'):ti,ab,kw OR ('behav*' NEAR/2 'therap*'):ti,ab,kw OR ('behav*' NEAR/2 'treatment*'):ti,ab,kw	54725
7	4 OR 5	180028
8	3 AND 7	330
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	133

Flow-chart of studies: Cognitive therapy

PICO

2.4: Cognitive therapy for the improvement of different symptoms of narcolepsy, all ages

Figure e9: August 2018 run (October 2019 update).



Search strategy: Hypnosis

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"Hypnosis"[Mesh] OR Hypnos*[title/abstract]	14337
3	1 AND 2	30

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Hypnoses] explode all tree	687
5	hypnoses:ti,ab,kw OR hypnosis:ti,ab,kw	1270
6	4 OR 5	1519
7	3 AND 6	0

EMBASE

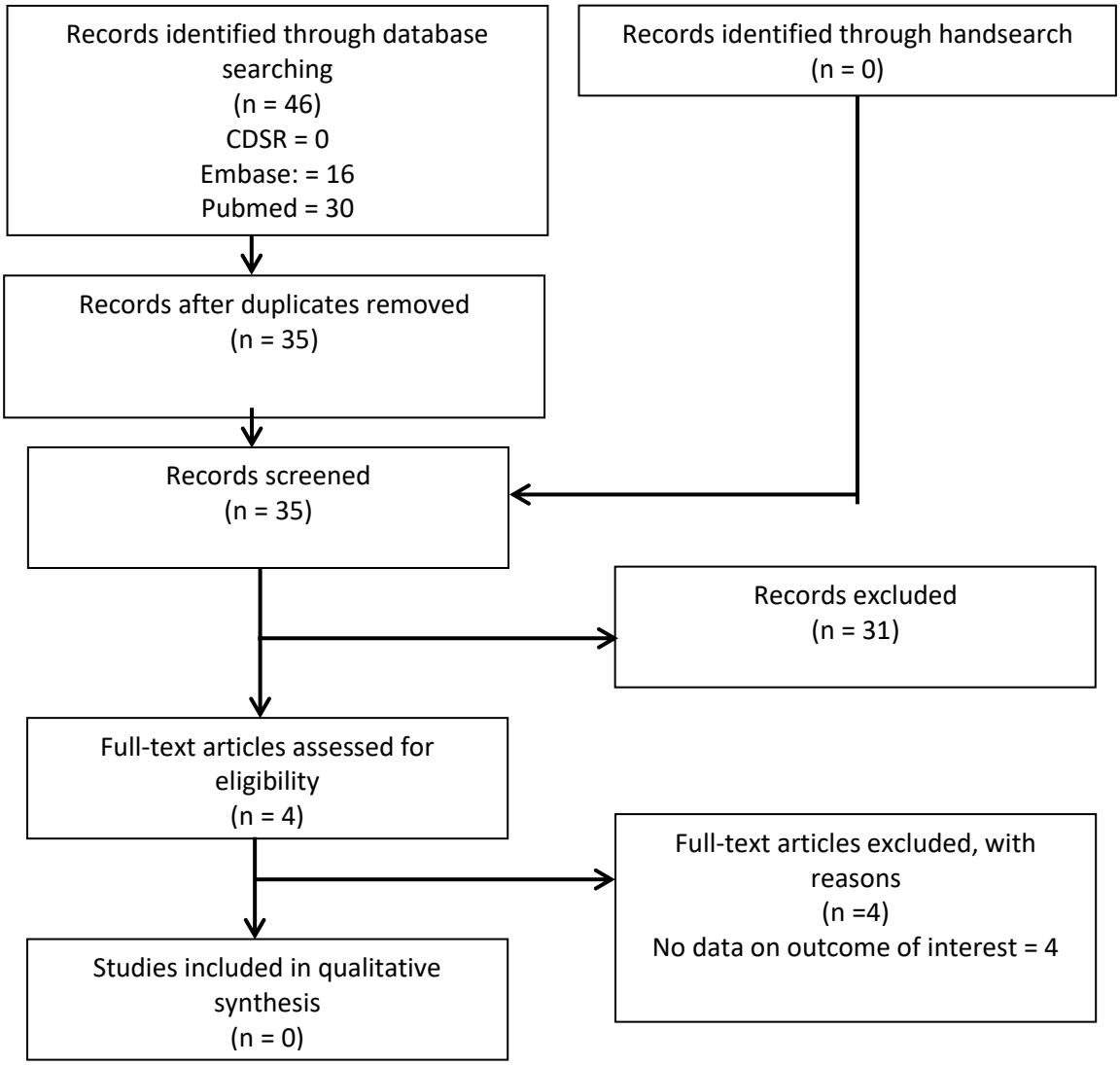
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'hypnosis'/exp	15994
5	'hypnos*':ti,ab,kw	9652
6	4 OR 5	17695
7	3 AND 6	52
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	16

Flow-chart of studies: Hypnosis

PICO

2.5: Hypnosis for the improvement of different symptoms of narcolepsy, all ages

Figure e10: August 2018 run (October 2019 update).



Search strategy: Sodium Oxybate

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	"4-hydroxybutyric acid"[Title/Abstract] or “4 hydroxybutanoate sodium” [Title/Abstract] or “4 hydroxybutanoic acid” [Title/Abstract] or “4 hydroxybutyrate sodium” [Title/Abstract] OR "Sodium Oxybate"[Title/Abstract] OR "sodium oxybutyrate"[Title/Abstract] OR "somsanit"[Title/Abstract] OR "gamma hydroxybutyrate"[Title/Abstract] or “hydroxybutyrate sodium” [Title/Abstract] OR Xyrem[Title/Abstract] OR "oxybate sodium"[Title/Abstract] OR "Sodium Oxybate"[Mesh]	2380
3	1 AND 2	311

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	"4-hydroxybutyric acid":ti,ab,kw OR "4 hydroxybutanoate sodium":ti,ab,kw OR "4 hydroxybutanoic acid":ti,ab,kw OR "4 hydroxybutyrate sodium":ti,ab,kw OR "Sodium Oxybate":ti,ab,kw OR "sodium oxybutyrate":ti,ab,kw OR "somsanit":ti,ab,kw or "gamma hydroxybutyrate":ti,ab,kw OR "hydroxybutyrate sodium":ti,ab,kw OR Xyrem:ti,ab,kw OR "oxybate sodium":ti,ab,kw	207
5	MeSH descriptor: [Sodium Oxybate] explode all trees	102
6	4 OR 5	207
7	3 AND 6	78

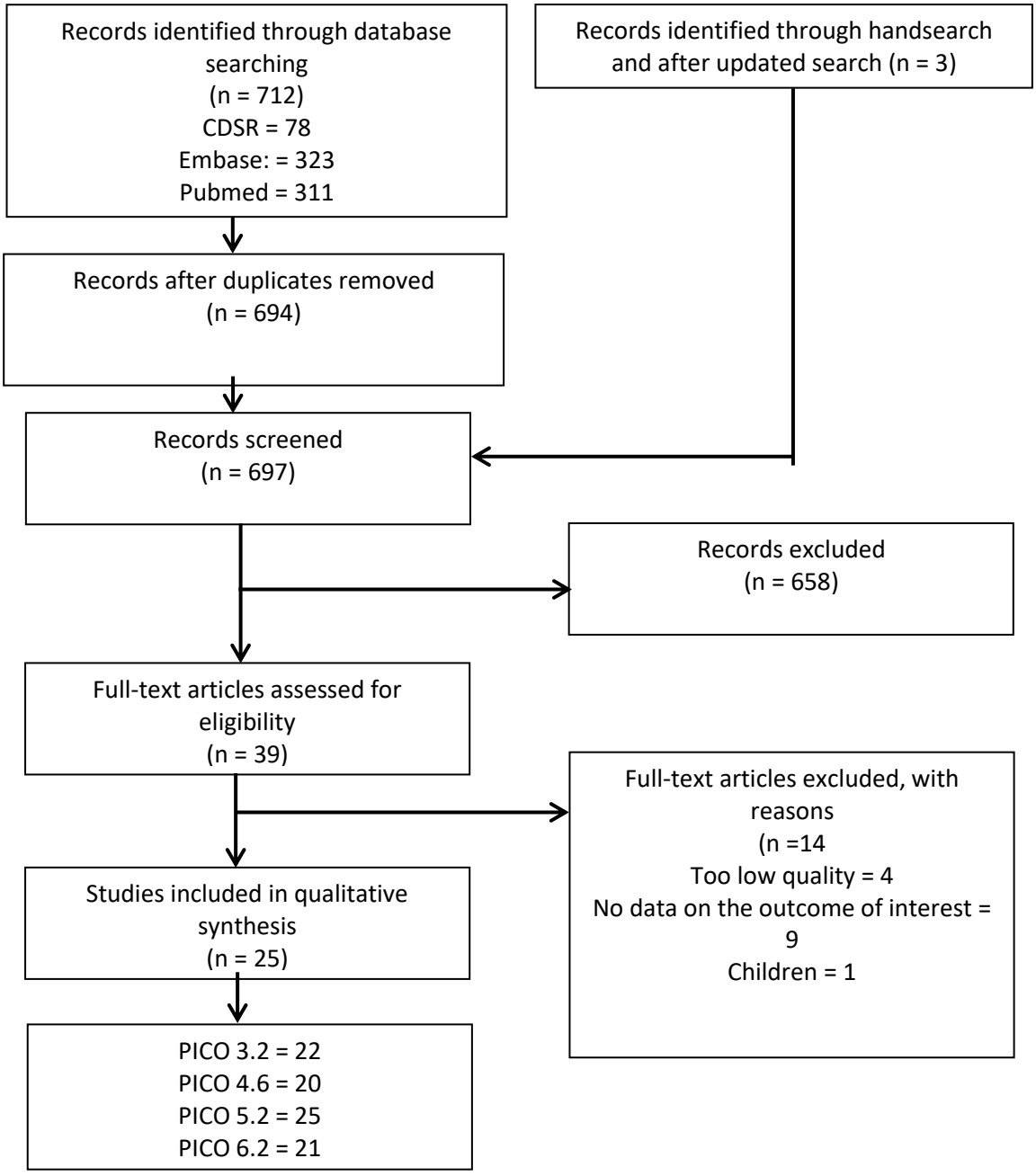
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9500
4	'4-hydroxybutyric acid':ti,ab,kw OR '4 hydroxybutanoate sodium':ti,ab,kw OR '4 hydroxybutanoic acid':ti,ab,kw OR '4 hydroxybutyrate sodium':ti,ab,kw OR 'sodium oxybate':ti,ab,kw OR 'sodium oxybutyrate':ti,ab,kw OR 'somsanit':ti,ab,kw OR 'gamma hydroxybutyrate':ti,ab,kw OR 'hydroxybutyrate sodium':ti,ab,kw OR 'xyrem':ti,ab,kw OR 'oxybate sodium':ti,ab,kw	1727
5	'oxybate sodium'/exp	1738
6	4 OR 5	2697
7	3 AND 6	786
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'human'/de	323

Flow-chart of studies: Sodium Oxybate

PICOs
3.2: Sodium Oxybate for improvement of excessive daytime sleepiness, adults
4.6: Sodium Oxybate for improvement of moderate to severe cataplexy, adults
5.2: Sodium Oxybate for improvement of moderate to severe night time disturbed sleep, adults
6.2: Sodium Oxybate for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e11: August 2018 run (October 2019 update).



Search strategy: Amphetamines

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	Dextroamphetamin*[Title/Abstract] OR "Lisdexamfetamine Dimesylate"[Title/Abstract] OR Chlorphentermine[Title/Abstract] OR Mephentermine[Title/Abstract] OR adderall[Title/Abstract] OR Benzphetamin*[Title/Abstract] OR Amphetamin*[Title/Abstract] OR Phentermin*[Title/Abstract] OR Iofetamine[Title/Abstract] OR Dexamphetamin*[Title/Abstract] OR dexamfetamin*[Title/Abstract] OR Dexedrine[Title/Abstract] OR DextroStat[Title/Abstract] OR Oxydess[Title/Abstract] OR curban OR "Amphetamines"[Mesh]	45772
3	1 AND 2	276

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	Dextroamphetamin*:ti,ab,kw OR "Lisdexamfetamine Dimesylate":ti,ab,kw OR Chlorphentermine:ti,ab,kw OR Mephentermine:ti,ab,kw OR adderall:ti,ab,kw OR Benzphetamin*:ti,ab,kw OR Amphetamin*:ti,ab,kw OR Phentermin*:ti,ab,kw OR Iofetamine:ti,ab,kw OR Dexamphetamin*:ti,ab,kw OR dexamfetamin*:ti,ab,kw OR Dexedrine:ti,ab,kw OR DextroStat:ti,ab,kw OR Oxydess:ti,ab,kw OR curban:ti,ab,kw	2398
5	MeSH descriptor: [Amphetamines] explode all trees	1677
6	4 OR 5	2788
7	3 AND 6	22

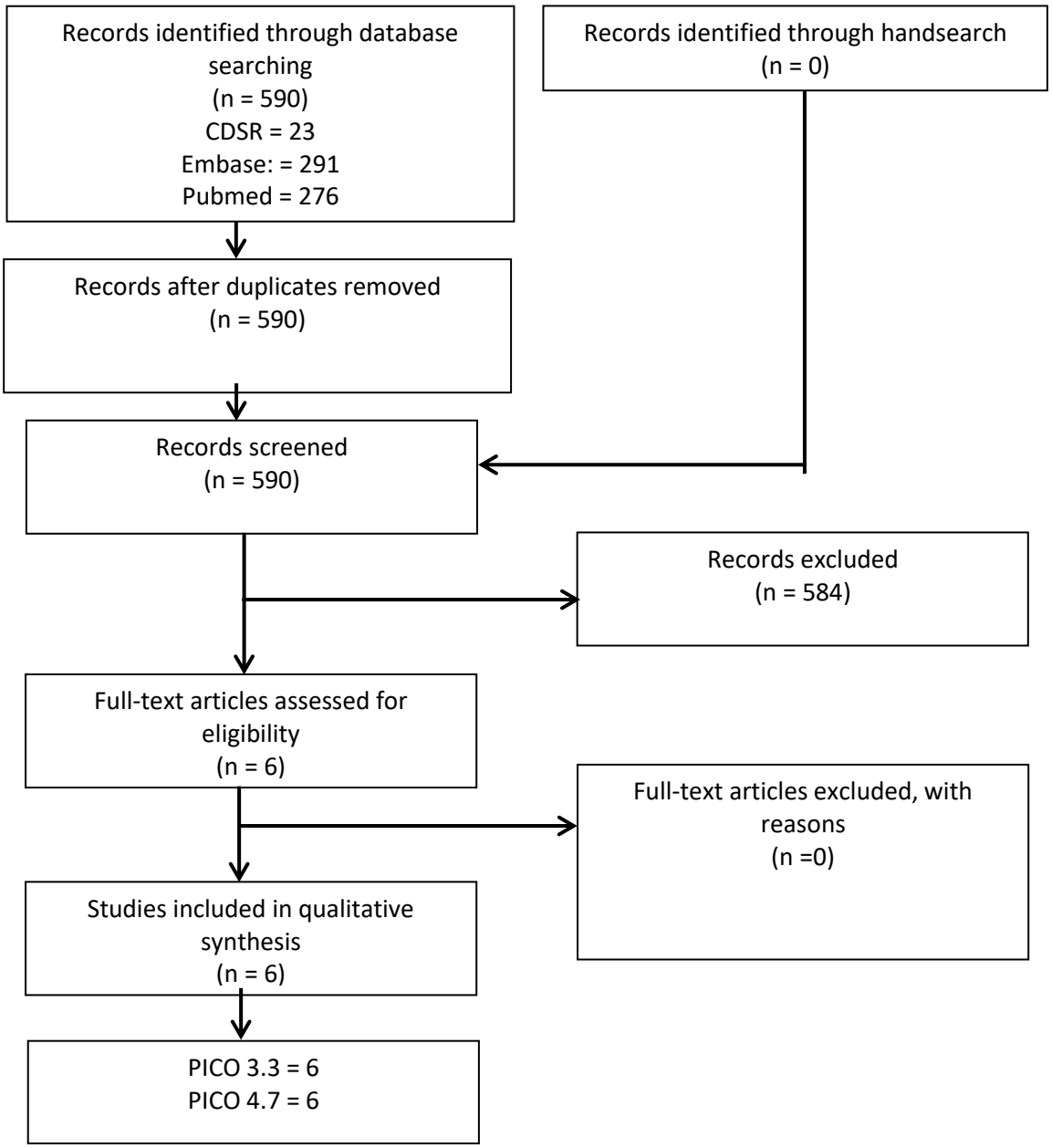
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9500
4	'amphetamine derivative'/exp	90432
5	3 AND 4	1026
6	5 AND 'human'/de AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	291

Flow-chart of studies: Amphetamines

PICOs
3.3: Amphetamines for improvement of excessive daytime sleepiness, adults
4.7: Amphetamines for improvement of moderate to severe cataplexy, adults

Figure e12: July 2018 run (October 2019 update).



Search strategy: Methylphenidate

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	"Methylphenidate"[Mesh] OR ritalin*[Title/Abstract] OR Metadate[Title/Abstract] OR "Dexmethylphenidate Hydrochloride"[Title/Abstract] OR Equasym[Title/Abstract] OR concerta[Title/Abstract] OR Phenidylate OR Centedrin[Title/Abstract] OR Daytrana[Title/Abstract] OR Methylphenidate[Title/Abstract]	313193
3	1 AND 2	224

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	360
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	ritalin*:ti,ab,kw OR Metadate:ti,ab,kw OR "Dexmethylphenidate Hydrochloride":ti,ab,kw OR Equasym:ti,ab,kw OR concerta:ti,ab,kw OR Phenidylate:ti,ab,kw OR Centedrin:ti,ab,kw OR Daytrana:ti,ab,kw OR Methylphenidate:ti,ab,kw	2413
5	MeSH descriptor: [Methylphenidate]	1477
6	4 OR 5	2413
7	3 AND 6	17

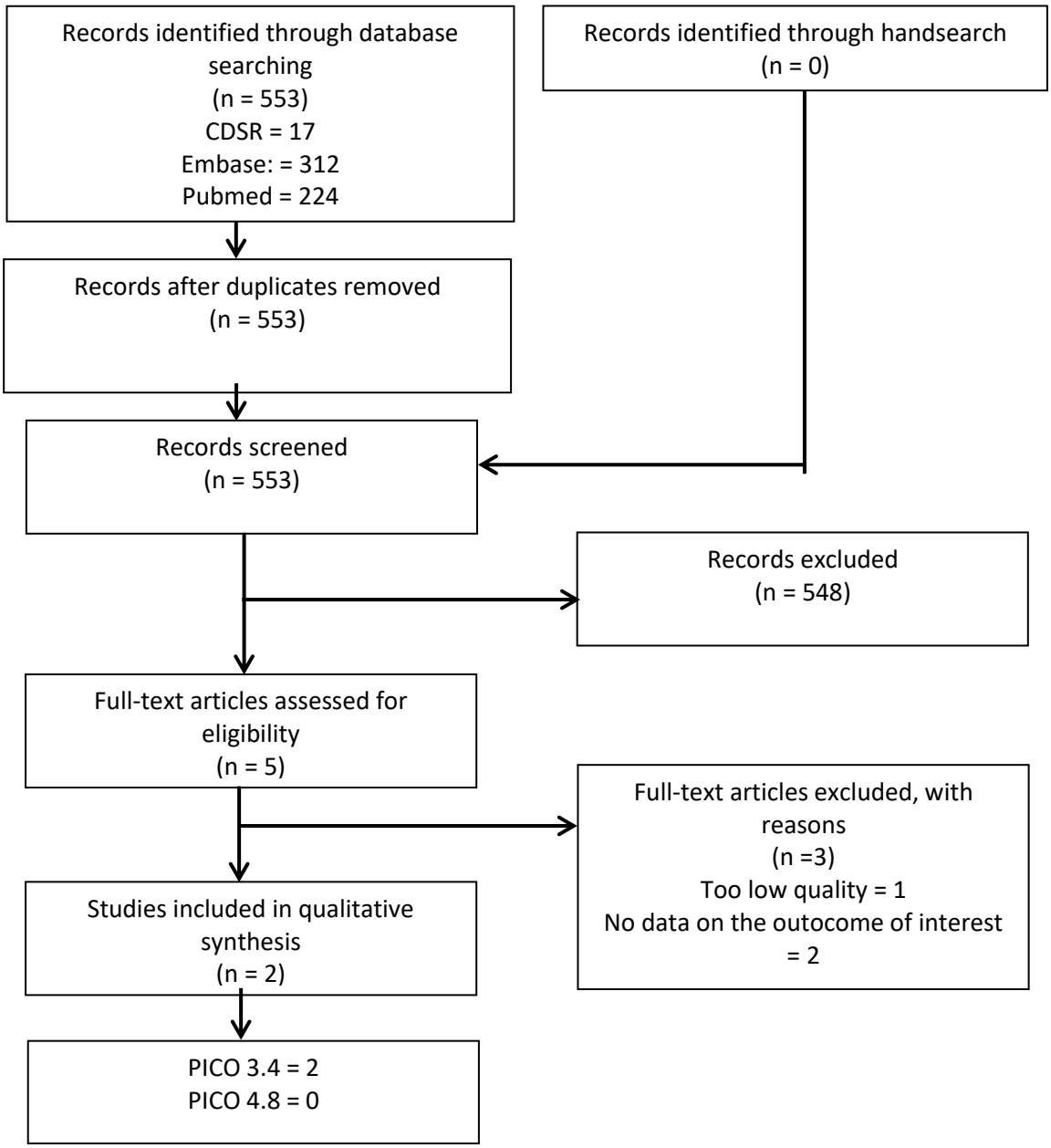
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9500
4	'methylphenidate'/exp	20386
5	'ritalin*':ti,ab,kw OR 'metadate':ti,ab,kw OR 'dexmethylphenidate hydrochloride':ti,ab,kw OR 'equasym':ti,ab,kw OR 'concerta':ti,ab,kw OR 'phenidylate':ti,ab,kw OR 'centedrin':ti,ab,kw OR 'daytrana':ti,ab,kw OR 'methylphenidate':ti,ab,kw	9461
6	4 OR 5	21029
7	3 AND 6	1030
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'human'/de	312

Flow-chart of studies: Methylphenidate

PICOs
3.4: Methylphenidate for improvement of excessive daytime sleepiness, adults
4.8: Methylphenidate for improvement of moderate to severe cataplexy, adults

Figure e13: July 2018 run (October 2019 update).



Search strategy: Solriamfetol

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5293
2	"jzp 110" OR "adx n05" OR Solriamfetol	8
3	1 AND 3	8

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	360
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	"jzp 110" OR "adx n05":ti,ab,kw OR Solriamfetol:ti,ab,kw	40
5	4 AND 3	24

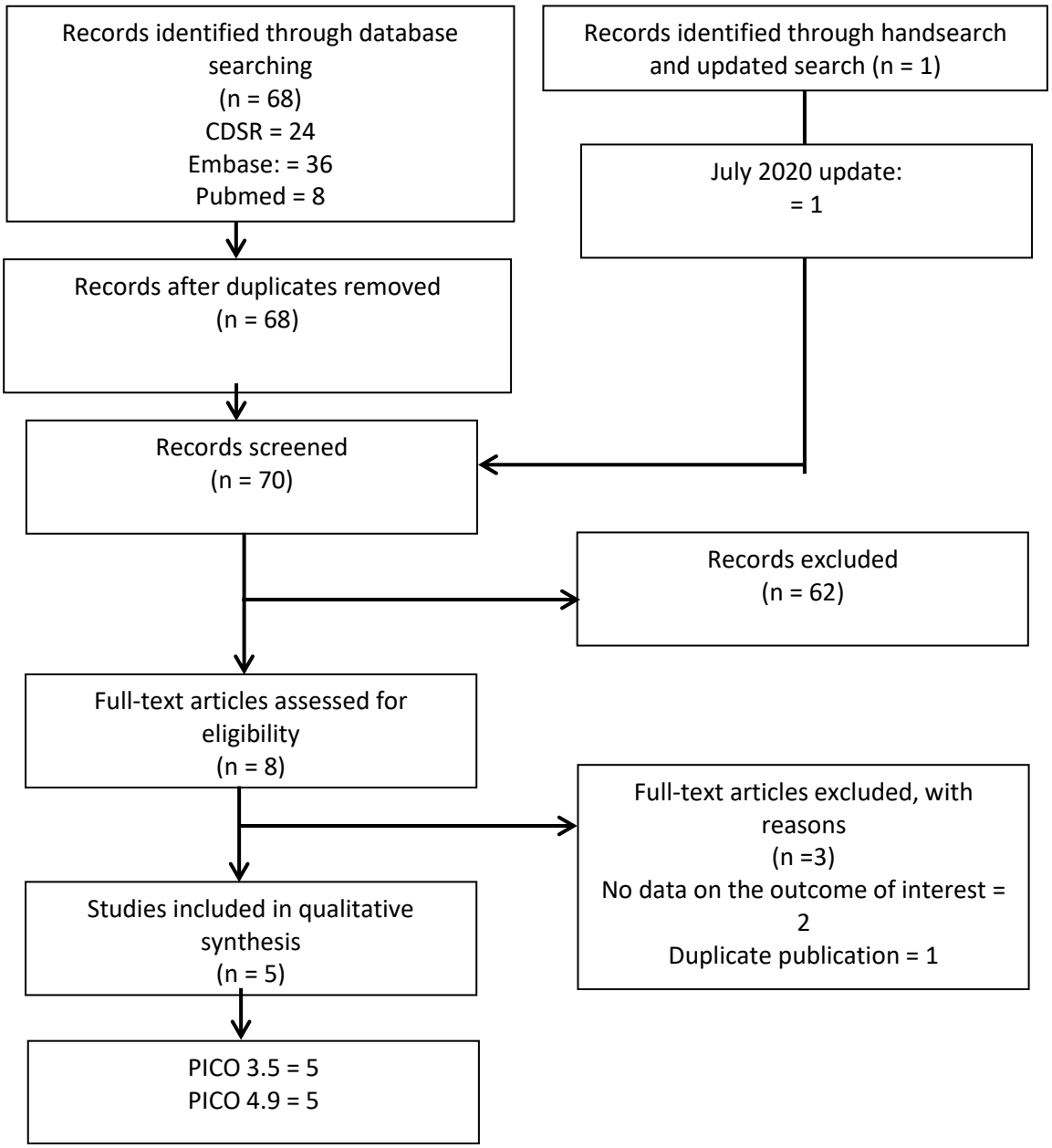
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9516
4	'solriamfetol'/exp	44
5	'jzp 110' OR 'adx n05'	52
6	4 OR 5	63
7	6 AND 3	42
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	36

Flow-chart of studies: Solriamfetol

PICOs
3.5: Solriamfetol for improvement of excessive daytime sleepiness, adults
4.9: Solriamfetol for improvement of moderate to severe cataplexy, adults

Figure e14: September 2018 run (October 2019 and July 2020 updates)



Search strategy: Mazindol

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	“an 448"[Title/Abstract] OR "sanjorex"[Title/Abstract] OR "sanorex"[Title/Abstract] OR "teronac”[Title/Abstract] OR "teronak"[Title/Abstract] OR mazindol*[Title/Abstract] OR "Mazindol"[Mesh]	919
3	1 AND 3	17

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	360
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Mazindol] explode all tree	50
5	"an 448":ti,ab,kw OR sanjore":ti,ab,kw OR Sanorex:ti,ab,kw OR teronac:ti,ab,kw OR teronak:ti,ab,kw OR mazindol*:ti,ab,kw	96
6	4 OR 5	96
7	3 AND 6	1

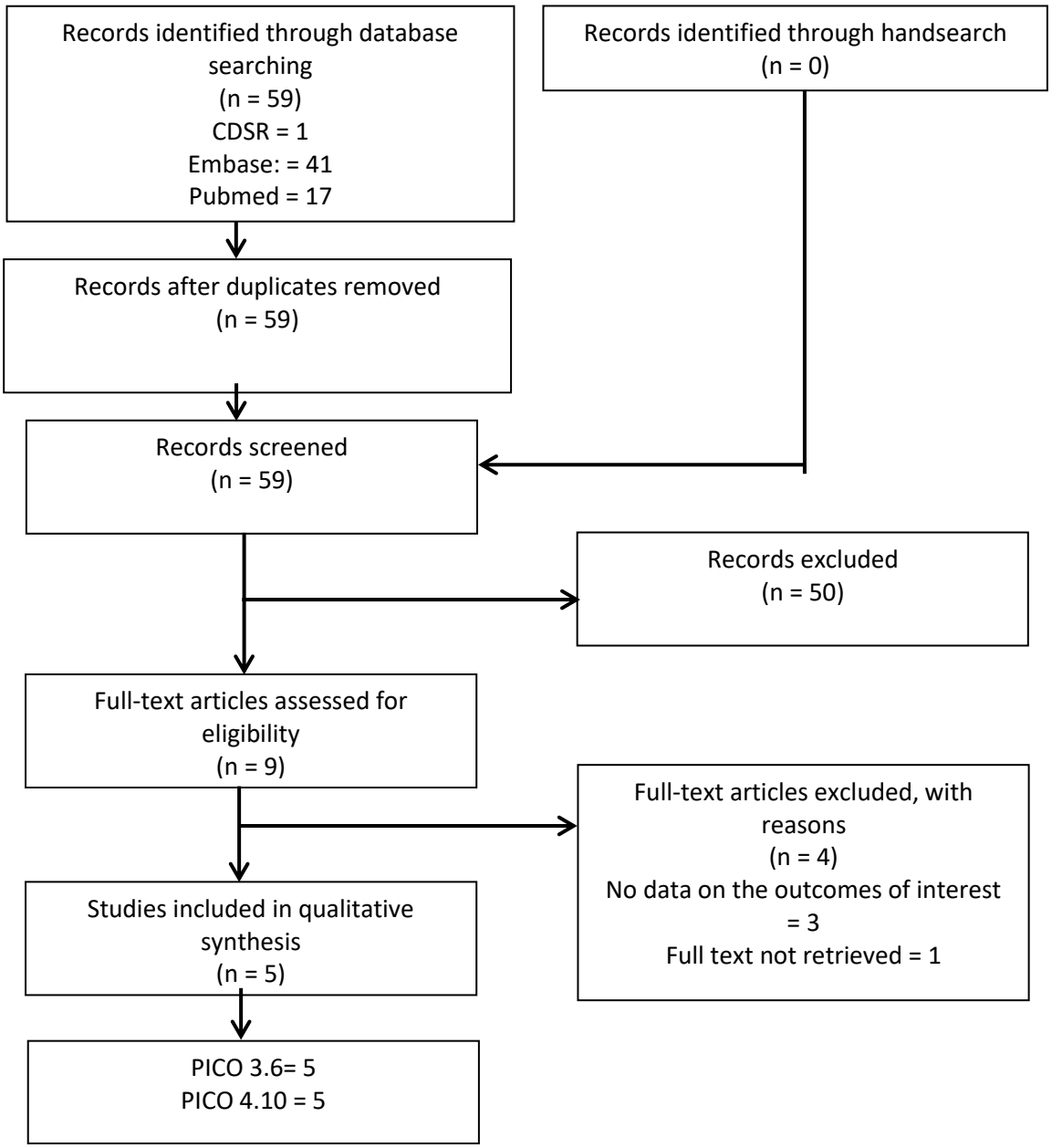
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9500
4	'sanjorex':ti,ab,kw OR 'sanorex':ti,ab,kw OR 'teronac':ti,ab,kw OR 'teronak':ti,ab,kw OR 'mazindol*':ti,ab,kw OR 'an 448':ti,ab,kw	914
5	'mazindol'/exp	1811
6	4 OR 5	1967
7	3 AND 6	138
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'human'/de	41

Flow-chart of studies: Mazindol

PICOs
3.6: Mazindol for improvement of excessive daytime sleepiness, adults
4.10: Mazindol for improvement of moderate to severe cataplexy, adults

Figure e15: September 2018 run (October 2019 update).



Search strategy: Modafinil

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5294
2	"Wakefulness-Promoting Agents"[MeSH Terms] OR "modafinil"[Supplementary Concept] OR "modanifil"[Title/Abstract] OR provigil[Title/Abstract] OR "modiodal"[Title/Abstract] OR "benzhydrylsulfinylacetamide"[Title/Abstract] OR "2 diphenylmethyl sulfinyl acetamide"[Title/Abstract]) OR "crl 40476"[Title/Abstract] OR "sparlon"[Title/Abstract] OR "nourypharma"[Title/Abstract] OR "lafon"[Title/Abstract] OR "cephalon"[Title/Abstract] OR "draxis"[Title/Abstract	1273
3	1 AND 2	289

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Wakefulness-Promoting Agents] explode all tree	57
5	modafinil:ti,ab,kw OR provigil:ti,ab,kw OR modiodal:ti,ab,kw OR benzhydrylsulfinylacetamide:ti,ab,kw OR "2 diphenylmethyl sulfinyl acetamide":ti,ab,kw OR "crl 40476":ti,ab,kw OR "sparlon":ti,ab,kw OR "nourypharma":ti,ab,kw OR "lafon":ti,ab,kw OR "cephalon":ti,ab,kw OR draxis:ti,ab,kw	710
6	4 OR 5	729
7	3 AND 6	117

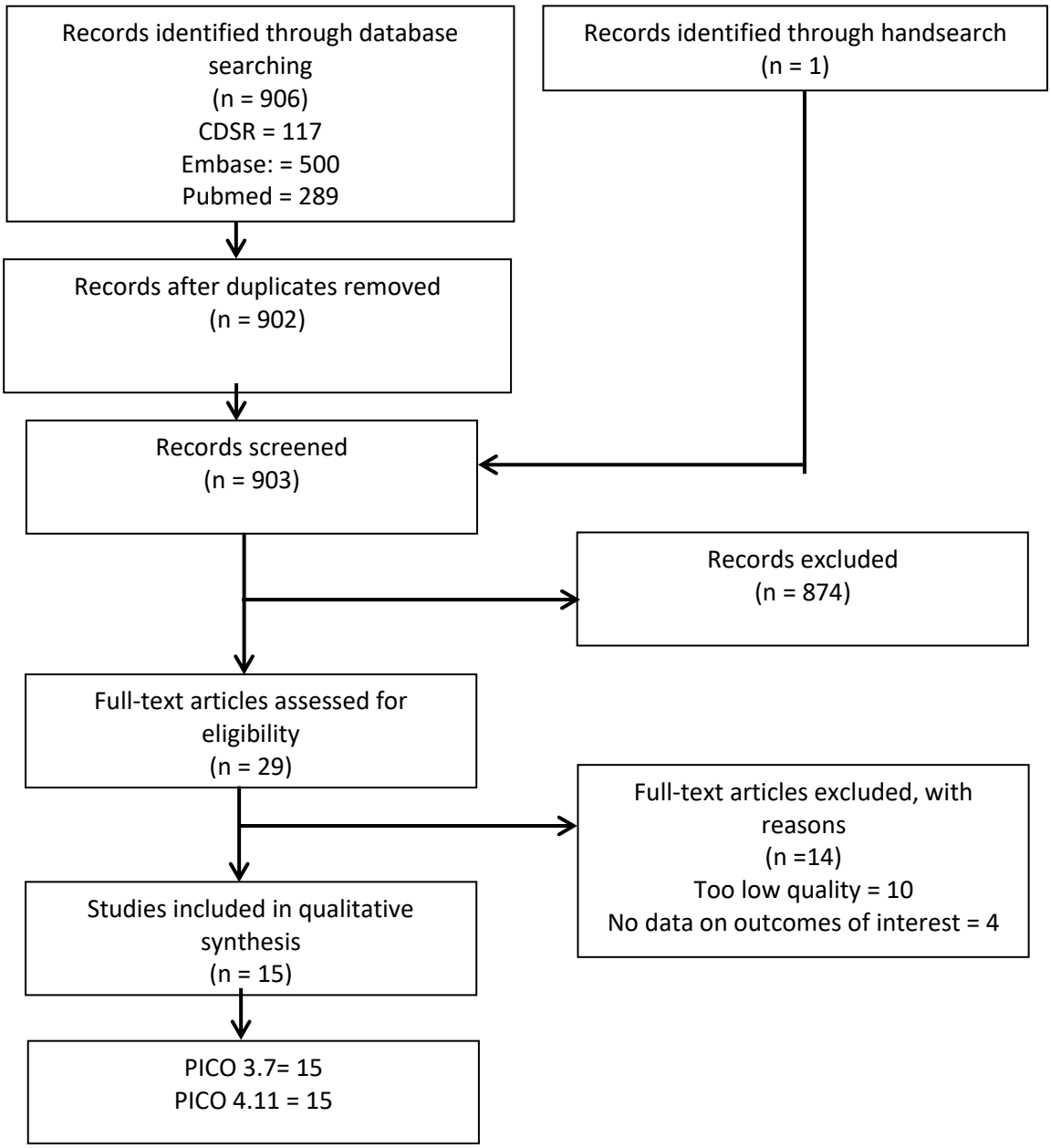
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9500
4	'modafinil':ti,ab,kw OR 'provigil':ti,ab,kw OR 'modiodal':ti,ab,kw OR 'benzhydrylsulfinylacetamide':ti,ab,kw OR '2 diphenylmethyl sulfinyl acetamide':ti,ab,kw OR 'crl 40476':ti,ab,kw OR 'sparlon':ti,ab,kw OR 'nourypharma':ti,ab,kw OR 'lafon':ti,ab,kw OR 'cephalon':ti,ab,kw OR 'draxis':ti,ab,kw	2390
5	'modafinil'/exp	5096
6	4 OR 5	5371
7	3 AND 6	1417
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'human'/de	500

Flow-chart of studies: Modafinil

PICOs
3.7: Modafinil for improvement of excessive daytime sleepiness, adults
4.11: Modafinil for improvement of moderate to severe cataplexy, adults

Figure e16: August 2018 run (October 2019 update).



Search strategy: Armodafinil

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh	5294
2	Armodafinil OR Nuvigil	176
3	1 AND 2	40

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	Armodafinil OR Nuvigil	264
5	3 AND 4	36

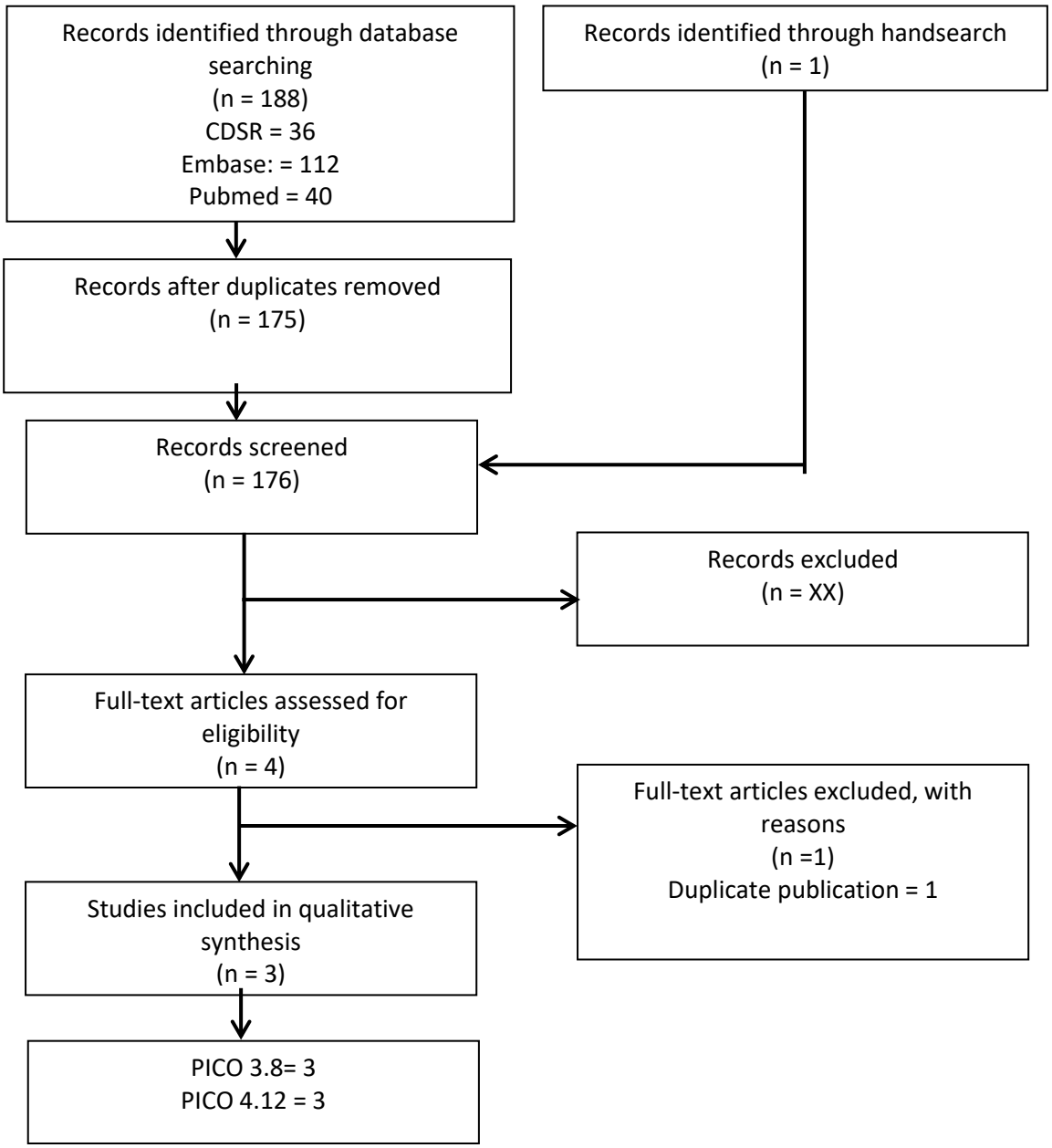
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9523
4	'armodafinil':ti,ab,kw OR 'nuvigil':ti,ab,kw	311
5	3 AND 4	212
6	5 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim	112

Flow-chart of studies: Armodafinil

PICOs
3.8: Armodafinil for improvement of excessive daytime sleepiness, adults
4.12: Armodafinil for improvement of moderate to severe cataplexy, adults

Figure e17: August 2018 run (October 2019 update).



Search strategy: Pitolisant

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5307
2	pitolisant OR wakix OR tiprolisant OR "bf2 649" OR "1 3 3 4 chlorophenyl propoxy propyl piperidine"	68
3	1 AND 2	36

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	pitolisant:ti,ab,kw OR wakix:ti,ab,kw OR tiprolisant:ti,ab,kw OR "bf2 649":ti,ab,kw OR "1 3 3 4 chlorophenyl propoxy propyl piperidine":ti,ab,kw	34
5	3 AND 4	17

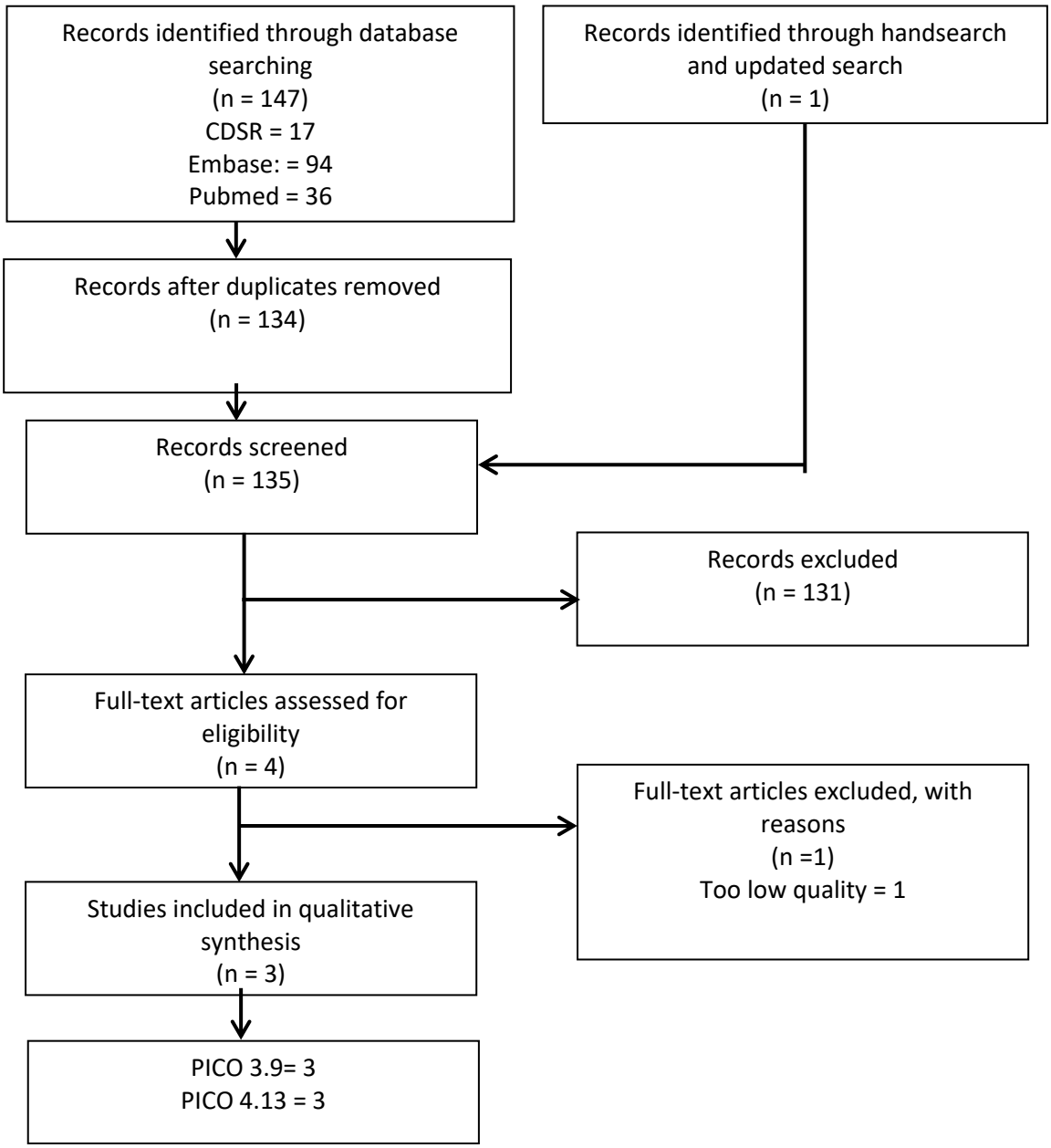
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9524
4	'1 [3 [3 (4 chlorophenyl) propoxy] propyl] piperidine':ti,ab,kw OR 'pitolisant':ti,ab,kw OR 'wakix':ti,ab,kw OR 'tiprolisant':ti,ab,kw OR 'bf2 649':ti,ab,kw	115
5	'pitolisant'/exp	195
6	4 OR 5	208
7	3 AND 6	120
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	94

Flow-chart of studies: Pitolisant

PICOs
3.9: Pitolisant for improvement of excessive daytime sleepiness, adults
4.13: Pitolisant for improvement of moderate to severe cataplexy, adults

Figure e18: August 2018 run (October 2019 update).



Search strategy: Selegiline

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	Selegiline[Title/Abstract] OR Eldepryl[Title/Abstract] OR Yumex[Title/Abstract] OR Jumex[Title/Abstract] OR Humex[Title/Abstract] OR Zelapar[Title/Abstract] OR Deprenyl[Title/Abstract] OR Deprenyl[Title/Abstract] OR E-250[Title/Abstract] OR E250[Title/Abstract] OR Emsam[Title/Abstract] OR Deprenalin[Title/Abstract] OR Deprenil[Title/Abstract] OR "Selegiline"[Mesh]	3543
3	1 AND 2	15

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Selegiline] explode all trees	245
5	Eldepryl:ti,ab,kw OR Yumex:ti,ab,kw Or Jumex:ti,ab,kw OR Humex:ti,ab,kw OR Zelapar:ti,ab,kw OR Deprenyl:ti,ab,kw OR E-250:ti,ab,kw OR E250:ti,ab,kw OR Emsam:ti,ab,kw OR Deprenalin:ti,ab,kw OR Deprenil:ti,ab,kw OR selegiline:ti,ab,kw	516
6	4 OR 5	516
7	3 AND 6	4

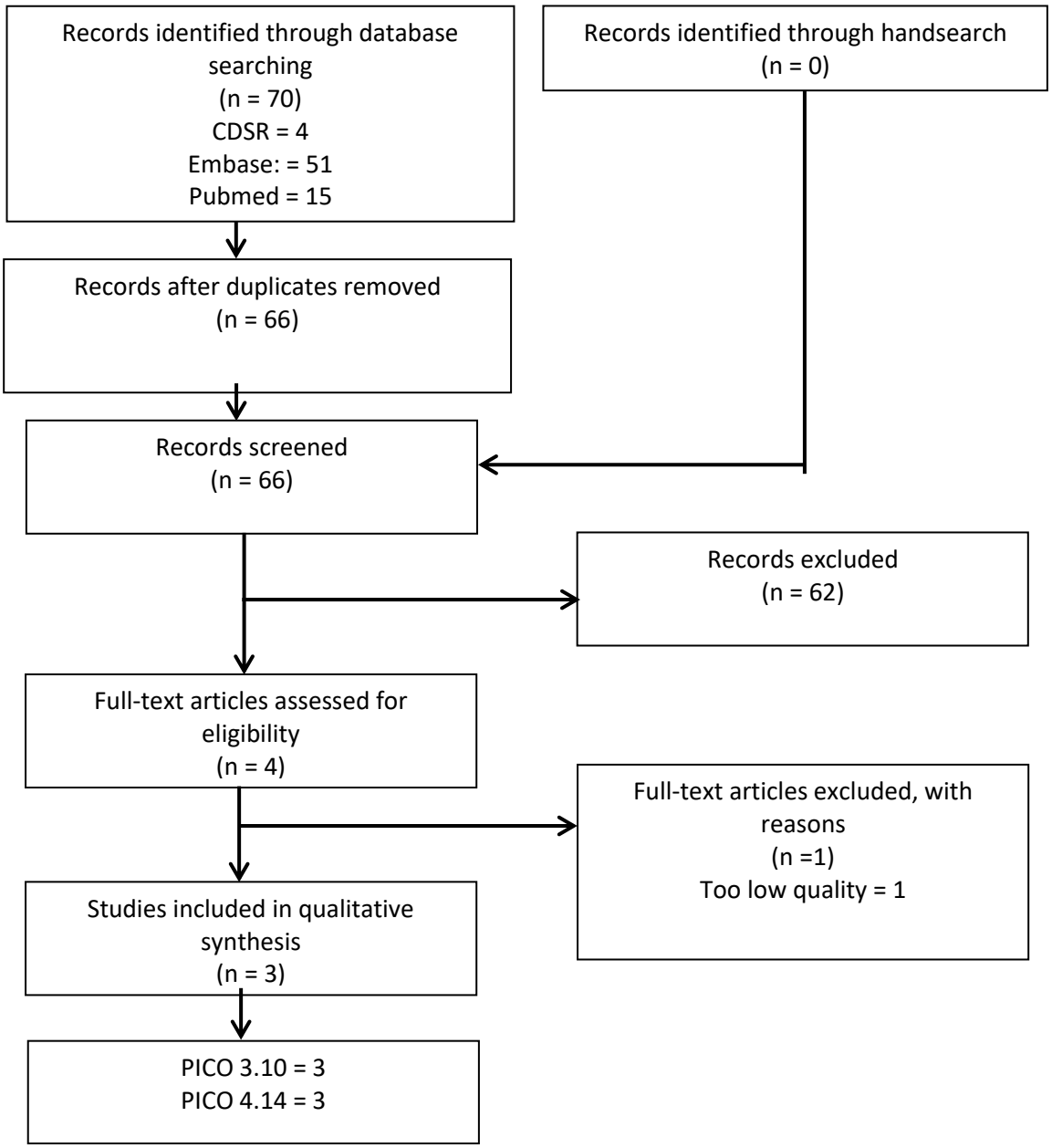
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'selegiline'/exp	9395
5	'eldepryl':ti,ab,kw OR 'yumex':ti,ab,kw OR 'jumex':ti,ab,kw OR 'humex':ti,ab,kw OR 'zelapar':ti,ab,kw OR 'deprenyl':ti,ab,kw OR 'e-250':ti,ab,kw OR 'e250':ti,ab,kw OR 'emsam':ti,ab,kw OR 'deprenalin':ti,ab,kw OR 'deprenil':ti,ab,kw OR 'selegiline':ti,ab,kw	3869
6	4 OR 5	10086
7	3 AND 6	151
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	51

Flow-chart of studies: Selegiline

PICOs
3.10: Selegiline for improvement of excessive daytime sleepiness, adults
4.14: Selegiline for improvement of moderate to severe cataplexy, adults

Figure e19: October 2018 run (October 2019 update).



Search strategy: Caffeine

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh	5309
2	Caffeine[MeSH Terms] OR Caffeine[Title/Abstract] OR “Coffee“[Mesh] OR Coffee[Title/Abstract] OR Coffea[Title/Abstract])	42470
3	1 AND 2	28

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Coffee] explode all tree	351
5	Caffeine:ti,ab,kw OR Coffee:ti,ab,kw OR Coffea:ti,ab,kw	4034
6	4 OR 5	4034
7	3 AND 6	3

EMBASE

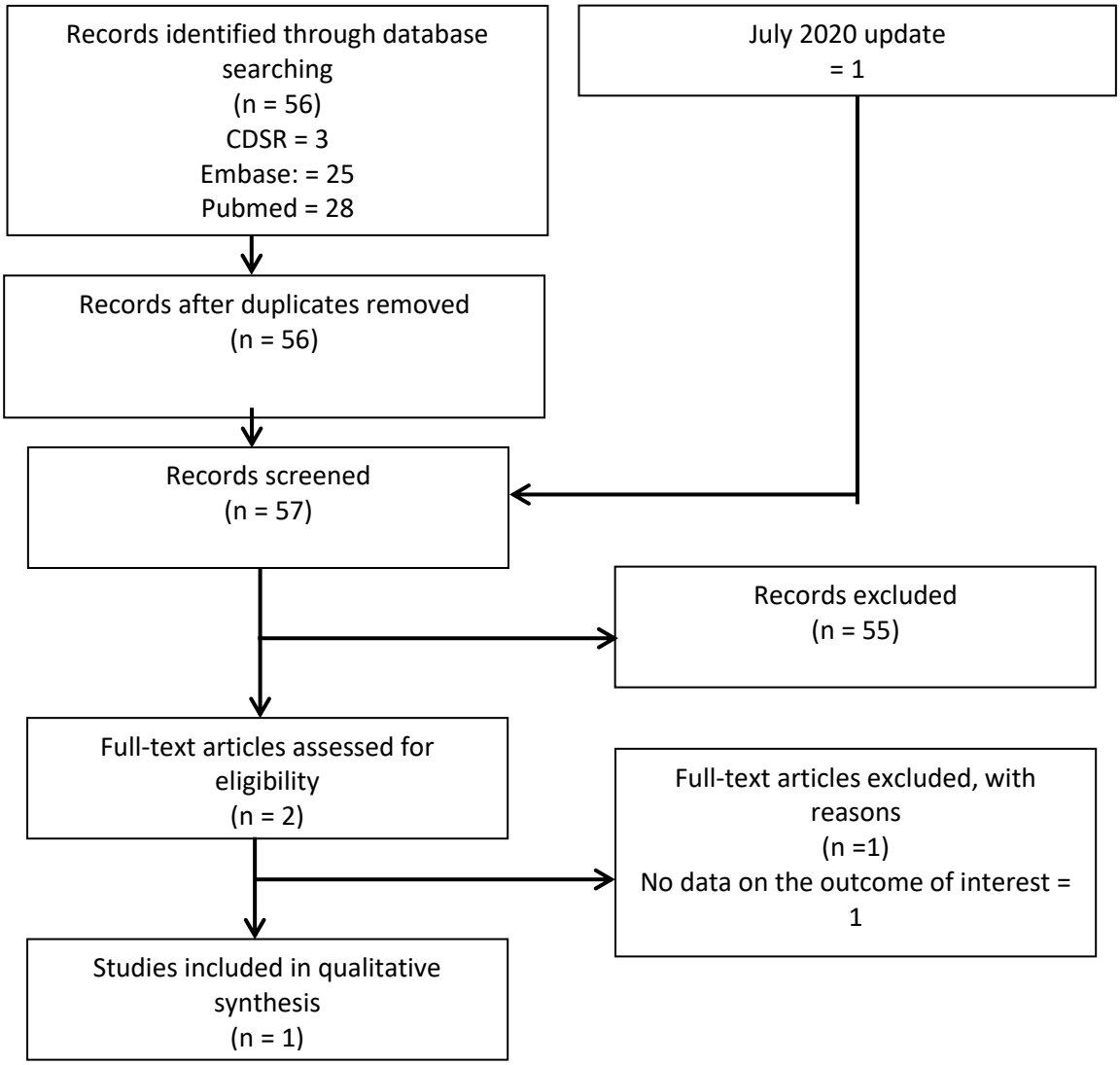
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'coffee'/exp	13169
5	'caffeine':ti,ab,kw OR 'coffee':ti,ab,kw OR 'coffea':ti,ab,kw	46130
7	4 OR 5	48168
8	3 AND 7	62
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	25

Flow-chart of studies: Caffeine

PICO

3.11: Caffeine for improvement of excessive daytime sleepiness, adults

Figure e20: August 2018 run (October 2019 and July 2020 updates).



Search strategy: Antidepressants

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"Clomipramine"[Mesh] OR "Venlafaxine Hydrochloride"[Mesh] OR Clomipramine[Title/Abstract] OR Chlorimipramine[Title/Abstract] OR Anafranil[Title/Abstract] OR Hydiphen[Title/Abstract] OR Venlafaxine[Title/Abstract] OR Effexor[Title/Abstract] OR Trevilor[Title/Abstract] OR Vandral[Title/Abstract] OR Efexor[Title/Abstract] OR Dobupal[Title/Abstract] OR "wy45030"[Title/Abstract] OR "Duloxetine Hydrochloride"[Mesh] OR Duloxetine[Title/Abstract] OR Cymbalta[Title/Abstract] OR "Viloxazine"[Mesh]) OR Emovit[Title/Abstract] OR viloxazine[Title/Abstract] OR reboxetine) OR "ly139603" OR "Atomoxetine Hydrochloride"[Mesh] OR Atomoxetine[Title/Abstract] OR Tomoxetine[Title/Abstract] OR strattera OR "Imipramine"[Mesh] OR "imizin"[Title/Abstract] OR "tofranil"[Title/Abstract] OR "melipramine"[Title/Abstract] OR "imipramine tofranil"[Title/Abstract]) OR "janimine"[Title/Abstract] OR "Protriptyline"[Mesh] OR "vivactil"[Title/Abstract] OR "protriptyline"[Title/Abstract] OR "selective serotonin re uptake" OR "selective serotonergic reuptake inhibitors" OR "selective serotonergic uptake" OR "selective serotonergic uptake inhibitors" OR "serotonin uptake inhibitors" OR "serotonin specific reuptake inhibitor" OR "Fluoxetine"[Mesh] OR "femoxetine" OR "femoxetine"[Supplementary Concept] OR "fluoxetin"[Title/Abstract] OR "lilly 110140"[Title/Abstract] OR Sarafem[Title/Abstract] OR prozac[Title/Abstract]OR Fluvoxadura[Title/Abstract] OR Fluvoxamin[Title/Abstract] OR Luvox[Title/Abstract] OR Floxyfral[Title/Abstract] OR Fevarin OR Dumirox OR Favoring OR Desiflu[Title/Abstract] OR "Fluvoxamine"[Mesh] OR "du 23000" OR "Citalopram"[Mesh] OR Cytalopram[Title/Abstract] OR Escitalopram OR Lexapro[Title/Abstract] OR paroxetine[MeSH Terms] OR Paroxetine[Title/Abstract] OR Seroxat[Title/Abstract] OR Paxil[Title/Abstract] OR Aropax[Title/Abstract] OR "Antidepressive Agents, Tricyclic"[MeSH Terms] OR "tricyclic anti depressant"[Title/Abstract] OR "tricyclic anti depressants"[Title/Abstract] OR "tricyclic anti depressives"[Title/Abstract] OR "tricyclic antidepressant"[Title/Abstract] OR "tricyclic antidepressant agent"[Title/Abstract] OR "tricyclic antidepressant agents"[Title/Abstract] OR "tricyclic antidepressant drugs"[Title/Abstract]	84253
3	1 AND 2	235

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	351
4	MeSH descriptor: [Clomipramine] OR MeSH descriptor: [Venlafaxine Hydrochloride] 0R MeSH descriptor: [Duloxetine Hydrochloride OR MeSH descriptor: [Viloxazine] OR MeSH descriptor: [Atomoxetine Hydrochloride] OR MeSH descriptor: [Imipramine] OR MeSH descriptor: [Protriptyline] OR MeSH descriptor: [Fluoxetine] OR MeSH descriptor: [Fluvoxamine] OR MeSH descriptor: [Citalopram] OR MeSH descriptor: [Paroxetine] OR MeSH descriptor: [Antidepressive Agents, Tricyclic]	12720
5	Clomipramine:ti,ab,kw OR Chlorimipramine:ti,ab,kw OR Anafranil:ti,ab,kw OR Hydiphen:ti,ab,kw OR Venlafaxine:ti,ab,kw OR Effexor:ti,ab,kw OR Trevilor:ti,ab,kw OR Vandral:ti,ab,kw OR Efexor:ti,ab,kw OR Dobupal:ti,ab,kw OR wy45030:ti,ab,kw OR Duloxetine:ti,ab,kw OR Cymbalta:ti,ab,kw OR Emovit:ti,ab,kw OR viloxazine:ti,ab,kw OR reboxetine:ti,ab,kw OR ly139603:ti,ab,kw OR Atomoxetine:ti,ab,kw OR Tomoxetine:ti,ab,kw OR strattera:ti,ab,kw OR imizin:ti,ab,kw OR tofranil:ti,ab,kw OR melipramin:ti,ab,kw OR "imipramine tofranil":ti,ab,kw OR janimine:ti,ab,kw OR vivactil:ti,ab,kw OR protriptyline:ti,ab,kw OR "selective serotonin re uptake":ti,ab,kw OR "selective serotonergic reuptake inhibitors":ti,ab,kw OR "selective serotonergic uptake":ti,ab,kw OR "selective serotonergic uptake inhibitors":ti,ab,kw OR "serotonin uptake inhibitors":ti,ab,kw OR "serotonin specific reuptake inhibitor":ti,ab,kw OR emoxetin:ti,ab,kw OR femoxetine:ti,ab,kw OR fluoxetin:ti,ab,kw OR "lilly 110140":ti,ab,kw OR Sarafem:ti,ab,kw OR prozac:ti,ab,kw OR Fluvoxadura:ti,ab,kw OR Fluvoxamin:ti,ab,kw OR Luvox:ti,ab,kw OR Floxyfral:ti,ab,kw OR Fevarin:ti,ab,kw OR Dumirox:ti,ab,kw OR Favoring:ti,ab,kw OR Desiflu:ti,ab,kw OR "du 23000":ti,ab,kw OR Cytalopram:ti,ab,kw OR Escitalopram:ti,ab,kw OR Lexapro:ti,ab,kw OR	29190

	Paroxetine:ti,ab,kw OR Seroxat:ti,ab,kw OR Paxil:ti,ab,kw OR Aropax:ti,ab,kw OR "tricyclic anti depressant":ti,ab,kw OR "tricyclic anti depressants":ti,ab,kw OR "tricyclic anti depressives":ti,ab,kw OR "tricyclic antidepressant":ti,ab,kw OR "tricyclic antidepressant agent":ti,ab,kw OR "tricyclic antidepressant agents":ti,ab,kw OR "tricyclic antidepressant drugs":ti,ab,kw	
6	4 OR 5	31397
7	3 AND 4	24

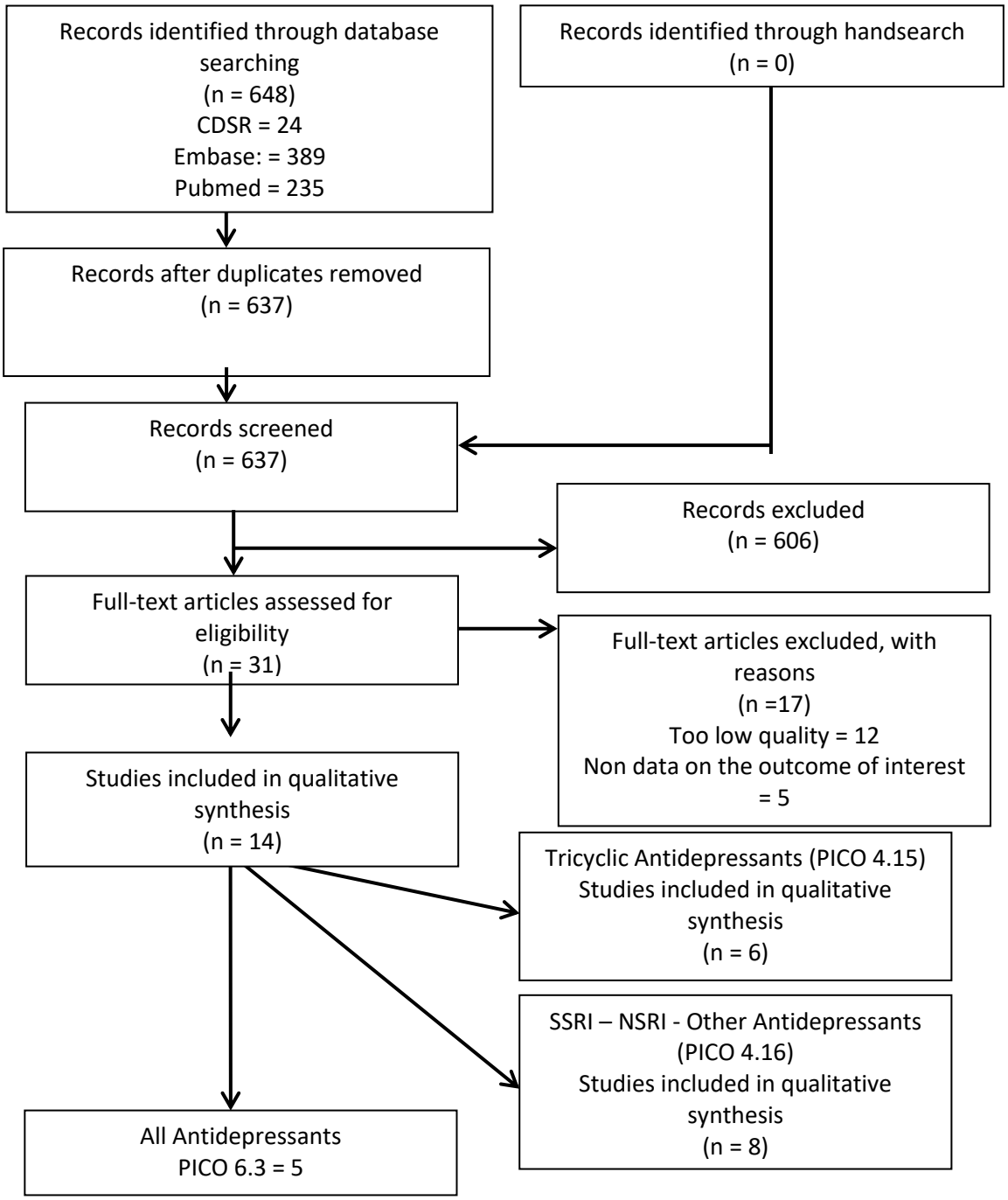
EMBASE

#	Search	Results
1	'narcolepsy'/exp	
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7995
3	1 OR 2	9526
4	'clomipramine'/exp OR 'venlafaxine'/exp OR 'duloxetine'/exp OR 'viloxazine'/exp OR 'atomoxetine'/exp OR 'imipramine'/exp OR 'protriptyline'/exp OR 'fluoxetine'/exp OR 'fluvoxamine'/exp OR 'citalopram'/exp OR 'paroxetine'/exp OR 'tricyclic antidepressant agent'/exp	164018
5	'clomipramine':ti,ab,kw OR 'chlorimipramine':ti,ab,kw OR 'anafranil':ti,ab,kw OR 'hydiphen':ti,ab,kw OR 'venlafaxine':ti,ab,kw OR 'effexor':ti,ab,kw OR 'trevilor':ti,ab,kw OR 'vandral':ti,ab,kw OR 'efexor':ti,ab,kw OR 'dobupal':ti,ab,kw OR 'wy45030':ti,ab,kw OR 'duloxetine':ti,ab,kw OR 'cymbalta':ti,ab,kw OR 'emovit':ti,ab,kw OR 'viloxazine':ti,ab,kw OR 'reboxetine':ti,ab,kw OR 'ly139603':ti,ab,kw OR 'atomoxetine':ti,ab,kw OR 'tomoxetine':ti,ab,kw OR 'strattera':ti,ab,kw OR 'imizin':ti,ab,kw OR 'tofranil':ti,ab,kw OR 'melipramine':ti,ab,kw OR 'imipramine tofranil':ti,ab,kw OR 'janimine':ti,ab,kw OR 'vivactil':ti,ab,kw OR 'protriptyline':ti,ab,kw OR 'selective serotonin re uptake':ti,ab,kw OR 'selective serotonergic reuptake inhibitors':ti,ab,kw OR 'selective serotonergic uptake':ti,ab,kw OR 'selective serotonergic uptake inhibitors':ti,ab,kw OR 'serotonin uptake inhibitors':ti,ab,kw OR 'serotonin specific reuptake inhibitor':ti,ab,kw OR 'femoxetine':ti,ab,kw OR 'fluoxetin':ti,ab,kw OR 'lilly 110140':ti,ab,kw OR 'sarafem':ti,ab,kw OR 'prozac':ti,ab,kw OR 'fluvoxadura':ti,ab,kw OR 'fluvoxamin':ti,ab,kw OR 'luvox':ti,ab,kw OR 'floxyfral':ti,ab,kw OR 'fevarin':ti,ab,kw OR 'dumirox':ti,ab,kw OR 'favoring':ti,ab,kw OR 'desiflu':ti,ab,kw OR 'du 23000':ti,ab,kw OR 'cytalopram':ti,ab,kw OR 'escitalopram':ti,ab,kw OR 'lexapro':ti,ab,kw OR 'paroxetine':ti,ab,kw OR 'seroxat':ti,ab,kw OR 'paxil':ti,ab,kw OR 'aropax':ti,ab,kw OR 'tricyclic anti depressant':ti,ab,kw OR 'tricyclic anti depressants':ti,ab,kw OR 'tricyclic anti depressives':ti,ab,kw OR 'tricyclic antidepressant':ti,ab,kw OR 'tricyclic antidepressant agent':ti,ab,kw OR 'tricyclic antidepressant agents':ti,ab,kw OR 'tricyclic antidepressant drugs':ti,ab,kw	54330
6	4 OR 5	190894
7	6 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim	389

Flow-chart of studies: Antidepressants

PICOs
4.15: Tricyclic Antidepressants for improvement of moderate to severe cataplexy, adults
4.16: SSRI – NSRI - Other Antidepressants for improvement of moderate to severe cataplexy, adults
6.3: Antidepressants for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e21: August 2018 run (October 2019 update).



Search strategy: Baclofen

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh	5294
2	Lebic[Title/Abstract] OR Lioresal[Title/Abstract] OR Atrofen[Title/Abstract] OR Clofen[Title/Abstract] OR baclofen[Title/Abstract] OR Baclofen[MeSH Terms]	7645
3	1 AND 2	15

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	MeSH descriptor: [Baclofen] explode all tree	244
5	lebic:ti,ab,kw OR Lioresal:ti,ab,kw OR Atrofen:ti,ab,kw OR Clofen:ti,ab,kw OR baclofen:ti,ab,kw	606
6	4 OR 5	606
7	3 AND 6	1

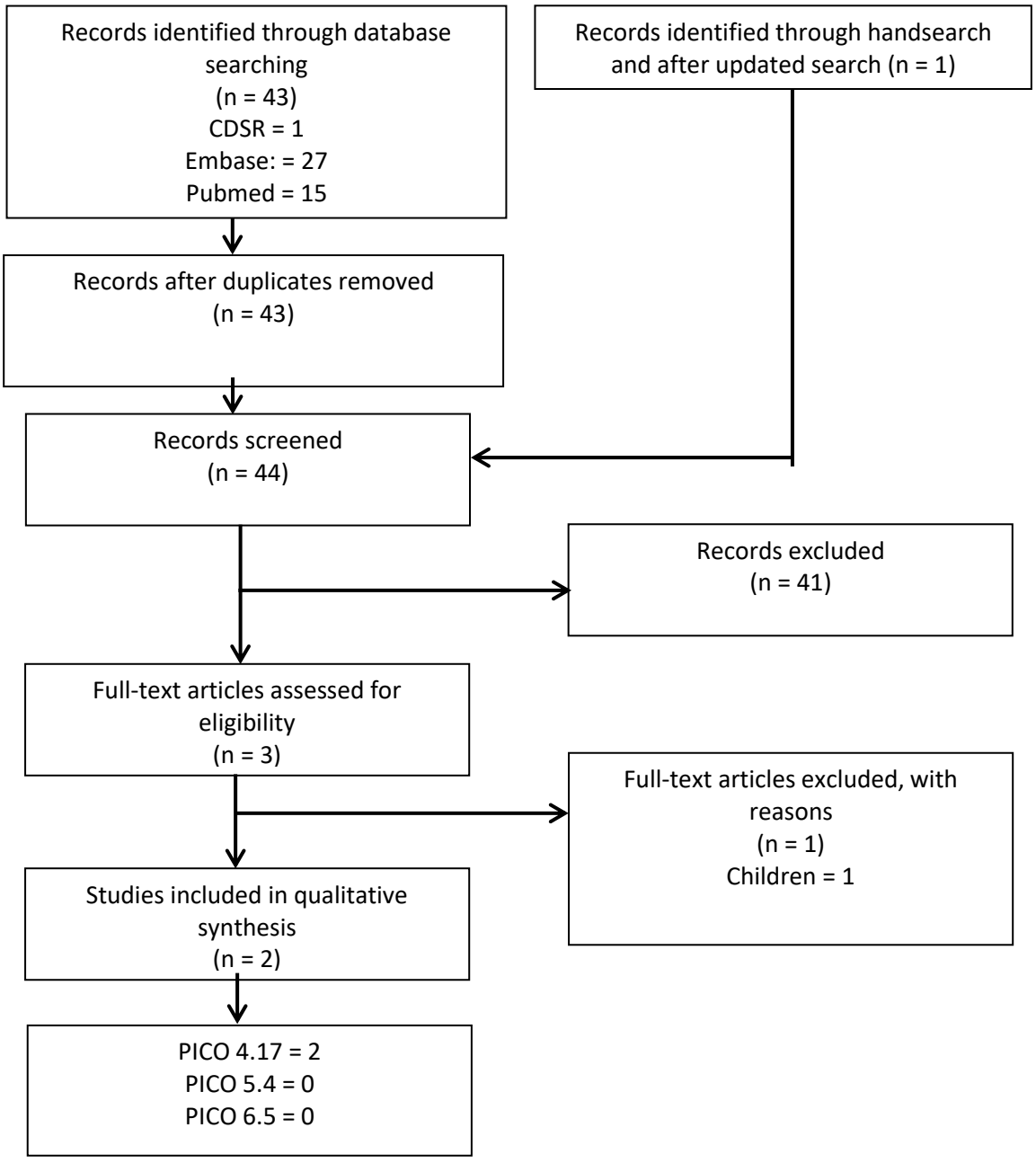
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9523
4	'baclofen'/exp	16907
5	'lebic':ti,ab,kw OR 'lioresal':ti,ab,kw OR 'atrofen':ti,ab,kw OR 'clofen':ti,ab,kw OR 'baclofen':ti,ab,kw	9065
7	4 OR 5	17642
8	3 AND 7	76
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	27

Flow-chart of studies: Baclofen

PICOs
4.17: Baclofen for improvement of moderate to severe cataplexy, adults
5.4: Baclofen for improvement of moderate to severe night time disturbed sleep, adults
6.5: Baclofen for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e22: August 2018 run (October 2019 update).



Search strategy: Benzodiazepines

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh	5309
2	(benzodiazepine*[title/abstract] OR Alprazolam[Title/Abstract] OR Nordazepam[Title/Abstract] OR Benzodiazepinone*[Title/Abstract] OR Bromazepam OR Clonazepam[Title/Abstract] OR Devazepide OR Diazepam[Title/Abstract] OR Flumazenil[Title/Abstract] OR Flunitrazepam[Title/Abstract] OR Flurazepam[Title/Abstract] OR Lorazepam[Title/Abstract] OR Nitrazepam[Title/Abstract] OR Oxazepam[Title/Abstract] OR Pirenzepine[Title/Abstract] OR Prazepam[Title/Abstract] OR Temazepam[Title/Abstract] OR Chlordiazepoxide[Title/Abstract] OR Clorazepate[Title/Abstract] OR Estazolam[Title/Abstract] OR Medazepam[Title/Abstract] OR Midazolam[Title/Abstract] OR Triazolam[Title/Abstract] OR "Benzodiazepines"[Mesh])	90041
3	1 AND 2	107

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Benzodiazepines] explode all trees	8727
5	benzodiazepine*:ti,ab,kw OR Alprazolam:ti,ab,kw OR Nordazepam:ti,ab,kw OR Benzodiazepinone*:ti,ab,kw OR Bromazepam:ti,ab,kw OR Clonazepam:ti,ab,kw OR Devazepide:ti,ab,kw OR Diazepam:ti,ab,kw OR Flumazenil:ti,ab,kw OR Flunitrazepam:ti,ab,kw OR Flurazepam:ti,ab,kw OR Lorazepam:ti,ab,kw OR Nitrazepam:ti,ab,kw OR Oxazepam:ti,ab,kw OR Pirenzepine:ti,ab,kw OR Prazepam:ti,ab,kw OR Temazepam:ti,ab,kw OR Chlordiazepoxide:ti,ab,kw OR Clorazepate:ti,ab,kw OR Estazolam:ti,ab,kw OR Medazepam:ti,ab,kw OR Midazolam:ti,ab,kw OR Triazolam:ti,ab,kw	20010
6	4 OR 5	2010
7	3 AND 6	17

EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9539
4	'benzodiazepine derivative'/exp	205772
5	'benzodiazepine*':ti,ab,kw OR 'alprazolam':ti,ab,kw OR 'nordazepam':ti,ab,kw OR 'benzodiazepinone*':ti,ab,kw OR 'bromazepam':ti,ab,kw OR 'clonazepam':ti,ab,kw OR 'devazepide':ti,ab,kw OR 'diazepam':ti,ab,kw OR 'flumazenil':ti,ab,kw OR 'flunitrazepam':ti,ab,kw OR 'flurazepam':ti,ab,kw OR 'lorazepam':ti,ab,kw OR 'nitrazepam':ti,ab,kw OR 'oxazepam':ti,ab,kw OR 'pirenzepine':ti,ab,kw OR 'prazepam':ti,ab,kw OR 'temazepam':ti,ab,kw OR 'chlordiazepoxide':ti,ab,kw OR 'clorazepate':ti,ab,kw OR 'estazolam':ti,ab,kw OR 'medazepam':ti,ab,kw OR 'midazolam':ti,ab,kw OR 'triazolam':ti,ab,kw	97453
7	4 OR 5	225084
8	3 AND 7	741
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	261

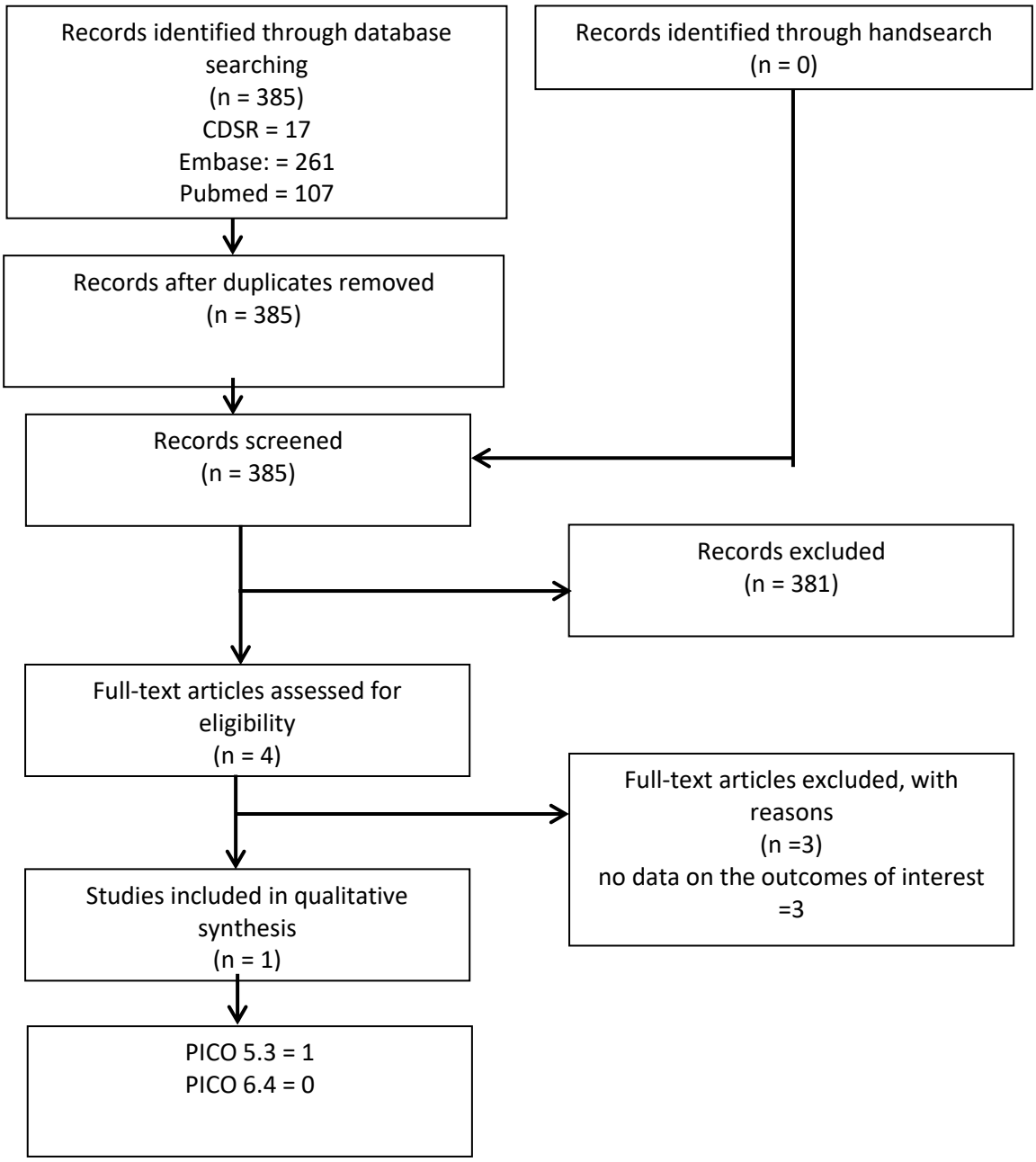
Flow-chart of studies: Benzodiazepines

PICOs

5.3: Benzodiazepines for improvement of moderate to severe night time disturbed sleep, adults

6.4: Benzodiazepines for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e23: August 2018 run (October 2019 update).



Search strategy: Gabapentin

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	gabapentin[Title/Abstract] OR Convalis[Title/Abstract] OR Neurontin[Title/Abstract]	6117
3	1 AND 2	2

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	gabapentin:ti,ab,kw OR Convalis:ti,ab,kw OR Neurontin:ti,ab,kw	1774
5	3 AND 4	1

EMBASE

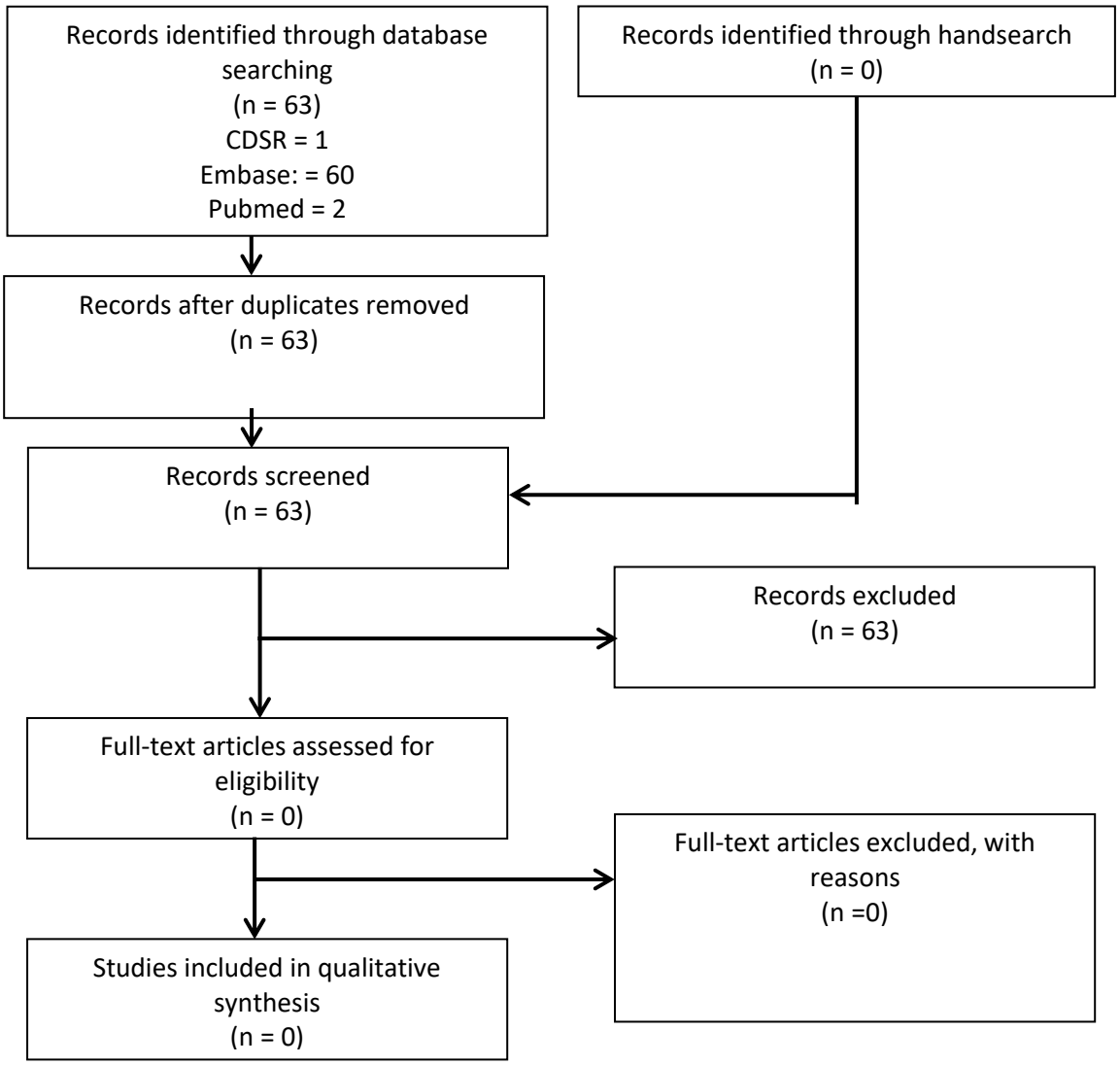
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'gabapentin'/exp	27050
5	'convalis':ti,ab,kw OR 'gabapentin':ti,ab,kw	8685
7	4 OR 5	27702
8	3 AND 7	148
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	60

Flow-chart of studies: Gabapentin

PICOs

5.5: Gabapentin for improvement of moderate to severe night time disturbed sleep, adults
6.6: Gabapentin for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e24: August 2018 run (October 2019 update).



Search strategy: Pregabalin

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"3 aminomethyl 5 methylhexanoic acid"[Title/Abstract] OR "s 3 aminomethyl 5 methylhexanoic acid"[Title/Abstract] OR "3 isobutyl gaba"[Title/Abstract] OR "ci1008"[Title/Abstract] OR "ci 1008"[Title/Abstract] OR Lyrica[Title/Abstract] OR Pregabalin[Title/Abstract] OR "Pregabalin"[Mesh]	3067
3	1 AND 2	1

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Pregabalin] explode all trees	611
5	"3 aminomethyl 5 methylhexanoic acid":ti,ab,kw OR "s 3 aminomethyl 5 methylhexanoic acid":ti,ab,kw OR "3 isobutyl gaba":ti,ab,kw OR "ci1008":ti,ab,kw OR "ci 1008":ti,ab,kw OR Lyrica:ti,ab,kw OR Pregabalin:ti,ab,kw	1411
6	4 OR 5	1411
7	3 AND 6	1

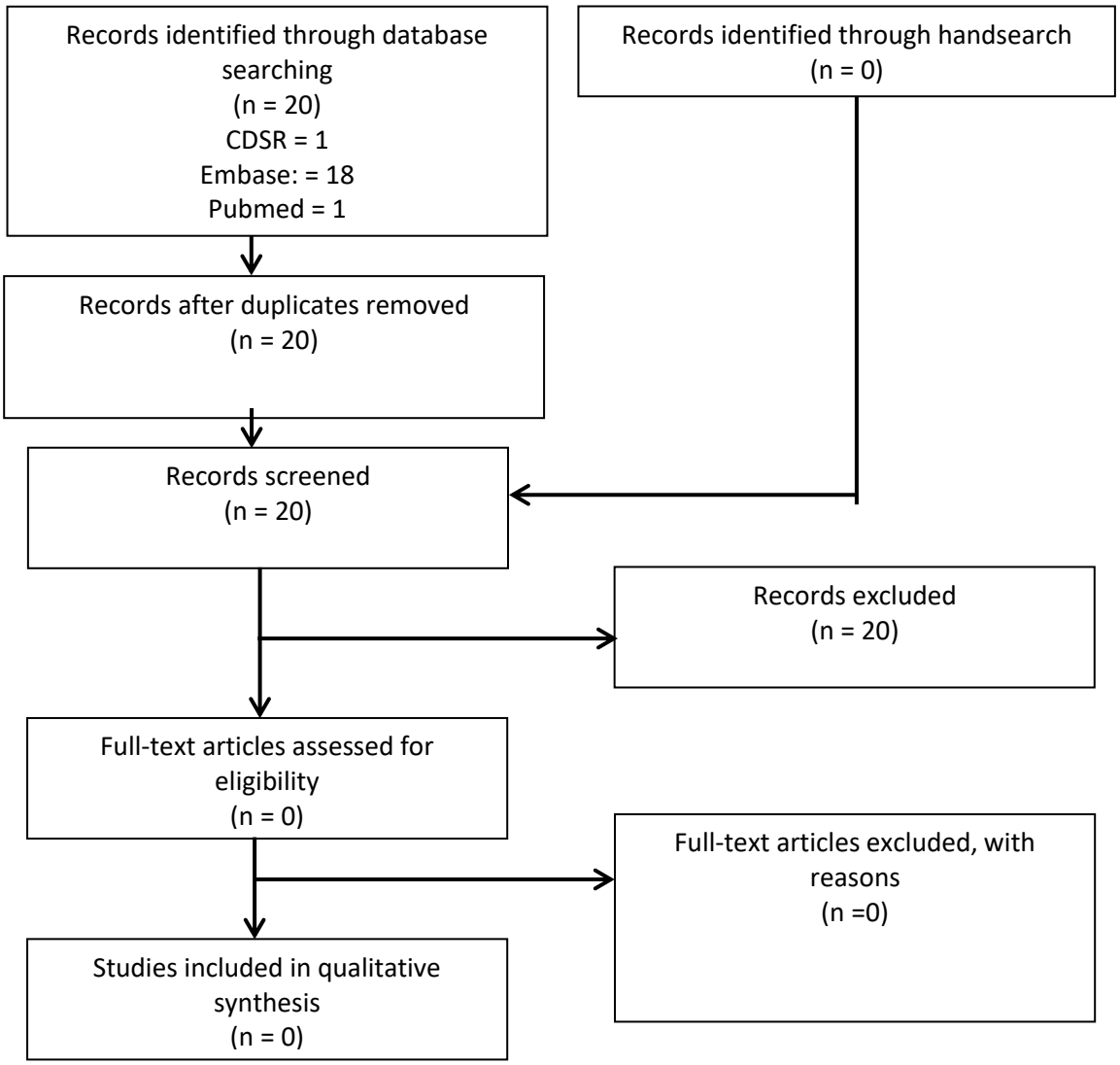
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'pregabalin'/exp	11817
5	"3 aminomethyl 5 methylhexanoic acid":ti,ab,kw OR "s 3 aminomethyl 5 methylhexanoic acid":ti,ab,kw OR "3 isobutyl gaba":ti,ab,kw OR "ci1008":ti,ab,kw OR "ci 1008":ti,ab,kw OR Lyrica:ti,ab,kw OR Pregabalin:ti,ab,kw:ti,ab,kw	5106
6	4 OR 5	12112
7	3 AND 6	50
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	18

Flow-chart of studies: Pregabalin

PICOs
5.6: Pregabalin for improvement of moderate to severe night time disturbed sleep, adults
6.7: Pregabalin for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e25: August 2018 run (October 2019 update).



Search strategy: Melatonin

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	Melatonin*[Title/Abstract]) OR "Melatonin"[Mesh]	23592
3	1 AND 2	48

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	360
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	MeSH descriptor: [Melatonin] explode all tree	1048
5	melatonin*:ti,ab,kw	1967
6	4 OR 5	1967
7	3 AND 6	4

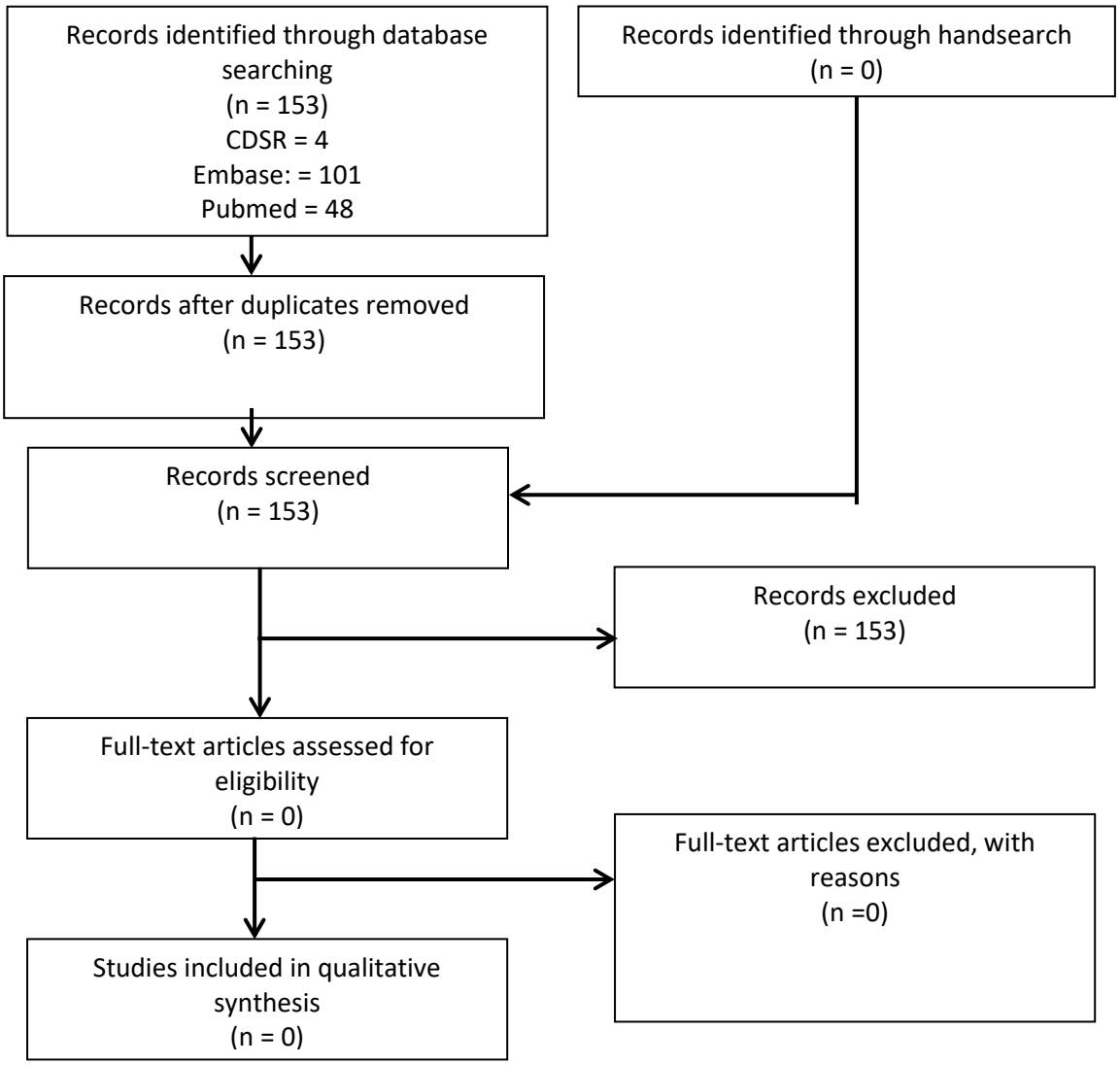
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'melatonin'/exp	30889
5	melatonin*:ti,ab,kw	27591
6	4 OR 5	34417
7	3 AND 6	296
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	101

Flow-chart of studies: Melatonin

PICOs
5.7: Melatonin for improvement of moderate to severe night time disturbed sleep, adults
6.8: Melatonin for improvement of moderate to severe sleep paralysis/ hypnagogic and hypnopompic hallucinations, adults

Figure e26: August 2018 run (October 2019 update).



Search strategy: psychiatric symptoms (insomnia scales improvement)

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5293
2	("Sleep Initiation and Maintenance Disorders"[Mesh:NoExp]) AND (index[Title/Abstract] OR scale*[Title/Abstract])	2237
3	"insomnia severity index"[Title/Abstract] OR insomnia severity scale*[Title/Abstract] OR insomnia scale*[Title/Abstract] OR narcolepsy scale*[Title/Abstract]	935
4	2 OR 3	2662
5	1 AND 4	48

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	360
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	MeSH descriptor: [Sleep Initiation and Maintenance Disorders] this term only 2013 AND (index OR scale*):ti,ab,kw	735
5	insomnia NEAR/3 scale*	317
6	insomnia NEAR/3 index	580
7	4 OR 5 OR 6	1549
8	3 AND 7	3

EMBASE

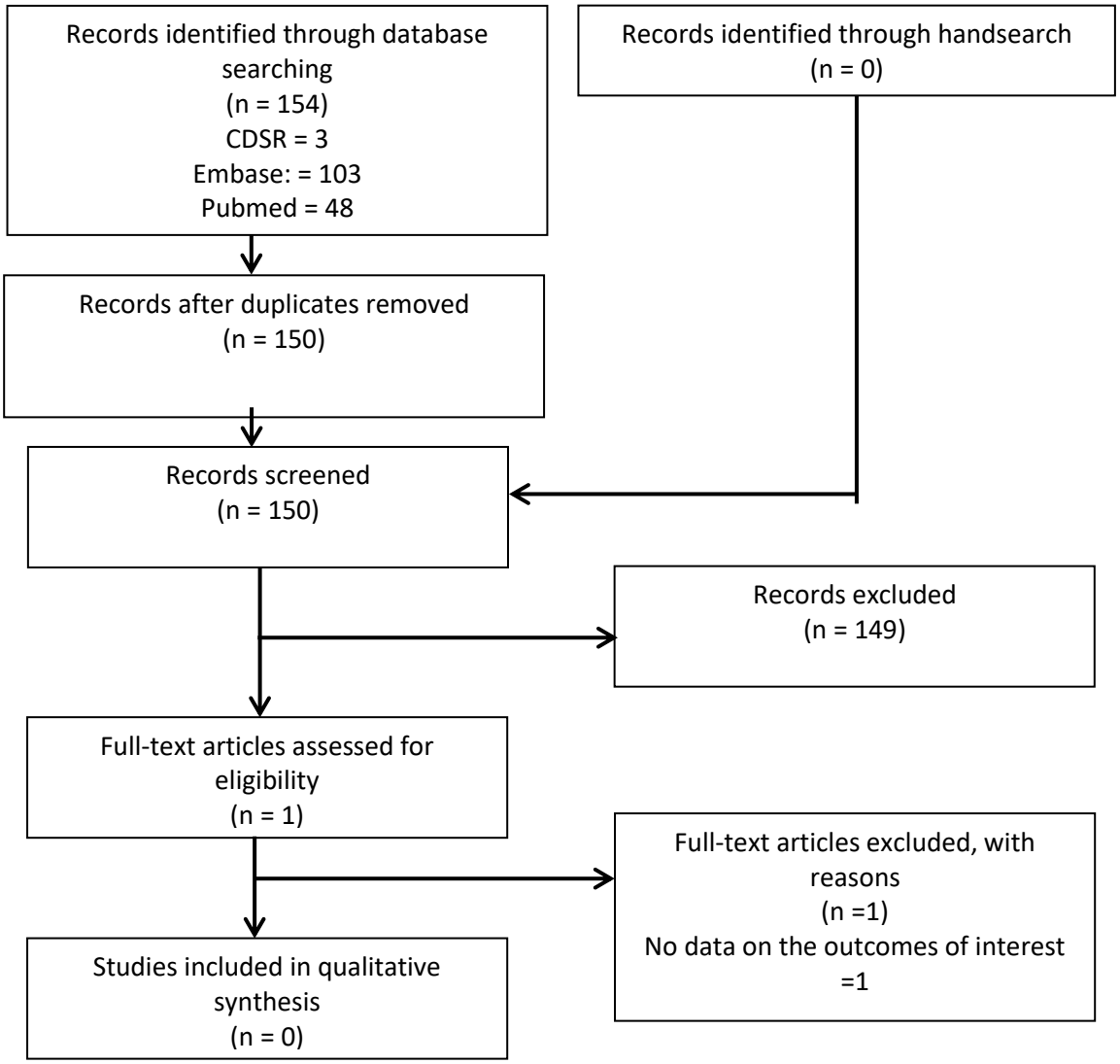
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9542
4	'insomnia'/de	59481
5	'scale*':ti,ab,kw OR 'index':ti,ab,kw	1753507
6	4 AND #5	12097
7	('insomnia' NEAR/3 'scale*'):ti,ab,kw OR ('insomnia' NEAR/3 'index'):ti,ab,kw	2621
8	6 OR 7	12453
9	3 AND 8	202
10	9 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	103

Flow-chart of studies: psychiatric symptoms (insomnia scales improvement)

PICO

7: Any symptomatic treatment for psychiatric symptoms (insomnia scales improvement)

Figure e27: August 2018 run (October 2019 update).



Search strategy: psychiatric symptoms (anxiety and mood scales)

PUBMED

#	Search	Results
1	(narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh])	5310
2	"Mental Disorders"[Mesh:NoExp]) AND (Scale*[Title/Abstract] OR index[Title/Abstract])	10883
3	"Hamilton Anxiety Rating Scale"[Title/Abstract] OR "Manifest Anxiety Scale"[Mesh] OR hamilton scale*[Title/Abstract] OR hamilton score*[Title/Abstract] OR "Test Anxiety Scale"[Mesh] OR anxiety scale*[Title/Abstract] OR "ymrs"[Title/Abstract] OR mood scale*[Title/Abstract] OR "Psychiatric Status Rating Scales"[Mesh] OR bdi[Title/Abstract] OR hamd[Title/Abstract]) OR "hamilton Rating Scale" OR "Young Mania Rating Scale"[Title/Abstract] OR "beck depression inventory"[Title/Abstract] OR Zung[Title/Abstract]	97905
4	2 OR 3	106225
5	1 AND 4	68

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	360
2	MeSH descriptor: [Narcolepsy] explode all tree	130
3	1 OR 2	360
4	'Hamilton Anxiety Rating Scale': ti,ab,kwn OR 'hamilton scale':ti,ab,kw OR 'hamilton scales':ti,ab,kw OR 'hamilton score':ti,ab,kw OR 'hamilton scores':ti,ab,kw OR 'anxiety scale':ti,ab,kw OR 'anxiety scales':ti,ab,kw OR 'ymrs':ti,ab,kw OR 'mood scale':ti,ab,kw OR 'mood scales':ti,ab,kw OR bdi: ti,ab,kw OR hamd: ti,ab,kw OR 'hamilton Rating Scale':ti,ab,kw OR 'Young Mania Rating Scale':ti,ab,kw OR 'beck depression inventory':ti,ab,kw OR Zung:ti,ab,kw	23561
5	MeSH descriptor:[Manifest Anxiety Scale]explode all tree OR MeSH descriptor:[Test Anxiety Scale]explode all tree OR MeSH descriptor: [Psychiatric Status Rating Scales] explode all tree	9585
6	4 OR 5	28999
7	3 AND 6	38

EMBASE

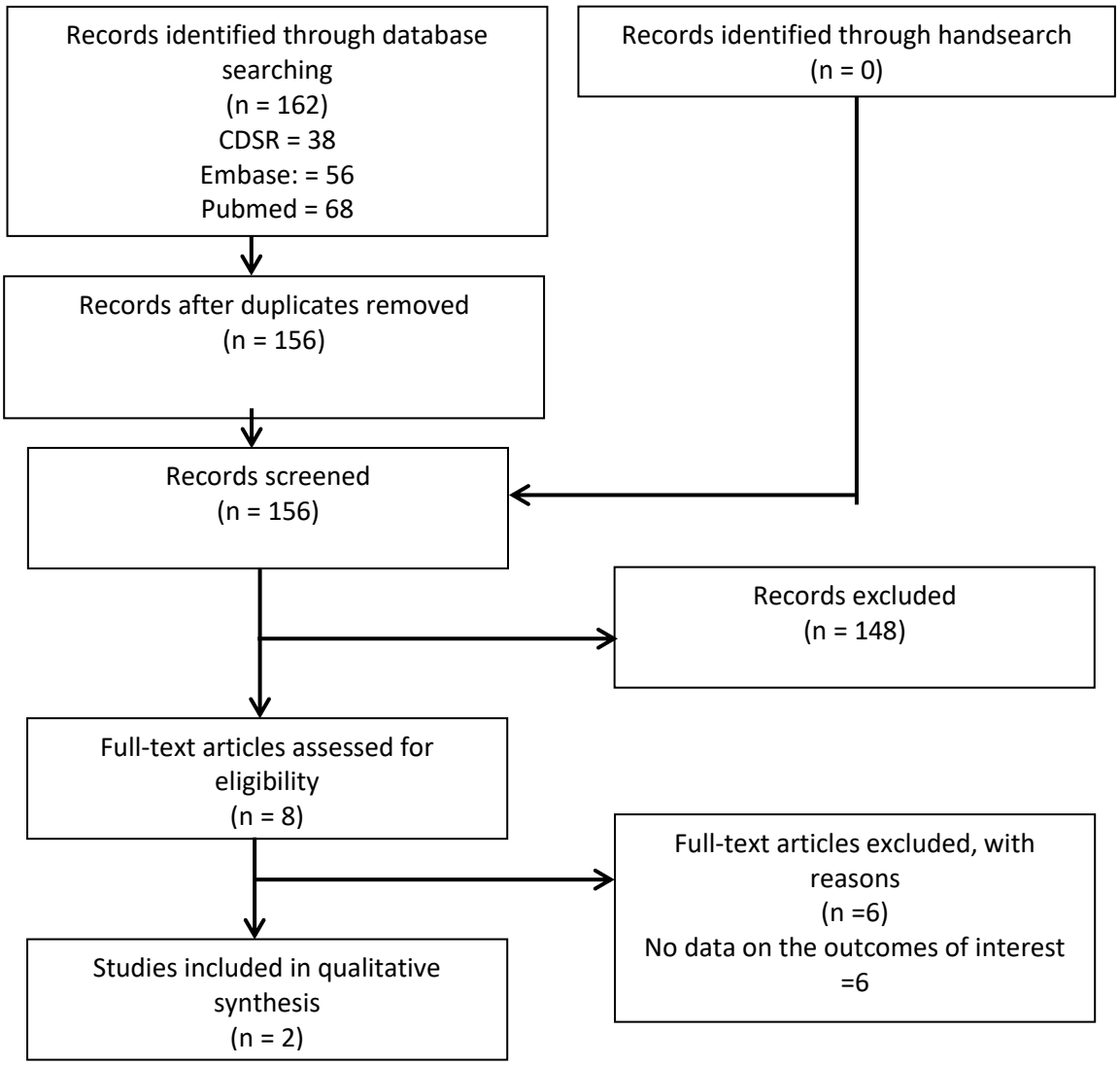
#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9545
4	'anxiety assessment'/exp OR 'mood disorder assessment'/exp	77836
5	('hamilton' NEAR/2 'scale*'):ti,ab,kw OR ('hamilton' NEAR/2 'score*'):ti,ab,kw OR ('anxiety' NEAR/2 'scale*'):ti,ab,kw OR ('anxiety' NEAR/2 'score*'):ti,ab,kw OR ('mood' NEAR/2 'scale*):ti,ab,kw OR ('mood' NEAR/2 'score*'):ti,ab,kw OR 'young mania rating scale':ti,ab,kw OR 'beck depression inventory':ti,ab,kw OR 'zung':ti,ab,kw	47425
6	4 OR 5	72,960
7	3 AND 6	84
8	7 AND [embase]/lim NOT ([embase]/lim AND[medline]/lim	56

Flow-chart of studies: psychiatric symptoms (anxiety and mood scales)

PICO

7: Any symptomatic treatment for psychiatric symptoms (anxiety and mood scales improvement)

Figure e28: August 2018 run (October 2019 update).



Search strategy: sleep disordered breathing

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5323
2	OSA [Title/Abstract] OR OSAS [Title/Abstract] OR OSAHS [Title/Abstract] OR SDB [Title/Abstract] OR SRBD [Title/Abstract] OR OSDB [Title/Abstract] OR SAHS [Title/Abstract] OR SAS[Title/Abstract] OR sleep apne*[Title/Abstract] OR sleep apnoe*[Title/Abstract] OR "sleep disordered breathing"[Title/Abstract] OR "Sleep Apnea Syndromes"[Mesh]	51817
3	1 AND 2	794
4	"oral appliance"[Title/Abstract] OR "intraoral appliance"[Title/Abstract] OR "dental appliance"[Title/Abstract] OR "manidbular advancement"[Title/Abstract] OR "mandibular repositioning"[Title/Abstract] OR positive pressure respiration*[Title/Abstract] OR positive pressure ventilation*[Title/Abstract] OR "positive airway pressure"[Title/Abstract]) OR "positive pressure airway"[Title/Abstract] OR "Positive-Pressure Respiration"[Mesh] OR "Oxygen Inhalation Therapy"[Mesh] OR "continuous distending"[Title/Abstract] OR "positive end expiratory pressure"[Title/Abstract] OR (ppv[Title/Abstract] OR cpap[Title/Abstract] OR ncpap[Title/Abstract] OR np-cpap[Title/Abstract] OR peep[Title/Abstract] OR a-pap[Title/Abstract] OR b-pap[Title/Abstract] OR c-pap[Title/Abstract] OR pap[Title/Abstract] OR apap[Title/Abstract] OR bpap[Title/Abstract]	91253
5	3 AND 4	94

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	"sleep disordered breathing":ti,ab,kw OR OSA:ti,ab,kw OR OSAS:ti,ab,kw OR OSAHS:ti,ab,kw OR SDB:ti,ab,kw OR SRBD:ti,ab,kw OR OSDB:ti,ab,kw OR SAHS:ti,ab,kw OR SAS :ti,ab,kw	6037
5	"sleep apnea" :ti,ab,kw OR "sleep apneas" :ti,ab,kw OR "sleep apneic":ti,ab,kw OR "sleep apneics":ti,ab,kw OR "sleep apnoe" :ti,ab,kw OR "sleep apnoea":ti,ab,kw OR "sleep apnoeas":ti,ab,kw OR "sleep apnoeic" :ti,ab,kw OR "sleep apnoeics:ti,ab,kw OR "sleep apnoics":ti,ab,kw	5322
6	(nighttime:ti,ab,kw OR sleep:ti,ab,kw OR 'night time':ti,ab,kw) AND (breath:ti,ab,kw OR airway:ti,ab,kw OR obstruct*:ti,ab,kw	5295
7	Mesh descriptor: [Sleep apnea syndrome] explode all trees	2119
8	Hypersomnia with Periodic Respiration" OR Hypoventilation OR "Ondine Syndrome" OR "Cheyne-stokes respiration" OR "periodic breathing"	733
9	Sleep NEAR/2 Hypopn*	326
10	4 OR 5 OR 6 OR 7 OR 8 OR 9	9477
11	3 AND 10	50

EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9563
4	('sleep' NEAR/2 'apnoe*'):ti,ab,kw OR ('sleep' NEAR/2 'apne*'):ti,ab,kw	53995
5	'sleep disordered breathing'/exp	67585
6	4 OR 5	71964
7	3 AND 6	1929
8	7 AND 'human'/de AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	679
9	'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it	5486603
10	7 NOT 9	366
11	'positive' NEAR/1 'pressure' NEAR/1 'ventilation'):ti,ab,kw OR ('positive' NEAR/1 'pressure' NEAR/1 'airway'):ti,ab,kw OR ('positive' NEAR/1 'pressure' NEAR/1 'respiration'):ti,ab,kw OR 'positive airway pressure':ti,ab,kw OR 'positive end expiratory pressure':ti,ab,kw OR 'ppv':ti,ab,kw OR 'cpap':ti,ab,kw OR 'ncpap':ti,ab,kw OR 'np-cpap':ti,ab,kw OR 'peep':ti,ab,kw OR 'a-pap':ti,ab,kw OR 'b-pap':ti,ab,kw OR 'c-pap':ti,ab,kw OR 'pap':ti,ab,kw OR 'apap':ti,ab,kw OR 'bpap':ti,ab,kw	91737
12	'oral appliance':ti,ab,kw OR 'intraoral appliance':ti,ab,kw OR 'dental appliance':ti,ab,kw OR 'manidbular advancement':ti,ab,kw OR 'mandibular repositioning appliance':ti,ab,kw	1062

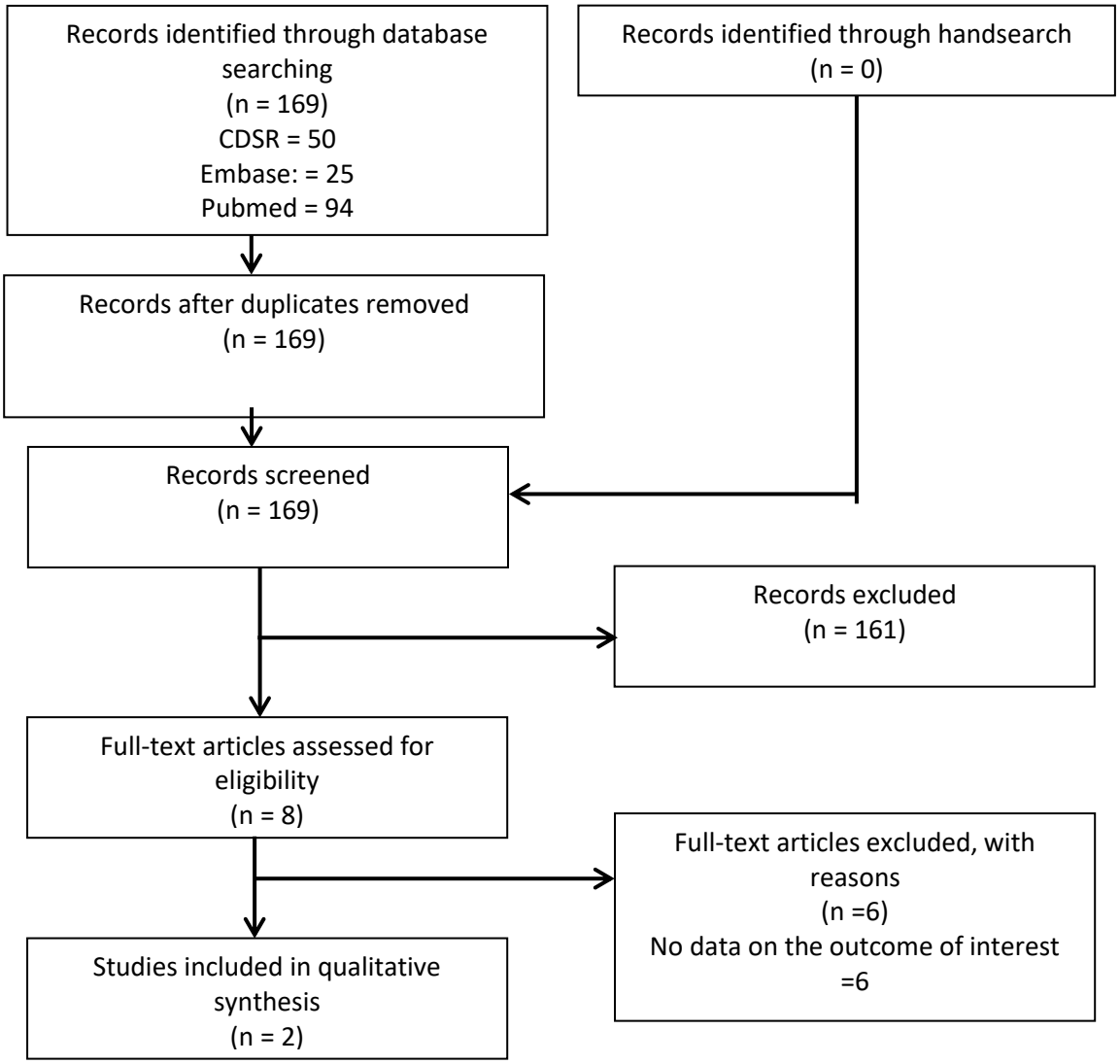
13	11 OR 12	92429
14	10 AND 13	25

Flow-chart of studies: sleep disordered breathing

PICO

8.1: Any symptomatic treatment for other sleep disorders (sleep disordered breathing)

Figure e29: September 2018 run (October 2019 update).



Search strategy: RBD

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5314
2	rem sleep*[Title/Abstract] OR rapid eye movement sleep*[Title/Abstract] or "Sleep, REM"[Mesh]	19006
3	behavior disorder*[Title/Abstract] OR behaviour disorder*[Title/Abstract] OR behavioral disorder*[Title/Abstract] OR behavioral disorder*[Title/Abstract] or behavior desease*[Title/Abstract] OR behaviour disease*[Title/Abstract] OR behavioral disease*[Title/Abstract] OR behavioral disease*[Title/Abstract]	8862
4	2 AND 3	1627
5	"REM Sleep Behavior Disorder"[Mesh]	1022
6	rbd[Title/Abstract] OR "rem behaviour disorder"[Title/Abstract] OR "rem behaviour disorders"[Title/Abstract] OR "rem behavioural disorder"[Title/Abstract] OR "rem behavioural disorders"[Title/Abstract] OR "rem behavior disorder"[Title/Abstract] OR "rem behavior disorders"[Title/Abstract] OR "rem behavioral disorder"[Title/Abstract] OR"rem behavioral disorders"[Title/Abstract] OR	2105
7	4 OR 5 OR 6	3037
8	1 AND 7	213

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	behav* NEAR/2 disorder*	2832
5	behav* NEAR/2 disease*	548
6	4 OR 5	3333
7	MeSH descriptor: [Sleep, REM] explode all trees	798
8	rem sleep" OR "rapid eye movement sleep"	1394
9	7 OR 8	1637
10	9 AND 6	90
11	MeSH descriptor: [REM Sleep Behavior Disorder] explode all trees	20
12	10 OR 11	90
13	3 AND 11	6

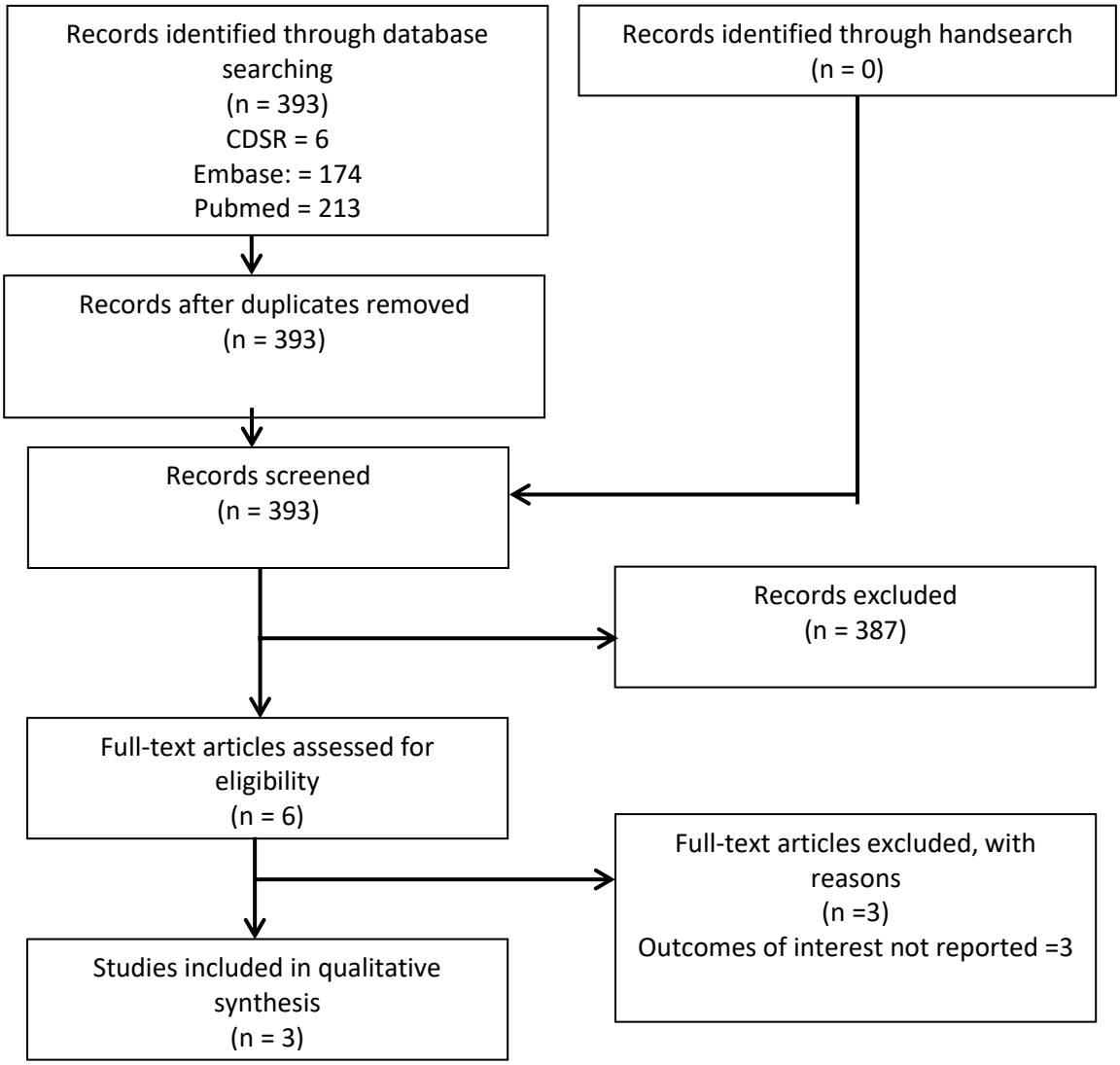
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9547
4	'rem sleep'/exp	25671
5	'rem' NEAR/2 'sleep*':ti,ab,kw OR 'rapid eye movement sleep':ti,ab,kw	19925
6	2 OR 3	31653
7	('behav*' NEAR/2 'diseases'):ti,ab,kwOR ('behav*' NEAR/2 'disease'):ti,ab,kw OR ('behav*' NEAR/2 'disorders'):ti,ab,kw OR ('behav*' NEAR/2 'disorder'):ti,ab,kw	24706
8	6 AND 7	3176
9	rem sleep behaviour disorder':ti,ab,kw OR 'rem sleep behaviour disorders':ti,ab,kw	535
10	('rem' NEAR/2 'behaviour disorder'):ti,ab,kw OR ('rem' NEAR/2 'behaviour disorders'):ti,ab,kw OR (('rem' NEAR/2 'behaviour diseases'):ti,ab,kw)	628
11	8 OR 9 OR 10	3230
12	3 AND 11	397
13	11 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	174

Flow-chart of studies: RBD

PICO
8.2: Any symptomatic treatment for other sleep disorders (RBD)

Figure e30: September 2018 run (October 2019 update).



Search strategy: RLS/PLMS

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5314
2	restless leg syndrome*[Title/Abstract] OR restless legs syndrome*[Title/Abstract] OR nocturnal myoclonus syndrome*[Title/Abstract] OR "Restless Legs Syndrome"[Mesh] OR "Nocturnal Myoclonus Syndrome"[Mesh] OR limb movement*[Title/Abstract] OR Ekbom[Title/Abstract] OR rls[Title/Abstract]	9499
3	1 AND 2	302

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	MeSH descriptor: [Restless leg syndrome] explode all trees	288
5	"MeSH descriptor: [nocturnal myoclonus syndrome] explode all trees	20
6	"restless leg syndrome" OR "restless legs syndrome" OR "nocturnal myoclonus syndrome" OR "limb movement" or "limb movements" OR Ekbom OR rls	1099
7	4 OR 5 OR 6	1099
8	3 AND 7	9

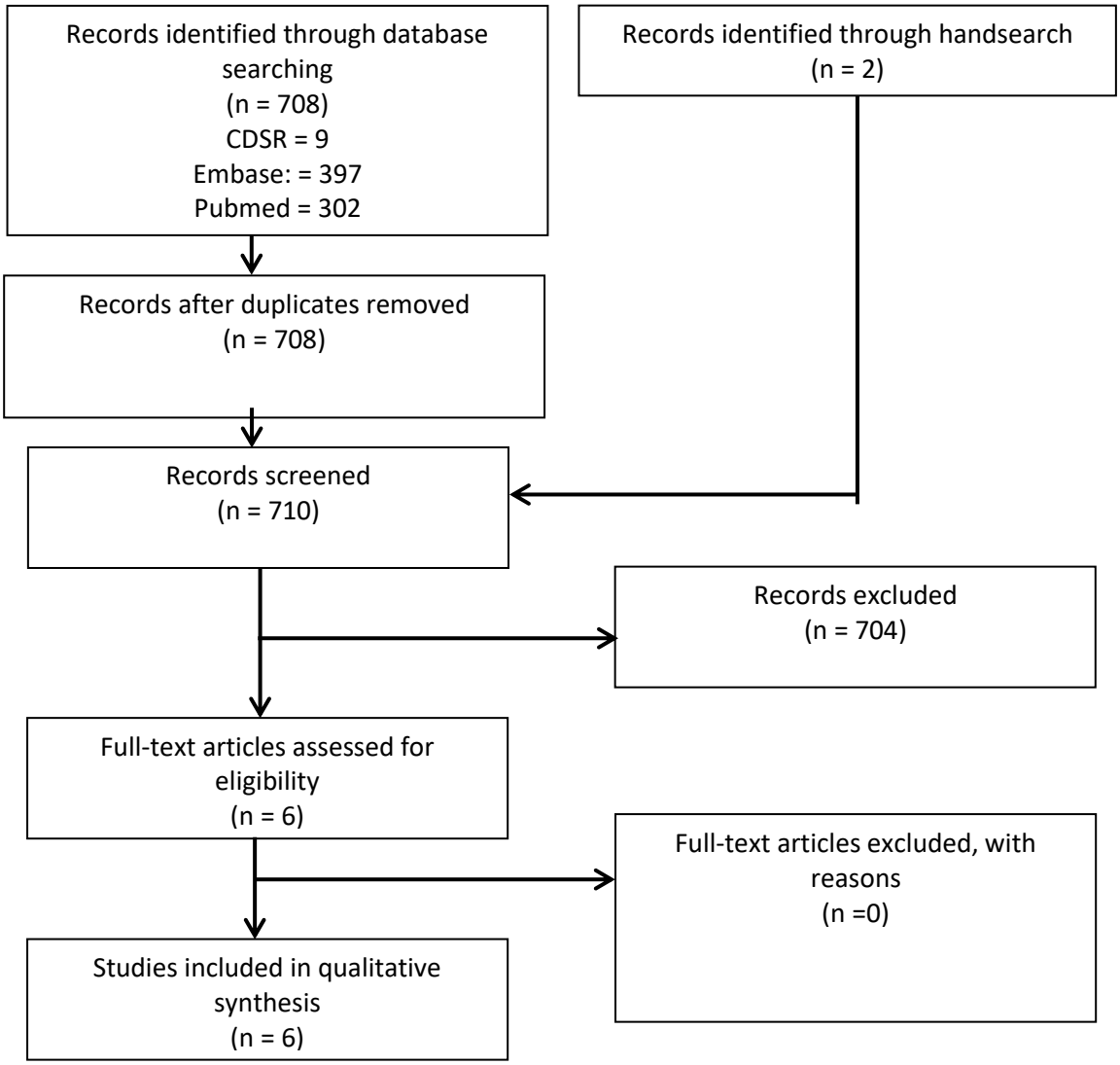
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9547
4	'restless legs syndrome'/exp	8842
5	'nocturnal myoclonus syndrome':ti,ab,kw OR 'restless leg syndrome':ti,ab,kw OR 'restless legs syndrome':ti,ab,kw OR 'limb movement':ti,ab,kw OR 'limb movements':ti,ab,kw OR 'ekbom':ti,ab,kw OR 'rls':ti,ab,kw	13400
6	4 OR 5	15977
7	3 AND 6	864
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	397

Flow-chart of studies: RLS/PLMS

PICO
8.3: Any symptomatic treatment for other sleep disorders (RLS/PLMS)

Figure e31: September 2018 run (October 2019 update).



Search strategy: global improvement of the disease

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR ("Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5310
2	clinical global impression*Title/Abstract] OR cgi[Title/Abstract]	8044
3	1 AND 2	30

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	368
4	"clinical global impression":ti,ab,kw OR cgi:ti,ab,kw	68073
5	3 AND 4	52

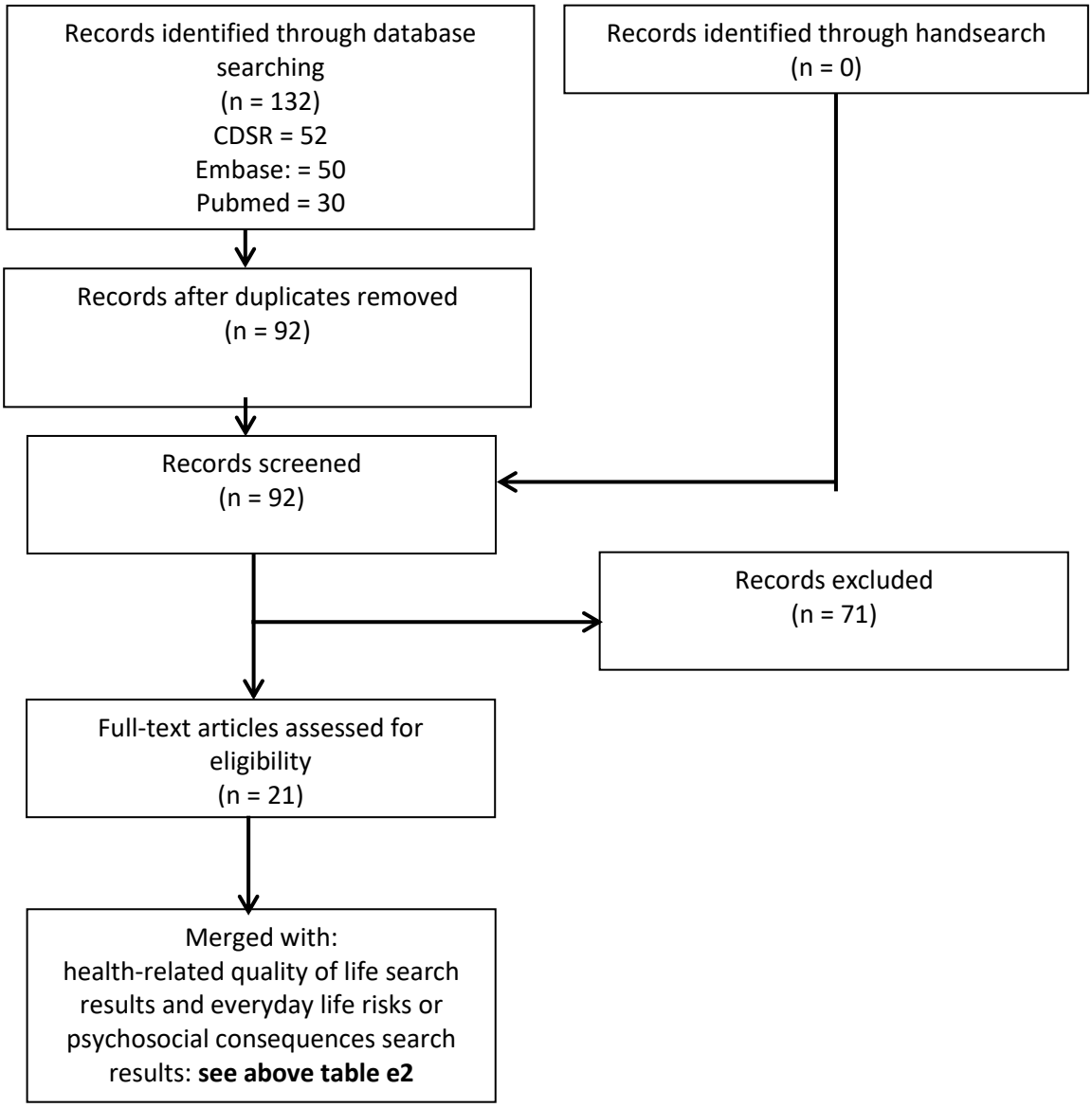
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'clinical global impression':ti,ab,kw OR 'cgi':ti,ab,kw	7523
5	'clinical global impression scale'/exp	9541
7	4 OR 5	1372
8	3 AND 7	81
9	8 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	50

Flow-chart of studies: global improvement of the disease

PICO
9: Any symptomatic treatment for the global improvement of the disease

Figure e33: September 2018 run (October 2019 update).



Search strategy: health-related quality of life

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	"Quality of Life"[Mesh] OR "Quality of Life"[title/abstract] OR "sf 36"[Title/Abstract] OR "euroqol"[Title/Abstract] OR QOLS[Title/Abstract]	284573
3	1 AND 2	185

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy]explode all trees	137
3	1 OR 2	360
4	MeSH descriptor: [Quality of Life]explode all trees	2025
5	"Quality of Life":ti,ab,kw OR "sf 36":ti,ab,kw OR euroqol OR QOLS:ti,ab,kw	69397
6	4 OR 5	69397
7	3 AND 6	30

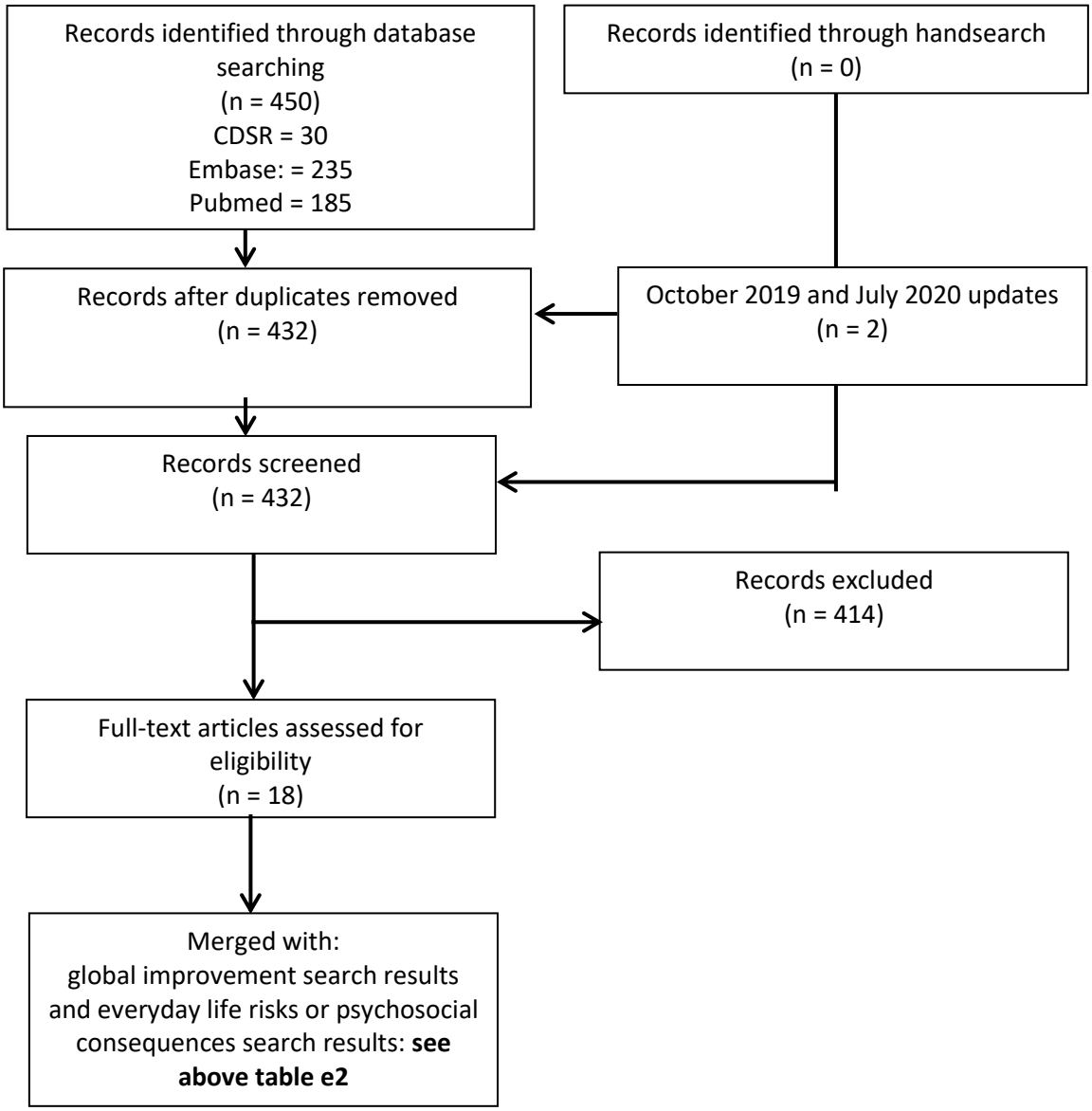
EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9526
4	'quality of life'/exp	23928
5	'quality of life':ti,ab,kw OR 'sf 36':ti,ab,kw OR 'euroqol':ti,ab,kw OR 'qols':ti,ab,kw	363068
6	4 OR 5	502045
7	3 AND 6	510
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	235

Flow-chart of studies: health-related quality of life

PICO
9: Any symptomatic treatment for the improvement of health-related quality of life

Figure e34: September 2018 run (October 2019 and July 2020 updates).



Search strategy: : everyday life risks or psychosocial consequences

PUBMED

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]	5309
2	psychosocial*[Title/Abstract] or schooling[Title/Abstract] or education*[Title/Abstract] or social environ*[Title/Abstract] or social support*[Title/Abstract] or "Socioeconomic Factors"[Mesh] OR school[title/abstract] OR "Schools"[Mesh:NoExp] or job*[title/abstract] OR "Job Satisfaction"[Mesh] OR Work*[title/abstract] OR Career[title/abstract] OR "Career Mobility"[Mesh] OR "Work Performance"[Mesh] OR "Employment"[Mesh] OR Underemployment[title/abstract] OR Unemployment[title/abstract] OR "Occupations"[Mesh] OR Occupation[title/abstract] or Accident*[title/abstract] OR "Accidents, Traffic"[Mesh] OR "Accidental Falls"[Mesh] OR fall[Title/Abstract]) OR falls[Title/Abstract] OR "Accidents, Home"[Mesh] OR "Accidents, Occupational"[Mesh] OR "Drowning"[Mesh] OR Drowning[Title/Abstract]	2467011
3	1 AND 2 AND Filters: Humans	499

PUBMED IN PROCESS

#	Search	Results
1	narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract]	5309
2	psychosocial*[Title/Abstract] or schooling[Title/Abstract] or education*[Title/Abstract] or social environ*[Title/Abstract] or social support*[Title/Abstract] or school[title/abstract] OR job*[title/abstract] OR Work*[title/abstract] OR Career[title/abstract] OR employment[title/abstract] or Underemployment[title/abstract] OR Unemployment[title/abstract] OR Occupation[title/abstract] or Accident*[title/abstract] OR fall[Title/Abstract]) OR falls[Title/Abstract] OR Drowning[Title/Abstract]	4554
3	inprocess[sb] or publisher[sb]	176192
4	1 AND 2 AND 3	28

COCHRANE LIBRARY (Central)

#	Search	Results
1	narcolep* OR cataple* OR Gelineau:ti,ab,kw (Word variations have been searched)	351
2	MeSH descriptor: [Narcolepsy] explode all tree	137
3	1 OR 2	360
4	"MeSH descriptor: [Socioeconomic Factors] explode all trees OR MeSH descriptor: [Schools] explode all trees OR "MeSH descriptor: [Job Satisfaction] explode all trees OR "MeSH descriptor: [Career Mobility] explode all trees OR "MeSH descriptor: [Work Performance] explode all trees OR"MeSH descriptor: [Employment] explode all trees OR "MeSH descriptor: [Occupations] explode all trees OR "MeSH descriptor: [Accidents, Traffic] explode all trees OR "MeSH descriptor: [Accidental Falls] explode all trees OR "MeSH descriptor: [Accidents, Home] explode all trees OR "MeSH descriptor: [Accidents, Occupational] explode all trees OR "MeSH descriptor: [Drowning] explode all trees	94158
5	psychosocial:ti,ab,kw OR schooling:ti,ab,kw OR education:ti,ab,kw OR "social environent":ti,ab,kw OR "social support":ti,ab,kw OR school:ti,ab,kw OR job*:ti,ab,kw OR work*:ti,ab,kw OR Career:ti,ab,kw OR Underemployment:ti,ab,kw OR Unemployment:ti,ab,kw OR Occupation:ti,ab,kw OR Accident*:ti,ab,kw OR fall:ti,ab,kw OR falls:ti,ab,kw OR Drowning:ti,ab,kw	101435
6	4 OR 5	147836
7	3 AND 7	62

EMBASE

#	Search	Results
1	'narcolepsy'/exp	7995
2	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR 'gelineau':ti,ab,kw	7189
3	1 OR 2	9557
4	'socioeconomics'/exp OR 'school'/de OR 'job satisfaction'/exp OR 'career mobility'/exp OR 'job performance'/exp OR 'employment'/exp OR 'traffic accident'/exp OR 'home accident'/exp OR 'occupational accident'/exp OR 'falling'/exp OR 'drowning'/exp	623043
5	'psychosocial':ti,ab,kw OR 'schooling':ti,ab,kw OR 'education':ti,ab,kw OR 'social environent':ti,ab,kw OR 'social support':ti,ab,kw OR 'school':ti,ab,kw OR 'job*':ti,ab,kw OR 'work*':ti,ab,kw OR 'career':ti,ab,kw OR 'underemployment':ti,ab,kw OR 'unemployment':ti,ab,kw OR 'occupation':ti,ab,kw OR 'accident*':ti,ab,kw OR 'fall':ti,ab,kw OR 'falls':ti,ab,kw OR 'drowning':ti,ab,kw	2704443
6	4 OR 5	3052100
7	3 AND 6	1244
8	7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND AND 'human'/de	483

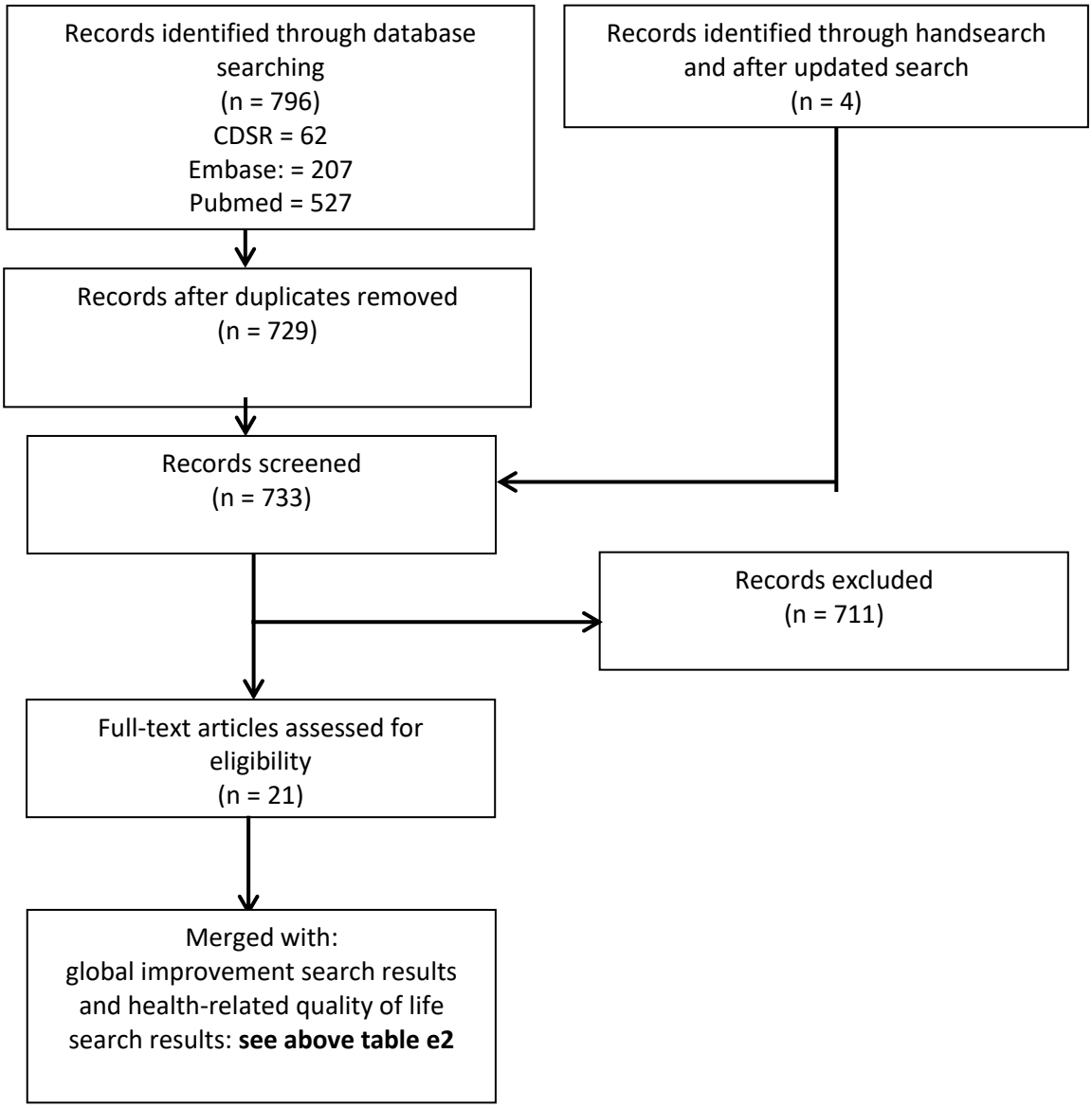
9	'conference abstract'/it OR 'editorial'/it OR 'letter'/it	4721526
10	8 NOT 9	207

Flow-chart of studies: everyday life risks or psychosocial consequences

PICO

9: Any symptomatic treatment for the prevention of everyday life risks or psychosocial consequences

Figure e35: September 2018 run (October 2019 update).



Search strategy: Children

PUBMED

#	Search	Results
1	(narcolep*[Title/Abstract] OR cataple*[Title/Abstract] OR Gelineau[Title/Abstract] OR "Narcolepsy"[Mesh] OR Cataplexy"[Mesh]) AND (treatment*[Title/Abstract] OR therap*[Title/Abstract]) Filters: Child: birth-18 years	390

COCHRANE LIBRARY (Central)

#	Search	Results
1	(narcolep*:ti,ab,kw OR cataple*:ti,ab,kw OR Gelineau:ti,ab,kw) AND (treatment*:ti,ab,kw OR therap*:ti,ab,kw):ti,ab,kw	272
2	MeSH descriptor: [Narcolepsy] explode all trees and with qualifier(s): [therapy - TH]	2
3	MeSH descriptor: [Cataplexy] explode all trees and with qualifier(s): [therapy - TH] 0	0
4	1 OR 2 OR 3	272
5	MeSH descriptor: [Child] explode all tree	1408
6	MeSH descriptor: [Infant] explode all trees	15022
7	MeSH descriptor: [Adolescent] explode all trees	97558
8	5 OR 6 OR 7	111466
9	8 AND 4	29

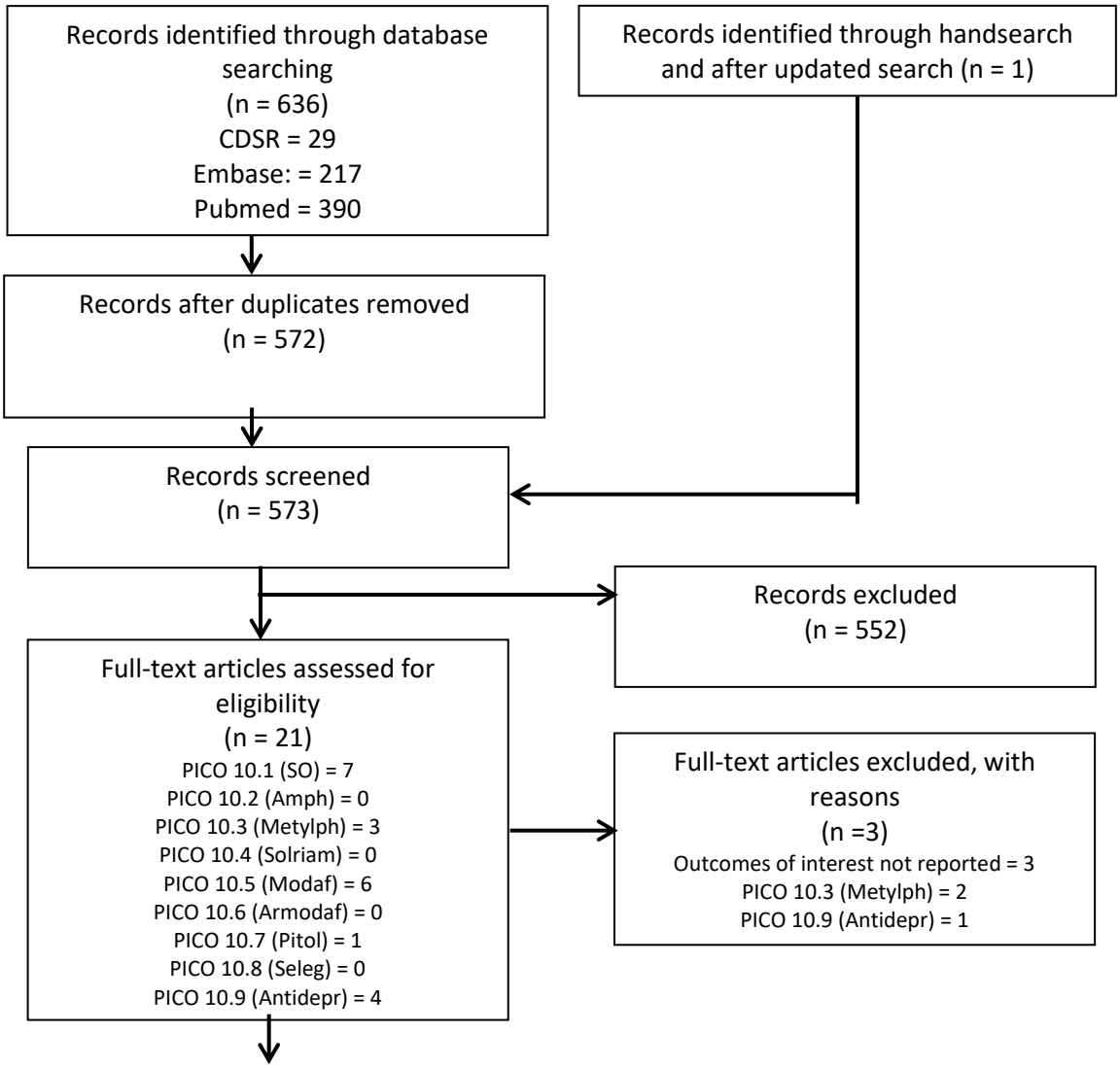
EMBASE

#	Search	Results
1	'narcolepsy'/exp/dm_th	198
2	'cataplexy'/exp/dm_th	26
3	'narcolep*':ti,ab,kw OR 'cataple*':ti,ab,kw OR gelineau':ti,ab,kw	7346
4	'treatment*':ti,ab,kw OR 'therapy':ti,ab,kw	6779912
5	3 AND 4	2357
6	1 OR 2 OR 5	2462
7	6 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ([adolescent]/lim OR [child]/lim)	217

Flow-chart of studies: Children

PICOs
10: Any pharmacological treatment for improvement of symptoms of narcolepsy, children
10.1: Sodium Oxybate
10.2: Amphetamines
10.3: Methylphenidate
10.4: Solriamfetol
10.5: Mazindol
10.6: Modafinil
10.7: Armodafinil
10.8: Pitolisant
10.9: Selegiline
10.10: Tricyclic Antidepressants
10.11: SSRI – NSRI - Other Antidepressants

Figure e36: October 2018 run (October 2019 update).



Studies included in qualitative synthesis
(n = 18)

PICO 10.1 (SO) = 7
PICO 10.3 (Metylph) = 1
PICO 10.5 (Modaf) = 6
PICO 10.7 (Pitol) = 1
PICO 10.9 (Antidepr) = 3

Group 1 - Disease modification

Question 1.1 - Hypocretin/Orexin

Studies included: 0.

Summary of Findings table

Patients or population: People with narcolepsy (any age) **Intervention: Hypocretin/Orexin** **Comparison:** any **Outcomes** Improvement of orexin levels - important but not critical Normalization of orexin levels - important but not critical Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments – Critical Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Question 1.2 - Immunoglobulins

Studies included: 11.

Dauvilliers Y, Carlander B, Rivier F, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. Ann Neurol 2004;56:905-8.

Dauvilliers Y. Follow-up of four narcolepsy patients treated with intravenous immunoglobulins. Ann Neurol 2006;60:153.

Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M. Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. Neurology 2009;73:1333-34.

Fronczek R, Verschuuren J, Lammers GJ . Response to intravenous immunoglobulins and placebo in a patient with narcolepsy with cataplexy. J Neurol 2007;254:1607–8.

Knudsen S, Biering-Sorensen B, Kornum BR, et al. Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. Neurology 2012;79:102–103.

Knudsen S, Mikkelsen JD, Bang B, Gammeltoft S, Jennum PJ. Intravenous immunoglobulin treatment and screening for hypocretin neuron-specific autoantibodies in recent onset childhood narcolepsy with cataplexy. Neuropediatrics 2010;41:217-22.

Lecendreux M, Maret S, Bassetti C, Mouren MC, Tafti M. Clinical efficacy of high-dose intravenous immunoglobulins near the onset of narcolepsy in a 10-year-old boy. J Sleep Res 2003;12:347-8.

Lecendreux M, Berthier J, Corny J, Bourdon O, Dossier C, Delclaux C. Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study. J Clin Sleep Med 2017,13:441-53.

Plazzi G, Poli F, Franceschini C, Parmeggiani A, Pirazzoli P, Bernardi F, Mignot E, Cicognani A, Montagna P. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. J Neurol 2008;255:1549-54.

Valko PO, Khatami R, Baumann CR et al. No persistent effect of intravenous immunoglobulins in patients with narcolepsy with cataplexy. J Neurol 2008;255:1900–3.

Viste R, Soosai J, Vikin T, Thorsby PM, Nilsen KB, Knudsen S. Long-term improvement after combined immunomodulation in early post-H1N1 vaccination narcolepsy. Neurol Neuroimmunol Neuroinflamm 2017;4:e389.

After update search (October 2019):

Ruppert E, Zagala H, Chambe J, et al. Intravenous Immunoglobulin Therapy Administered Early after Narcolepsy Type 1 Onset in Three Patients Evaluated by Clinical and Polysomnographic Follow-Up. Behav Neurol 2018:1671072.

→ case series of three patients (2 adults, 1 child): it does not modify the main findings reported below.

Summary of Findings table

Patients or population: People with narcolepsy (any age)
Intervention: Immunoglobulins
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Improvement of orexin levels important but not critical	Improvement: 1 pt out of 7	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	7 NC pts (any age) from 2 case series, 2 case reports	⊕⊖⊖⊖ Very Low

Normalization of orexin levels important but not critical	No normalization	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	7 NC pts (any age) from 2 case series, 2 case reports	⊕⊖⊖⊖ Very Low
Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments - Critical	Long term improvement of symptoms: 6 pts out 44	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	44 NC pts (any age) from 5 case series, 4 case reports, 1 open label study with controls	⊕⊖⊖⊖ Very Low
Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments - Critical	No remission	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	44 NC pts (any age) from 5 case series, 4 case reports, 1 open label study with controls	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	Headache, fever, flushing, Allergic reaction to ivIg in one patient, rise of CSF leucocytes	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	6 NC (any age) pts from 1 case series, 2 case reports	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Only few patients with improvement; none with remission Adverse reactions not negligible
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 1.3 - Plasmapheresis

Studies included: 1.

Chen W, Black J, Call P, Mignot E. Late-onset narcolepsy presenting as rapidly progressing muscle weakness: response to plasmapheresis. Ann Neurol 2005;58:489-90.

Summary of Findings table

Patients or population: People with narcolepsy (any age)
Intervention: Plasmapheresis
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence *

Improvement of orexin levels important but not critical	No data			
Normalization of orexin levels important but not critical	No data			
Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments - Critical	No long term improvement	A 5-day course plasmapheresis, followed by IVIg	1 adult pt (NC) from 1 case report	⊕⊖⊖⊖ Very Low
Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments - Critical	No remission	A 5-day course plasmapheresis, followed by IVIg	1 adult pt (NC) from 1 case report	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	No data			

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Very little published evidence
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 1.4 - Steroids

Studies included: 4.

Coelho FM, Pradella-Hallinan M, Alves GR, Bittencourt LR, Tufik S. Report of two narcoleptic patients with remission of hypersomnolence following use of prednisone. Arq Neuropsiquiatr 2007;65:336-7.

Hecht M, Lin L, Kushida CA et al. Report of a case of immunosuppression with prednisone in an 8-year-old boy with an acute onset of hypocretin-deficiency narcolepsy. Sleep 2003;26:809–810

Miyata R, Hayashi M, Kohyama J, Honda M. Steroid therapy ameliorated cataplexy in three children with recent-onset of narcolepsy. Sleep Med 2017;29:86-87.

Viste R, Soosai J, Vikin T, Thorsby PM, Nilsen KB, Knudsen S. Long-term improvement after combined immunomodulation in early post-H1N1 vaccination narcolepsy. Neurol Neuroimmunol Neuroinflamm 2017; 4:e389.

Summary of Findings table

Patients or population: People with narcolepsy (any age)
Intervention: Steroids
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence

Improvement of orexin levels important but not critical	No improvement	Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	5 NC pts (children) from 2 case series	⊕⊖⊖⊖ Very Low
Normalization of orexin levels important but not critical	No normalization	Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	5 NC pts (children) from 2 case series	⊕⊖⊖⊖ Very Low
Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments - Critical	Long term improvement in 4 pts out of 8	Prednisone, Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	8 NC pts (any age) from 3 case series and 1 case report	⊕⊖⊖⊖ Very Low
Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments - Critical	No remission	Prednisone, Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	8 NC pts (any age) from 3 case series and 1 case report	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	No AEs	Prednisolone	3 NC pts (children) from 1 case series	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Only few patients with improvement; none with remission Adverse reactions not assessed
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 1.5 - Monoclonal antibodies

Studies included: 2.

Donjacour CE, Lammers GJ. A remarkable effect of alemtuzumab in a patient suffering from narcolepsy with cataplexy. J Sleep Res 2012;21:479-80.

Sarkanen T, Alén R, Partinen M. Transient Impact of Rituximab in H1N1 Vaccination-associated Narcolepsy With Severe Psychiatric Symptoms. Neurologist 2016;21:85-6.

Summary of Findings table

Patients or population: People with narcolepsy (any age)
Intervention: Monoclonal antibodies / Immune modifying therapies
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence

Improvement of orexin levels important but not critical	No data			
Normalization of orexin levels important but not critical	No data			
Significant and persistent (>6-12 months) improvement of symptoms, without use of symptomatic treatments - Critical	Long term improvement (cataplexy = 1 pt)	Alemtuzumab (after methotrexate)	1 adult pt (NC) from 1 case report	⊕⊖⊖⊖ Very Low
	No Long term improvement	Rituximab (after methyl-prednisolone)	1 child (NC) from 1 case report	
Significant and persistent (>6-12 months) disappearance of symptoms, without use of symptomatic treatments - Critical	No remission	Alemtuzumab (after methotrexate) Rituximab (after methyl-prednisolone)	2 NC pts (any age) from 2 case reports	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	No data			

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Very little published evidence
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Group 2 - Symptomatic treatment, non-pharmacological management

Question 2.1 - Scheduled naps

Studies included: 6.

Helmus T, Rosenthal L, Bishop C, Roehrs T, Syron ML, Roth T. The alerting effects of short and long naps in narcoleptic, sleep deprived, and alert individuals. Sleep 1997;20:251-7.

Mullington J, Broughton R. Scheduled naps in the management of daytime sleepiness in narcolepsy-cataplexy. Sleep 1993;16:444-56.

Roehrs T, Zorick F, Wittig R, Paxton C, Sicklesteel J, Roth T. Alerting effects of naps in patients with narcolepsy. Sleep 1986;9:194-9.

Rogers AE, Aldrich MS. The effect of regularly scheduled naps on sleep attacks and excessive daytime sleepiness associated with narcolepsy. Nurs Res 1993; 42:111-7.

Rogers AE, Aldrich MS, Lin X. A comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. Sleep 2001;24:385-91.

Uchiyama M, Mayer G, Meier-Ewert K. Differential effects of extended sleep in narcoleptic patients. Electroencephalogr Clin Neurophysiol 1994;91:212-8.

Summary of Findings table

Patients or population: Patients (any age) with narcolepsy → but data only on adults
Intervention: Scheduled naps (any regimen)
Comparison: none / any

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values) - Critical	Intervention 2 and 3: sig reduction of narcolepsy composite score (p=0.047) and (p=0.027) Intervention 1,3: sig. reduction of subjective sleepiness severity (p=0.002) and p=0.013 → Only combination of daytime naps and regular nocturnal sleep times improved subjective severity of sleepiness and duration of unintended sleep	3 interventions: 1) two 15-minute naps per day 2) regular nocturnal sleep schedule 3) combination of scheduled naps and regular nocturnal sleep Duration 2-week intervention	29 pts, 1 open RCT (Rogers 2001)	⊕⊕⊖⊖ Low (short period, small sample size, indirectness)
	Sig. decreased mean score of sleepiness Standford scale (p<0.02) after sleep extension (score 2.7) compared to baseline (3.7)	One intervention: nocturnal sleep extension; baseline night 22.00-6:00 to extension night 22.00 -10:00	10 pts, 1 open before-after (Uchiyama 1994)	⊕⊕⊖⊖ Low
	Non-Sig. improvement of narcolepsy composite score Sleep diaries: unchanged numbers of sleep attacks per day (0.5/day vs 0.6/day)	One nap intervention: Three regularly scheduled 15 min daytime naps based on the subjects perferred time	16 pts, 1 open before-after (Rogers 1993)	⊕⊕⊖⊖ Low
Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	MWT: sig. increase mean latency of 2.6 min (P< 0.05). Non-significant increase of successful MWT trials: 18.8% to 27.5%	One nap intervention: Three regularly scheduled 15 min daytime naps based on the subjects perferred time	16 pts, 1 open before-after (Rogers 1993)	⊕⊕⊖⊖ Low

objective measures: MSLT: mean EDS improvement important but not critical	Both 15min and 30min naps improved sleep latency on MSLT, but the longer nap duration did not outperform the benefit of the short nap	Participants allowed to sleep in nap 1-3 for 15 min. Intervention on nap 4 with time in bed and wake duration to nap 5 Regimens in comparison 1) 15min-15min 2) 30min- 15min 3) 15min – 30min	45 pts, 1 open before-after (Roehrs 1986)	⊕⊕⊖⊖ Low
	Sig. increased mean sleep latency ($p<0.01$) and decreased number of daytime naps with latencies shorter than 10min ($p>0.02$) after sleep extension. No differences in naps containing a REMS episode	One intervention: nocturnal sleep extension; baseline night 22.00-6:00 to extension night 22.00 -10:00	10 pts, 1 open before-after (Uchiyama 1994)	⊕⊕⊖⊖ Low
	MSLT: sig. increased MSL after 2 compared to 1 ($p<0.01$) in all groups → Sleep benefit from 120 nap was lost when tested 3 hours later in the 1 hour sleep period	two nap interventions: 1) one 15min nap 2) one 120 min nap	11 pts, 1 open before-after with controls (Helmus 1997)	⊕⊕⊖⊖ Low
objective measures: SART: mean improvement of n° of errors important but not critical	Performance and cognitive task: sig. improved reaction times of 11% for intervention 1 vs 3	Three daytime nap/sleep interventions: 1) one single long daytime nap 2) five multiple short daytime naps 3) no nap 6 consecutive days with each intervention maintained for 2 days	8 pts, 1 open before-after (Mullington 1993)	⊕⊕⊖⊖ Low
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical				
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical				
Global Clinical Impression: mean improvement of				

nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	Objective daytime naps (36h recording) : trend of reduced number and duration of unintended short naps intervention 3 <2 <1 with 3 vs 1: p=0.08 Nocturnal sleep (PSG): Intervention 2 vs 3: reduced WASO p< 0.05 and increased sleep efficacy p<0.05 Main result is that a single long napping improves performance compared to no napping condition	Three daytime nap/sleep interventions: 1) one single long daytime nap 2) five multiple short daytime naps 3) no nap 6 consecutive days with each intervention maintained for 2 days	8 pts, 1 open before-after (Mullington 1993)	⊕⊕⊖⊖ Low
	Daytime sleep in 24-hour recording: Intervention 3: sig reduction of unscheduled daytime naps (difference of 54 min, p=0.001) → Only combination of daytime naps and regular nocturnal sleep times improved subjective severity of sleepiness and duration of unintended sleep	3 interventions: 1) two 15-minute naps per day 2) regular nocturnal sleep schedule 3) combination of scheduled naps and regular nocturnal sleep Duration 2-week intervention	29 pts, 1 open RCT (Rogers 2001)	⊕⊕⊕⊖ Moderate (short period, small sample size)
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - **Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations -** Critical				
Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - **Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations** Critical				
Weight: mean reduction of weight Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	9/16 (=56%) could not adhere to the 2 nap schedule	One nap intervention: Three regularly scheduled 15 min daytime naps based on the subjects perferred time	16 pts, 1 open before-after (Rogers 1993)	⊕⊕⊖⊖ Low
Any adverse event of the drugs - important but not critical	Decrease of 16% in logical reasoning test in 1 vs 3	Three daytime nap/sleep interventions:	8 pts, 1 open before-after	⊕⊕⊖⊖ Low

	→ Napping result in sleep inertia which may interfere with performance benefit in the multiple napping condition.	1) one single long daytime nap 2) five multiple short daytime naps 3) no nap 6 consecutive days with each intervention maintained for 2 days	(Mullington 1993)	

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Improvement of EDS and sleep parameters. Adverse events neither probable nor severe.
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 2.2 - Physical activity

Studies included: 0.

Summary of Findings table

Patients or population: Patients (any age) with narcolepsy **Intervention: Physical activity (any regimen)** **Comparison:** - **Outcomes** subjective measures: Epworth Sleepiness Scale: mean improvement of EDS; percentage of patients with remission of EDS (according to normative values) – Critical Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement – Critical objective measures: MWT: mean EDS improvement - Critical objective measures: MSLT: mean EDS improvement - important but not critical objective measures: SART: mean improvement of n° of errors - important but not critical subjective measures: Sleep diaries: mean reduction of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep – Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations; Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations; Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Question 2.3 - Nutrition, diet

Studies included: 1.

Husain AM, Yancy WS, Carwile ST, Miller PP, Westman EC. Diet therapy for narcolepsy. Neurology 2004;62:2300-2.

Summary of Findings table

Patients or population: Patients (any age) with narcolepsy → only data on adults
Intervention: Nutrition, diet (any regimen)
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values) - Critical	ESS: ns; SSS: ns Sig. improvement in subscores sleepiness (p>0.017), sleep attacks (p< 0.016), sleep paralysis (p<0.015) of NSSQ Sig. increase of total score NSSQ (p=0.0019)	Low carbohydrate, ketogentic Diet, restrict carbohydrate intake to < 20g/day for 8 weeks	9 pts, 1 open before-after	⊕⊕⊖⊖ Low
Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical				
objective measures: MSLT: mean EDS improvement important but not critical				
objective measures: SART: mean improvement of n° of errors important but not critical				
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical				
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical				
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				

PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical				
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations - Critical	Sig improvement in subscores sleepiness of sleep paralysis ($p<0.015$) of NSSQ	Low carbohydrate, ketogentic Diet, restrict carbohydrate intake to < 20g/day for 8 weeks	9 pts, 1 open before-after	⊕⊕⊖⊖ Low
Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations Critical				
Weight: mean reduction of weight Critica	Sig. BMI reduction from 99.2 kg to 92.3 kg	Low carbohydrate, ketogentic Diet, restrict carbohydrate intake to < 20g/day for 8 weeks	9 pts, 1 open before-after	⊕⊕⊖⊖ Low
Adverse events leading to withdrawal from the drugs - important but not critical	One patient out of 9 dropped out because of inability to adhere to diet	Low carbohydrate, ketogentic Diet, restrict carbohydrate intake to < 20g/day for 8 weeks	9 pts, 1 open before-after	⊕⊕⊖⊖ Low
Any adverse event of the drugs - important but not critical	Headache, leg cramps, irritability	Low carbohydrate, ketogentic Diet, restrict carbohydrate intake to < 20g/day for 8 weeks	9 pts, 1 open before-after	⊕⊕⊖⊖ Low

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Doubtful improvement of some symptoms. Adverse events not negligible.
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No recommendation**

Question 2.4 - Cognitive therapy

Studies included: 0.

Summary of Findings table

Patients or population: Patients (any age) with narcolepsy **Intervention: Cognitive therapy (any regimen)** **Comparison:** - **Outcomes** subjective measures: Epworth Sleepiness Scale: mean improvement of EDS; percentage of patients with remission of EDS (according to normative values) – Critical Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement – Critical objective measures: MWT: mean EDS improvement - Critical objective measures: MSLT: mean EDS improvement - important but not critical objective measures: SART: mean improvement of n° of errors - important but not critical subjective measures: Sleep diaries: mean reduction of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep – Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations; Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations; Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No recommendation**

Question 2.5 - Hypnosis

Studies included: 0.

Summary of Findings table

Patients or population: Patients (any age) with narcolepsy **Intervention: Hypnosis** **Comparison:** - **Outcomes** subjective measures: Epworth Sleepiness Scale: mean improvement of EDS; percentage of patients with remission of EDS (according to normative values) – Critical Global Clinical Impression: mean EDS improvement percentage of patients with EDS improvement – Critical objective measures: MWT: mean EDS improvement - Critical objective measures: MSLT: mean EDS improvement - important but not critical objective measures: SART: mean improvement of n° of errors - important but not critical subjective measures: Sleep diaries: mean reduction of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep – Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep – Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations; Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations; Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight – Critical Adverse events leading to withdrawal from the drugs - important but not critical	No study found

Any adverse event of the drugs - important but not critical	

VOTE

Direction of the Recommendation	□ For □ Against □ **X No Recommendation**

Group 3 - Symptomatic treatment, pharmacological management, Adults

Treatment of excessive daytime sleepiness

Question 3.1 - Hypocretin/Orexin

Studies included: 1.

Weinhold SL, Seeck-Hirschner M, Nowak A, Hallschmid M, Goder R, Baier PC.The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. Behav Brain Res 2014:262:8-13.

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Hypocretin/Orexin
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)** **-** Critical		-	-	-
Global Clinical Impression: **mean EDS improvement** **percentage of patients with EDS improvement** - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical MWT: percentage of patients with remission of EDS (according to normative values) important but not critical	-	-	-	-
objective measures: MSLT: mean EDS improvement important but not critical	-	-	-	-
objective measures: SART: mean improvement of n° of errors important but not critical	Fewer false reactions (O: 0.43 ± 0.63; P: 0.69 ± 0.78; p = 0.026) Tndency towards a reduced reaction time (O: 715.94 ± 68.28 ms; P:732.60 ± 69.47 ms; p = 0.079).	Orexin A 774.35 ug/m applied intranasaly by pump at 7 am vs placebo – 1 treatment night	14 narcolepsy patients, 1 RCT	⊕⊖⊖⊖ Very Low (for indirecteness and imprecision)
Adverse events leading to withdrawal from the drugs - important but not critical		-	-	-
Any adverse event of the drugs - important but not critical		-	-	-

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence

Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	no difference compared to placebo unknown adverse events
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.2 - Sodium Oxybate

Studies included: 19.

Studies on effectiveness and safety (8)

Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451-8.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431-43.

Lammers GJ, Arends J, Declerck AC, Ferrari MD, Schouwink G, Troost J. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. Sleep 1993;16:216-20.

Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. Sleep 1990;13:479-90.

Scrima L, Hartman PG, Johnson FH, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. Biol Psychiatry 1989;26:331-43.

The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.

The Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.

Studies on safety (11)

Akins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). J Forensic Sci 2009;54:495-6.

Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010;6:596-602.

Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med 2015;11:427-32.

Drakatos P, Lykouras D, D'Ancona G, Higgins S, Gildeh N, Macavei R, Rosenzweig I, Steier J, Williams AJ, Muza R, Kent BD, Leschziner G. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. Sleep Med 2017;35:80-84.

Langford J, Gross WL. Psychosis in the context of sodium oxybate therapy. J Clin Sleep Med 2011;7:665-6.

Mamelak M, Swick T, Emsellem H, Montplaisir J, Lai C, Black J. A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy. Sleep Med 2015;16: 52-8.

Mayer G, Plazzi G, Iranzo A, Ortega-Albas J, Quinnell T, Pesch H, Serralheiro P, Schlit AF, Wuiame D, Bentz JWG. Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Post-Authorization, Non-Interventional Surveillance Study. Sleep 2018;41(9).

Ortega-Albas JJ, Lopez-Bernabe R, Garcia AL, Gomez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci 2010;22:352r.e26-52.e26.

Poryazova R, Tartarotti S, Khatami R, Baumann CR, Valko P, Kallweit U, Werth E, Bassetti CL. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. Eur Neurol 2011;65:175-82.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol 2014;5:136.

Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. Sleep Med 2009;10:490-3.

After update search (October 2019):

Buckley PJ, Wolf CT. Psychosis in a 22-Year-Old Woman With Narcolepsy After Restarting Sodium Oxybate. Psychosomatics 2018;59:298-301.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Noujaim MG, Mourad A, Clough JD. Sodium Oxybate: A Cause of Extreme Involuntary Weight Loss in a Young Lady. Case Rep Med 2019;2019:6537815.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczek R, Lammers GJ. Decreased body mass index

during treatment with sodium oxybate in narcolepsy type 1. J Sleep Res 2019;28:e12684.
→2-year before-after study: treatment with sodium oxybate is associated with a body mass index reduction in narcolepsy type 1,

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Sodium Oxybate (SO) / Gamma Hydroxybutyrate (GHB)
Comparison: placebo / nothing

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)-** Critical	ESS: -2.81 (95% CI -4.13/-1.49) point of mean reduction across all dosage (around 5 point at 9 g SO)	3-9g SO, 4-8-12 weeks studies	254 SO pts+ 273 plac pts, from 2 RCT (Xyrem 2002 and Xyrem 2005), included in a metanalysis, (Boscolo Berto 2012)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	Daytime sleep attacks reduction: daily basis - 0.27 ns weekly basis - 9.30 (95% CI -19.92 / - 2.68)	4 g (1 mo) 6-9 g (12 weeks)	198 pts from, 3 RCT (Black 2006; Lammers 1993; Scrima 1989), included in a metanalysis (Boscolo Berto 2012)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	MWT: 5.18 min (2.59-7.78) mean improvement	4.5-9g SO, 4-12 weeks studies	192 pts, from 2 RCT (Black 2006 and Xyrem 2005), included in a metanalysis, Alshaikh 2012)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
objective measures: MSLT: mean EDS improvement important but not critical	MSLT: no difference	GHB: 25 mg/kg h.s. and 3 h later – FU 29 days	20 NT1 pts, 1 RCT (Scrima 1990)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
objective measures: SART: mean improvement of n° of errors - important but not critical		-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	At 9g sig 9.2% withdrew due to AEs SAE: 1 NT with acute confusion at 6g	4-12 weeks studies with 4.5-9g SO	741 pts (1 metanalysis Alshaikh 2012)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
	21 patients discontinued due to an adverse event, with most occurring in the 9 g/night dose group	8 week treatment (4.5 / 6 / 9 gr) with titration up to 9g/day over 4 weeks	228 pts, 1 RCT (Black 2010)	

	9 out 171 discontinued 5 thought to be serious, 2 of which linked to drug – respiratory disorder, headache and psychosis	Started on 9g per night and titrated up or down. FU 12 mo	171 pts, open label study (Mamelak 2015)	⊕⊕⊖⊖ Low
	26% discontinued: nausea, mood disturbance and enuresis main SAEs	Common dose: 9 g/night (33.3%), 22.2% 4.5 g/night, 22% 6 g/night, and 18%7.5 g/night. FU: median 35.5 mo	90 pts, 1 case series (Drakatos 2017)	
	37% drop-outs due to AEs	3-9 gr, 12 mo	136 pts, 1 post-hoc analysis of U.S. Xyrem. Multicenter Study Group 2002 (Bogan 2015)	
	discontinuation in 8.8%	median dose 6 g per night. Median (range) duration of exposure 507 (1–577) days.	670 pts, phase IV study (Mayer 2018)	
	discontinuation in 1 pt out of 18 because of AEs (nausea, worsening of nighttime sleep and cataplexy)	mean dosage 6.4 8 1.2 g, mean duration 26 mo	18 pts, 1 case series (Poryazova 2011)	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	more frequent AEs vs placebo: nausea (RR: 7.74, 95% CI: 3.2, 19.2), vomiting (RR: 2.87, 95% CI: 0.84, 9.80), dizziness (RR: 11.8, 95% CI: 1.6, 89.4), enuresis (RR 4.32 95% CI: 1.14, 16.41).	4-12 weeks studies with 4.5-9g SO	6 studies included 741 pts (1 SR Alshaikh 2012)	⊕⊕⊕⊖ Moderate (risk of bias and short duration)
	Nausea, vomiting, dizziness and enuresis seen as dose-dependent adverse effects, vertigo causing a fall and trauma; raised ALT	8 week treatment (4.5 / 6 / 9 gr) with titration up to 9g/day over 4 weeks	364 pts, 2 RCTs (Black 2010; The U.S. Xyrem. Multicenter Study Group 2002)	
	56% reported AE's. Most mild or moderate severity. Most common: nausea (10%), headache (7%), and dizziness (5%), not dose related	Started on 9g per night and titrated up or down. FU 12 mo	171 pts open label study Mamelak 2015	⊕⊕⊖⊖ Low
	Around 50% had at least one SE Psychosis seen early after initiation	Common dose: 9 g/night (33.3%), 22.2% 4.5 g/night, 22% 6 g/night, and 18%7.5 g/night. FU: median 35.5 mo	90 pts, 1 case series (Drakatos 2017)	

	AEs 67% pts Headache and nasopharyngitis main SE's; no particular concerns in elderly,children or apnoea subjects	median dose 6 g per night. Median (range) duration of exposure 507 (1–577) days.	670 pts, phase IV study (Mayer 2018)	
	Nighttime confusion in 6 (of 18). Others: nausea (n = 2), enuresis (n = 2), diffuse muscle pain, headache, flatulence, disturbance in attention and forgetfulness (n =1)	mean dosage 6.4 8 1.2 g, mean duration 26 mo	18 pts, 1 case series (Poryazova 2011)	⊕⊖⊖⊖ Very Low
	Death (4 pts): 1 overdose other unexplained	7-7.5 gr/night (taking other CNS drugs)	4 pts, 2 case reports (Akins 2009 Zvosec 2009)	
	Major psychiatric SE (incl suicidal ideation): 5 pts	range 4.5-8 gr/night	5 pts, 3 case series (Ortega-Albas 2010, Langford 2011, Sarkanen 2014)	

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Sodium Oxybate
Comparison: Modafinil

Outcomes	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS - Critical	Improvement G 2: 15 to 12 points G 4: 15 to -11 points	At 8 weeks G1 Placebo G2 SO G3 Modafinil G4 SO + Modafinil SO dose increased from 6 to 9g after 4 wks; total 8 week treatment	222 pts, 1 RCT (Black 2006)	⊕⊕⊕⊖ Moderate (risk of bias > allocation unclear)
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	G4 Naps/ day from 11.8 to 5.6, g, no difference between other groups			
objective measures: MWT: mean EDS improvement - Critical	MWT: medication groups had longer average sl, highest in SO+mod. Greatest change after 4 weeks			
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	13 TEAs in medication groups Group 4: hypertension, hypotension, hyperventilation and low grade fever	At 8 weeks G1 Placebo G2 SO G3 Modafinil G4 SO + Modafinil SO dose increased from 6 to 9g after 4 wks; total 8 week treatment	222 pts, 1 RCT (Black 2006)	⊕⊕⊕⊖ Moderate (risk of bias > short duration)

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Sodium oxybate effective in improving EDS Adverse reactions are generally rare although several adverse events (nocturnal confusion, enuresis, nausea, vomiting, dizziness, raised ALT, vertigo causing fall and trauma, headache) can be limiting factors. Very serious AEs are very rare but must be considered in selecting patients to be treated
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.3 - Amphetamines

Studies included: 6.

Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. Sleep 2005;28:667-72

Chen SY, Clift SJ, Dahlitz MJ, Dunn G, Parkes JD. Treatment in the narcoleptic syndrome: self assessment of the action of dexamphetamine and clomipramine. J Sleep Res 1995;4:113-18.

Mitler MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. Sleep 1993;16:306-17.

Parkes JD, Fenton GW. Levo(-) amphetamine and dextro(+) amphetamine in the treatment of narcolepsy. Journal of Neurology Neurosurgery and Psychiatry 1973;36:1076-81.

Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. Br Med J (Clin Res Ed) 1985;290:1167-70.

Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, Steier J, Rosenzweig I, Williams AJ, Leschziner GD, Drakatos P. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. Journal of Sleep Research 2018;27:e12627.

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Amphetamines
Comparison: none / placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)- -** Critical	Sig reduction of ESS 20 down to 15 ($p<0.001$)	5-60 mg dexamphetamine/d	60 pts, 1 case series, (Chen 1995)	⊕⊖⊖⊖ Very Low
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	Reduced sleep attacks significantly	l-amphetamine. FU 3 mo vs placebo	12 pts, 1 cross-over RCT (Parkes 1973)	⊕⊖⊖⊖ Very Low

	Reduction of sleep attacks of about 50% compared to no treatment for 10 and 20 mg 30 mg dex was only slightly better in reducing sleep attacks than 10 mg (2.2 vs 2.7 sleep attacks)	Dexedrine; Dexamphetamine	20 pts, 1 cross-over RCT (Shindler 1985)	(all methodological aspects unclear)
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	-	-	-	-
objective measures: MSLT: mean EDS improvement important but not critical	Dose dependent increase of sleep latency on MSLT (4.3 minutes on placebo to 9.3 minutes on high dose)	metamphetamine 0, 20, 40-60 mg; 7 days	8 pts, 1 cross-over RCT (Mitler 1993)	⊕⊕⊖⊖ Low (unclear randomization; short follow up)
objective measures: SART: mean improvement of n° of errors - important but not critical	Errors in driving task markedly reduced (Stear Clear 30 min, 650 obstacles)			
Adverse events leading to withdrawal from the drugs - critical	-	-	-	-
Any adverse event of the drugs - critical	Nervousness, sweating, palpitations, headache, Irritability, weight loss and weight gain	l-amphetamine, metamphetamine; Dexedrine; Dexamphetamine	100 pts (4 studies)	⊕⊖⊖⊖ Very Low
	psychosis OR = 12.0 [1.6-92.0] alcohol or polysubstance misuse OR = 4.3 [1.2-15.2] psychiatric hospitalization (odds ratio = 3.2 [1.1-10.0]) tachyarrhythmias OR = 3.3 [0.92-12.1] anorexia or weight loss OR = 11.0 [1.4-85.2]. The frequency of physician-diagnosed depression, drug-seeking and suicide-related behaviors, hypertension, and cardiovascular disease did not differ significantly between the groups.	Methylphenidate over 120 mg Methamphetamine over 100 mg Dextroamphetamine, over 120 mg Pemoline over 180 mg Amphetamine over 120 mg	116 pts N or IH (1 study Auger 2015)	⊕⊕⊖⊖ Low

	Side effects: methylphenidate 37% Most frequent: headache, mood swings, palpitations 30% had side effects that lead to combination therapy	Drug naïve pats were started with modafinil followed by methylphenide, amphetamines or SO, if partial or no response: combinations	72 pts, 1 case series (Thakrar 2018)	

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	very little published evidence and safety concern
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 3.4 - Methylphenidate

Studies included: 2.

Mitler MM, Shafor S, Hajdukovich R, Timms RM, Browman CP. Treatment of narcolepsy: objective studies on methylphenidate, pemoline, and protriptyline. Sleep 1986;9:260-64.

Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, Steier J, Rosenzweig I, Williams AJ, Leschziner GD, Drakatos P. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. Journal of Sleep Research 2018;27:e12627.

Summary of Findings table

Patients or population Adults with narcolepsy and excessive daytime sleepiness
Intervention: Methylphenidate
Comparison: placebo / none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values) - Critical	Difference baseline last visit ESS: methylphenidate: 3.1 ± 4.7min	Drug naïve pats were started with modafinil followed by methylphenidate, amphetamines or SO, if partial or no response: combinations	72 pts, 1 case series (Thakrar 2018)	⊕⊕⊖⊖ Low
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	-			

Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	39% had complete response, 25% partial response After combination change to complete response in another 17.6% and improvement in 38.2%	Drug naïve pats were started with modafinil followed by methylphenide, amphetamines or SO, if partial or no response: combinations	72 pts, 1 case series (Thakrar 2018)	⊕⊕⊖⊖ Low
objective measures: MWT: mean EDS improvement - Critical	Improvement from baseline sl 12.8 min to 18 min	16 mg methylphenidate	6 pts, 1 open label study (Mitler 1986)	⊕⊕⊖⊖ Low
objective measures: MSLT: mean EDS improvement important but not critical	-			
objective measures: SART: mean improvement of n° of errors - important but not critical	-			
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	-
Any adverse event of the drugs - important but not critical	Side effects: methylphenidate 37%, Most frequent: headache, mood swings, palpitations 30% had side effects that lead to combination therapy	Drug naïve pats were started with modafinil followed by methylphenide, amphetamines or SO, if partial or no response: combinations	72 pts, 1 case series (Thakrar 2018)	⊕⊕⊖⊖ Low

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	very little published evidence and safety concern
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 3.5 - Solriamfetol

Studies included: 5.

Bogan RK, Feldman N, Emsellem HA, Rosenberg R, Lu Y, Bream G, Khayrallah M, Lankford Da. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. Sleep Med 2015;16:1102-8.

Ruoff C, Swick TJ, Doekel D, Emsellem HA, Feldman NT, Rosenberg R, Bream G, Khayrallah MA, Lu Y, Black J. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: a Phase 2b Study. Sleep 2016;39:1379-87.

Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y, Black J, Dauvilliers Y. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. Ann Neurol 2019; 85:359-370.

Update searches (October 2019 and July 2020):

Malhotra A, Shapiro C, Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, Strollo PJ, Mayer G, Sarmiento K, Baladi M, Chandler P, Lee L, Schwab R. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep 2020;43(2).

→50-week open-label study (with a nested 2-week withdrawal rct) of patients with narcolepsy and OSAS: it does not modify the main findings reported below.

Dauvilliers Y, Shapiro C, Mayer G, et al. Solriamfetol for the Treatment of Excessive Daytime Sleepiness in Participants with Narcolepsy with and without Cataplexy: Subgroup Analysis of Efficacy and Safety Data by Cataplexy Status in a Randomized Controlled Trial. CNS Drugs. 2020 34: 773-784.

→Subgroup analyses of data from a previous 12-week randomized, double-blind, placebo-controlled, phase III trial of solriamfetol for EDS in narcolepsy evaluated the efficacy and safety of solriamfetol by cataplexy status: it does not modify the main findings reported below.

Summary of Findings table

Patients or population Adults with narcolepsy and excessive daytime sleepiness
Intervention: Solriamfetol
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values)- - Critical	Mean ESS score: from -2 to -6 point score improvement (from lower to higher doses)	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 pts, 3 RCTs (Bogan 2015; Ruoff 2016/Scrima 2017, Thorpy 2019)	⊕⊕⊕⊖ Moderate (short duration/ high attrition)
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	-	-	-	-
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	Mean MWT: from -2 to -10 min improvement (from lower to higher doses → sig 150 and 300 mg)	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 pts, 3 RCTs (Bogan 2015; Ruoff 2016/Scrima 2017, Thorpy 2019)	⊕⊕⊕⊖ Moderate (short duration/ high attrition)
objective measures: MSLT: mean EDS improvement important but not critical	-			
objective measures: SART: mean improvement of n° of errors - important but not critical	-			
Adverse events leading to withdrawal from the drugs - important but not critical	TEAE leading to study drug discontinuation Plac 1 (1.7%) All doses 9 (5.1%) 75 mg 1 (1.7%) 150 mg 3 (5.1%) 300 mg 5 (8.5%)	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 pts, 3 RCTs (Bogan 2015; Ruoff 2016/Scrima 2017, Thorpy 2019)	⊕⊕⊕⊖ Moderate (no data on long term use)
Any adverse event of the drugs - important but not critical	most common versus placebo: insomnia (23% versus 8%), headache (16% versus 10%), nausea (14% versus 6%), diarrhea (11% versus 6%), decreased appetite (14% versus 0%), and anxiety (11% versus 0%)	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 pts, 3 RCTs (Bogan 2015; Ruoff 2016/Scrima 2017, Thorpy 2019)	⊕⊕⊕⊖ Moderate (no data on long term use)

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation

Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	No major safety concern however long term treatment data not available
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

AFTER TWO ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.6 - Mazindol

Studies included: 5.

Alvarez B, Dahlitz M, Grimshaw J, Parkes JD. Mazindol in long-term treatment of narcolepsy. Lancet 1991; 337:1293-4.

Iijima S, Sugita Y, Teshima Y, Hishikawa Y. Therapeutic effects of mazindol on narcolepsy. Sleep 1986;9:265-8.

Nittur N, Konofal E, Dauvilliers Y, Franco P, Leu-Semenescu S, Cock VC, Inocente CO, Bayard S, Scholtz S, Lecendreux M, Arnulf I. Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. Sleep Med 2013;14:30-6.

Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. British medical journal (clinical research ed.) 1985;290:1167-70.

Vespignani H, Barroche G, Escaillas JP, Weber M. Importance of mazindol in the treatment of narcolepsy. Sleep 1984;7:274-5.

Summary of Findings table

Patients or population Adults with narcolepsy and excessive daytime sleepiness
Intervention: Mazindol
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values)- - Critical	ESS reduction 17.7 ± 3.5 to 12.8 ± 5.1,	Mean dose 3.4 ± 1.3 mg for about 30 months	94 pts (1 study; Nittur 2013)	⨁⊖⊖⊖ Very Low
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	Improved EDS / Sig increase of subjective alertness on rating scale / 60% had excellent effect on eds / Good stimulant effect in 22, moderate 10, in other 11 NT1 none-slight	various schemes: 1-16 mg per day; 4 wks-28 mo	81 pts (4 studies; Vespignani 1984; Shindler 1985; Iijima 1986; Alvarez 1991)	⨁⊖⊖⊖ Very Low
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	-	-	-	-
objective measures: MSLT: mean EDS improvement important but not critical	-	-	-	-

objective measures: SART: mean improvement of n° of errors - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	22% stopped due to lack of efficacy	Mean dose 3.4 ± 1.3 mg for about 30 months	94 pts (1 study; Nittur 2013)	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical	Headache, insomnia, decreased appetite, tolerance; urinary retention, restlessness, dry mouth, constipation; palpitation	various schemes: 1-16 mg per day; 4 wks-28 mo	81 pts (4 studies; Vespignani 1984; Shindler 1985; Iijima 1986; Alvarez 1991)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Absence of enough good benefit-risk ratio evaluation
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation** because the drug is out of market

Question 3.7 - Modafinil

Studies included: 15.

Studies on effectiveness and safety (10)

Besset A, Tafti M, Villemin E, Billiard M. [The effects of modafinil (300mg) on sleep, sleepiness and arousal in narcoleptic patients]. Neurophysiol Clin 1993;23: 47-60.

Billiard M, Besset A, Montplaisir J, Laffont F, Goldenberg F, Weill JS, Lubin S. Modafinil: a double-blind multicentric study. Sleep 1994;17:S107-12.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Boivin DB, Montplaisir J, Petit D, Lambert C, Lubin S. Effects of modafinil on symptomatology of human narcolepsy. Clinical neuropharmacology 1993;16:46-53.

Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, Montplaisir JY, Morehouse RL, Moscovitch A, Murphy WF. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997;49:444-51.

Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. Med Sci Monit 2010;16: Ra177-86.

Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med 2000;1:109-16.

Saletu M, Anderer P, Saletu-Zyhlarz GM, Mandl M, Arnold O, Nosiska D, Zeitlhofer J, Saletu B. EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil. Eur Arch Psychiatry Clin Neurosci 2005;255:20-32.

US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97.

US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000;54:1166-75.

Studies on safety (5)

Prince V, Philippidou M, Walsh S, Creamer D. Stevens-Johnson syndrome induced by modafinil. Clin Exp Dermatol 2018:43:191-192.
Sanyal D, Ghosh M. A case of modafinil induced mania in a child suffering from Narcolepsy. Bengal Journal of Private Psychiatry 2017;8:14-15.
Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry 2005;162:813–14.
Wu P, Jones S, Ryan CJ, Michail D, Robinson TD. Modafinil-induced psychosis. Intern Med J. 2008;38:677-8.
Yasui-Furukori N, Kusunoki M, Kaneko S. Hallucinations associated with modafinil treatment for narcolepsy. J Clin Psychopharmacol 2009;29:408.

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Modafinil
Comparison: placebo / none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)-** Critical	ESS weighted mean improvement (WMD) -2.73 points (95%CI –3.39, –2.08)	Modafinil 200-400 mg 3-16 weeks	1054 pts; data from 1 metanalysis (Golicki 2010), from 9 RCT (Besset 1993, Billiard 1994, Black 2006, Boivin 1993, Broughton 1997, Moldofski 2000, Saletu 2005, US Modafinil study group 1998, US Modafinil study group 2000)	⊕⊕⊕⊖ Moderate (various flaws for each study: small sample, attrition, short duration, uncler allocation concealment)
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	-	-	-	-
Global Clinical Impression: **mean EDS improvement / percentage of patients with EDS improvement -** Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	MWT test: mean improvement of 2.82 minutes (95%CI 2.40, 3.24)	Modafinil 200-400 mg 3-16 weeks	1054 pts; data from 1 metanalysis (Golicki 2010), from 9 RCT (Besset 1993, Billiard 1994, Black 2006, Boivin 1993, Broughton 1997, Moldofski 2000, Saletu 2005, US Modafinil study group 1998, US Modafinil study group 2000)	⊕⊕⊕⊖ Moderate
objective measures: MSLT: mean EDS improvement important but not critical	MSLT test: mean improvement 1.11 minutes (95%CI 0.55, 1.66)	Modafinil 200-400 mg 3-16 weeks	1054 pts; data from 1 metanalysis (Golicki 2010), from 9 RCT (Besset 1993, Billiard 1994, Black 2006, Boivin 1993, Broughton 1997, Moldofski 2000, Saletu 2005, US Modafinil study group 1998, US	⊕⊕⊕⊖ Moderate

			Modafinil study group 2000)	
objective measures: SART: mean improvement of n° of errors - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	4% withdrawn due to AEs in mod; 1.6% in placebo group	Modafinil 200-400 mg 3-16 weeks	1054 pts; data from 1 metanalysis (Golicki 2010), from 9 RCT (Besset 1993, Billiard 1994, Black 2006, Boivin 1993, Broughton 1997, Moldofski 2000, Saletu 2005, US Modafinil study group 1998, US Modafinil study group 2000)	⊕⊕⊕⊖ Moderate
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	Headache, backpain, nausea, dry mouth; nervousness, dyspepsia, pain, and vomiting (all 6%). Other rare: hypothermia, infection, rash, increase in heart rate	Modafinil 200-400 mg 3-16 weeks	1054 pts; data from 1 metanalysis (Golicki 2010), from 9 RCT (Besset 1993, Billiard 1994, Black 2006, Boivin 1993, Broughton 1997, Moldofski 2000, Saletu 2005, US Modafinil study group 1998, US Modafinil study group 2000)	⊕⊕⊕⊖ Moderate
	Major psychiatric SE (psychosis; mania): 4 pts (2 children)	Modafinil 200-400 mg	4 pts (2 children) (Sanyal 2017; Vorspan 2005; Wu 2008; Yasui-Furukori 2009)	⊕⊖⊖⊖ Very Low
	Stevens-Johnson syndrome: 1 case	Modafinil	1 pt (NOT with narcolepsy), 1 case report (Prince 2018)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Modafinil which is effective in improving EDS. No major concern on safety Headache, nausea, dry mouth; nervousness, dyspepsia and

		vomiting, pain, increased heart rate and blood pressure. 1 case of Steven-Johnson syndrome (not a narcoleptic patient)
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.8 - Armodafinil

Studies included: 3.

Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. J Clin Sleep Med 2010;6:458-66.

Harsh JR, Hayduk R, Rosenberg R, Wesnes KA, Walsh JK, Arora S, Niebler GE, Roth T. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin 2006;22:761-74.

Holfinger S, Roy A, Schmidt M. Stevens-Johnson Syndrome After Armodafinil Use. J Clin Sleep Med 2018;14:885-887.

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Armodafinil
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)-** - Critical	ESS: placebo 17.5 (3.9), ArM 150 17.3 (3.4), ArM 250 15.7 (4.7)(sig)	Armodafinil 150-250 mg; 12 weeks	196 pts, 1 RCT (Harsh 2006)	⊕⊕⊕⊕ High
	Long term ESS: hange of 4.3 after 12 months	Armodafinil 150-250 mg; 12 mo	156 pts, 1 open label study (Black 2010)	⊕⊕⊖⊖ Low
Subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	Diaries: no of intended/unintended naps lower for ArM 250, but ns	Armodafinil 150-250 mg; 12 weeks	196 pts, 1 RCT (Harsh 2006)	⊕⊕⊕⊕ High
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
Objective measures: MWT: mean EDS improvement - Critical	Mean MWT sleep latencies Placebo 12.5 (6.6), ArM 150 mg 12.1 (6.6), ArM 250 mg 9.5 (6.1)(sig)	Armodafinil 150-250 mg; 12 weeks	196 pts, 1 RCT (Harsh 2006)	⊕⊕⊕⊕ High
Objective measures: MSLT: mean EDS improvement important but not critical	-	-	-	-
Objective measures: SART: mean improvement of n° of errors - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	misses/accidents ns reduced in ArM groups	Armodafinil 150-250 mg; 12 weeks	196 pts, 1 RCT (Harsh 2006)	⊕⊕⊕⊕ High

Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	Most frequent headache (30%), nasopharyngitis (21%),nausea 15%, insomnia 8%. SAE in 4 NT (coronary artery heart disease (1), hemorrhoidal hemorrhage (1), hypertension (1), dry mouth, dizziness, cough each 8%	Armodafinil 150-250 mg; 12 mo	156 pts, 1 open label study (Black 2010)	⊕⊕⊖⊖ Low
	Stevens-Johnson syndrome: 1 case	Armodafinil	1 pt (NOT with narcolepsy), 1 case report (Holfinger 2018)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Armodafinil which is effective in improving EDS. No major concern on safety Armodafinil has no additional benefit compared to modafinil.
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.9 - Pitolisant

Studies included: 3.

Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding CL, Lecomte JM, Schwartz JC. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol 2013;12:1068-75.

Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, Sonka K, Lehert P, Lecomte I, Lecomte JM, Schwartz JC. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:200-07.

After update search (October 2019):

Dauvilliers Y, Arnulf I, Szakacs Z, Leu-Semenescu S, Lecomte I, Scart-Gres C, Lecomte JM, Schwartz JC. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep 2019;42(11).

→ open-label study: it does not modify the main findings reported below, except for **1 possibly related miscarriage**, as serious adverse effect.

Summary of Findings table

Patients or population: Adults with narcolepsy and excessive daytime sleepiness
Intervention: Pitolisant
Comparison: placebo / Modafinil

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)-** - Critical	Improvement compared to placebo > ESS: Pit -3.0, vs mod +0.12 ESS: -3·48 (–5·03 to –1·92)	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (1 study attrition bias; short

	ESS reponders (final score ≤10) 20/51 (39%); 9/50 (18%) p 0·035			duration: 7-8 weeks)
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	-	-	-	-
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	CGI-C EDS improved: plac 56%, Pit 73%, mod 86% CGI-C eds: 69% Pit vs 24% placebo	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (1 study attrition bias; short duration: 7-8 weeks)
objective measures: MWT: mean EDS improvement - Critical	MWT: Pit vs plac +1.47, vs mod +0.77 MWT: Pit 3.54 vs 6.91; Plac 4.08 vs 4.32 min (sig) → 1.85 min (1·24–2·74) p=0·003	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (1 study attrition bias; short duration: 7-8 weeks)
objective measures: MSLT: mean EDS improvement important but not critical	-	-	-	-
objective measures: SART: mean improvement of n° of errors - important but not critical	SART NO GO: no difference in placebo baseline end (8.0±1.8 vs 8.1±1.8), sig different pitolisant (9.2±2.0 vs 7.5±1.9) and modaf (8.5±2.0 vs 7.1±1.9)	mod 100,200, 400 mg, pit 10, 20, 40 mg 8 weeks	94 pts, 1 RCT (Dauvilliers 2013)	⊕⊕⊕⊕ High
Adverse events leading to withdrawal from the drugs - important but not critical	ns reduced in Pit groups	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (1 study attrition bias; short duration: 7-8 weeks)
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	more AEs for Pitolisant 35% vs placebo 31%); sig more TEAs for Pitolisant 28% vs 6%; 1 SAE with severe nausea Most frequent: headache 35%, insomnia 10%, abdominal discomfort, nausea each 6%; irritability, anxiety; 1 SAE due to abdominal discomfort	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (1 study attrition bias; short duration: 7-8 weeks)

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	effective no major concern on safety

Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.10 - Selegiline

Studies included: 3.

Hublin C, Partinen M, Heinonen EH, Puukka P, Salmi T. Selegiline in the treatment of narcolepsy. Neurology 1994;44:2095-101.

Mayer G, Ewert Meier K, Hephata K. Selegeline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. Clin Neuropharmacol 1995;18:306-19.

Reinish LW, MacFarlane JG, Sandor P, Shapiro CM. REM changes in narcolepsy with selegiline. Sleep 1995;18:362-7.

Summary of Findings table

Patients or population Adults with narcolepsy and excessive daytime sleepiness
Intervention: Selegiline
Comparison: placebo / none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Epworth Sleepiness Scale: mean improvement of EDS percentage of patients with remission of EDS (according to normative values)- - Critical	-	-	-	-
subjective measures: Sleep diaries: mean reduction of sleep time important but not critical	Sig decrease of no of sleep attacks on diary 13.5+/-4.7 vs 8.7+/-5.2 at 20, 30,40 mg Mean duration of sleep episodes sig reduced 8.8+/-7.8 vs 5.8+/-7.3 in all doses	10,20,30,40 mg (3tbl./d); 4 wks	17 pts, 1 cross-over RCt (Hublin 1994)	⊕⊕⊖⊖ Low (fixed sequence; small sample)
Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical	-	-	-	-
objective measures: MWT: mean EDS improvement - Critical	-	-	-	-
objective measures: MSLT: mean EDS improvement important but not critical	Non sig increase in sleep latencies in MSLT MSLT: 2x5mg baseline 118+/-102 vs 161.3+/-143sec 2x10: 146.6+/-182.2 vs 131.5+/-122.6	10,20,30,40 mg (3tbl./d); 4 wks 10, 20 mg; 2 weeks,	47 pts, 2 RCTs (Hublin 1994; Mayer 1995)	⊕⊕⊖⊖ Low (fixed sequence; small sample; high risk of bias, short duration, imprecision)
objective measures: SART: mean improvement of n° of errors - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	-
Any adverse event of the drugs - important but not critical	Slight increase of alanine aminotransferase in 2 NT1; Most common side effects:	10,20,30,40 mg (3tbl./d); 4 wks 10, 20 mg; 2 weeks,	58 pts (3 studies; Hublin 1994; Mayer 1995; Reinish)	⊕⊕⊖⊖ Low (fixed sequence;

	dry mouth, headache, insomnia, sweating			small sample; high risk of bias, short duration, imprecision)

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Little / uncertain improvement of EDS at best. Safety concern at higher doses
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 3.11 - Caffeine

Studies included: 1.

Summary of Findings table

Patients or population Adults with narcolepsy and excessive daytime sleepiness **Intervention: Caffeine** **Comparison:** - **Outcomes:** subjective measures: Epworth Sleepiness Scale: mean improvement of EDS; percentage of patients with remission of EDS (according to normative values)- - Critical subjective measures: Sleep diaries: mean reduction of sleep time important but not critical Global Clinical Impression: mean EDS improvement / percentage of patients with EDS improvement - Critical objective measures: MWT: mean EDS improvement - Critical objective measures: MSLT: mean EDS improvement important but not critical objective measures: SART: mean improvement of n° of errors - important but not critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found (2018 and 2019 search)

Update Search (July 2020)

Aldosari MS, Olaish AH, Nashwan SZ, Abulmeaty MMA, BaHammam AS. The effects of caffeine on drowsiness in patients with narcolepsy: a double-blind randomized controlled pilot study. Sleep Breath. 2020.

→ randomized, double-blind, placebo-control clinical pilot trial. Participants attended two study visits 7 days apart. The drug was administered orally in a single opaque capsule containing 200 mg caffeine/placebo daily in the morning for 1 week. Sixteen participants with narcolepsy were included. Significant improvements in alertness were observed using the Karolinska Sleepiness Scale. No changes in reaction time or Stanford Sleepiness Scale scores were noted.

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Group 3 - Symptomatic treatment, pharmacological management, Adults

Treatment of moderate to severe cataplexy

Question 4.1 - Hypocretin/Orexin

Studies included: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy **Intervention: Hypocretin/Orexin** **Comparison:** - **Outcomes** subjective measures: Sleep diaries: mean reduction of cataplexy – Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.2 - Immunoglobulins

Studies included: 9.

Dauvilliers Y, Carlander B, Rivier F, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. Ann Neurol 2004;56:905-8.

Dauvilliers Y. Follow-up of four narcolepsy patients treated with intravenous immunoglobulins. Ann Neurol 2006;60:153.

Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M. Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. Neurology 2009;73:1333-34.

Fronczek R, Verschuuren J, Lammers GJ . Response to intravenous immunoglobulins and placebo in a patient with narcolepsy with cataplexy. J Neurol 2007;254:1607–8.

Knudsen S, Biering-Sorensen B, Kornum BR, et al. Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. Neurology 2012;79:102–103.

Knudsen S, Mikkelsen JD, Bang B, Gammeltoft S, Jennum PJ. Intravenous immunoglobulin treatment and screening for hypocretin neuron-specific autoantibodies in recent onset childhood narcolepsy with cataplexy. Neuropediatrics 2010;41:217-22.

Lecendreux M, Maret S, Bassetti C, Mouren MC, Tafti M. Clinical efficacy of high-dose intravenous immunoglobulins near the onset of narcolepsy in a 10-year-old boy. J Sleep Res 2003;12:347-8.

Plazzi G, Poli F, Franceschini C, Parmeggiani A, Pirazzoli P, Bernardi F, Mignot E, Cicognani A, Montagna P. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. J Neurol 2008;255:1549-54.

Valko PO, Khatami R, Baumann CR et al. No persistent eff ect of intravenous immunoglobulins in patients with narcolepsy with cataplexy. J Neurol 2008;255:1900–3.

After update search (October 2019):

Ruppert E, Zagala H, Chambe J, et al. Intravenous Immunoglobulin Therapy Administered Early after Narcolepsy Type 1 Onset in Three Patients Evaluated by Clinical and Polysomnographic Follow-Up. Behav Neurol 2018:1671072.

→ case series of three patients (2 adults, 1 child): it does not modify the main findings reported below.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Immunoglobulins
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy **-** Critical	7/16 improvement	IVIg perfusion at 1 g/ kg/day (with various long term schemes)	16 cases, 7 case reports/case series, (Dauvilliers 2004 / 2006;	⨁⊖⊖⊖ Very Low

			Fronczek 2007; Plazzi 2008; Valko 2008; Knudsen 2010/2012)	
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	-			
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	2/2 improvement	IVIg perfusion at 1 g/ kg/day (with various long term schemes)	2 child/adult, 2 case reports, (Lecendreux 2003; Dauvilliers 2009)	⊕⊖⊖⊖ Very Low
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	1/4 pt (allergic reaction)	IVIg perfusion at 1 g/ kg/day (with various long term schemes)	4 pts, 1 case series (Valko 2008)	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical	headache, fever, flushing, Allergic reaction, rise of CSF leucocytes	IVIg perfusion at 1 g/ kg/day (with various long term schemes) In 2 studies + steroids	6 NC (any age) pts from 1 case series, 2 case reports (Knudsen 2012; Lecendreux 2003; Plazzi 2008)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Some patients with improvement; none with remission Adverse reactions not negligible
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**
Strength of the Recommendation	☐ Weak ☐ Strong

Question 4.3 - Plasmapheresis

Studies included: 1.

Chen W, Black J, Call P, Mignot E. Late-onset narcolepsy presenting as rapidly progressing muscle weakness: response to plasmapheresis. Ann Neurol 2005;58:489-90.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Plasmapheresis
Comparison: none

Outcomes →improvement or remission of cataplexy	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	1/1 (Shortlasting (several days) impressive improvement. Same for repeated treatments but catheter infection prevented her from continuation)	A 5-day course plasmapheresis, followed by IVIg	1 adult pt (NC) from 1 case report	⊕⊖⊖⊖ Very Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	1/1 Severe catheteher infection	-	-	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical	1/1 Severe catheteher infection			⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Very little published evidence
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**
Strength of the Recommendation	☐ Weak ☐ Strong

Question 4.4 - Steroids

Studies included: 3.

Coelho FM, Pradella-Hallinan M, Alves GR, Bittencourt LR, Tufik S. Report of two narcoleptic patients with remission of hypersomnolence following use of prednisone. Arq Neuropsiquiatr 2007;65:336-7.

Miyata R, Hayashi M, Kohyama J, Honda M. Steroid therapy ameliorated cataplexy in three children with recent-onset of narcolepsy. Sleep Med 2017;29:86-87.

Viste R, Soosai J, Vikin T, Thorsby PM, Nilsen KB, Knudsen S. Long-term improvement after combined immunomodulation in early post-H1N1 vaccination narcolepsy. Neurol Neuroimmunol Neuroinflamm 2017; 4:e389.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy **Intervention: Steroids** **Comparison:** none				
Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	(4/5 improvement)	Prednisone, Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	5 NC pts (any age) from 2 case series	⊕⊖⊖⊖ Very Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	(1/2 remission)	Prednisone, Prednisolone or methylprednisolone with various long term schemes (1 case preceded by IVIg)	2 NC pts (adults) from 1 case series	⊕⊖⊖⊖ Very Low
Ssubjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	No AEs	Prednisolone	3 NC pts (children) from 1 case series	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Only few patients with improvement Adverse reactions not assessed
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**
Strength of the Recommendation	☐ Weak ☐ Strong

Question 4.5 - Monoclonal antibodies

Studies included: 2.

Donjacour CE, Lammers GJ. A remarkable effect of alemtuzumab in a patient suffering from narcolepsy with cataplexy. J Sleep Res 2012;21:479-80.

Sarkanen T, Alén R, Partinen M. Transient Impact of Rituximab in H1N1 Vaccination-associated Narcolepsy With Severe Psychiatric Symptoms. Neurologist 2016;21:85-6.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Monoclonal antibodies / Immune modifying therapies
Comparison: none

Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	No Long term improvement (Dramatic improvement of cataplexy during 2 months, no improvement after repeated treatment (twice))	Rituximab (after methyl-prednisolone)	1 child (NC) from 1 case report	⊕⊖⊖⊖ Very Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	1/1 Long term remission (>1.5y) No formal assessment	Alemtuzumab (after methotrexate)	1 NC pt (adult) from 1 case report	⊕⊖⊖⊖ Very Low
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical		-	-	
Any adverse event of the drugs - important but not critical				

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Very little published evidence
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**
Strength of the Recommendation	☐ Weak ☐ Strong

Question 4.6 - Sodium Oxybate

Studies included: 17.

Studies on effectiveness and safety (6)

Ahmed M, Bassetti C, Becker P, Michael B, Black J, Bogan R, Chesson J, Cook J, Duntley S, Emsellem H, Ermine M, Hayduk R, Feldman N, Fleming J, Geisler P, Hagaman M, Hill D, Houghton WC, Hornfeldt CS, Husain AM, Kaelin T, Lammers GJ, Lankford DA, Leech J, Mamelak M, Mayer G, Moldofsky H, Montplaisir J, Morehouse R, Moscovitch A, Nevsimalova S, Sonka K, Orr W, Pascualy R, Pegram V, Perkins T, Phadke J, Ristanovic R, Shneerson J, Stevens J, Swick T, Walsleben J, Walter T, Ware JC, Whitten P, Winslow D. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med 2005;6: 415-21.

Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010;6:596-602.

Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431-43.

Lammers, G. J., J. Arends, A. C. Declerck, M. D. Ferrari, G. Schouwink, and J. Troost. 1993. 'Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study', Sleep, 16: 216-20.

Scrima L., Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. Sleep 1990;13:479-90.

Scrima L., Hartman PG, Johnson FH, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. Biol Psychiatry 1989;26:331-43.

The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.

Studies on safety (11)

Akins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). J Forensic Sci 2009;54:495-6.

Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med 2015;11:427-32.

Drakatos P, Lykouras D, D'Ancona G, Higgins S, Gildeh N, Macavei R, Rosenzweig I, Steier J, Williams AJ, Muza R, Kent BD, Leschziner G. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. Sleep Med 2017;35:80-84.

Langford J, Gross WL. Psychosis in the context of sodium oxybate therapy. J Clin Sleep Med 2011;7:665-6.

Mamelak M, Swick T, Emsellem H, Montplaisir J, Lai C, Black J. A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy. Sleep Med 2015;16: 52-8.

Mayer G, Plazzi G, Iranzo A, Ortega-Albas J, Quinnell T, Pesch H, Serralheiro P, Schlit AF, Wuiame D, Bentz JWG. Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Post-Authorization, Non-Interventional Surveillance Study. Sleep 2018;41(9).

Ortega-Albas JJ, Lopez-Bernabe R, Garcia AL, Gomez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci 2010;22:352r.e26-52.e26.

Poryazova R, Tartarotti S, Khatami R, Baumann CR, Valko P, Kallweit U, Werth E, Bassetti CL. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. Eur Neurol 2011;65:175-82.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol 2014;5:136.

Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. Sleep Med 2009;10:490-3.

After update search (October 2019):

Buckley PJ, Wolf CT. Psychosis in a 22-Year-Old Woman With Narcolepsy After Restarting Sodium Oxybate. Psychosomatics 2018;59:298-301.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Noujaim MG, Mourad A, Clough JD. Sodium Oxybate: A Cause of Extreme Involuntary Weight Loss in a Young Lady. Case Rep Med 2019;2019:6537815.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczek R, Lammers GJ. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. J Sleep Res 2019;28:e12684.

→2-year before-after study: treatment with sodium oxybate is associated with a body mass index reduction in narcolepsy type 1,

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Sodium Oxybate (SO) / Gamma Hydroxybutyrate (GHB)
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Reduction of weekly cataplexy attacks of 57.0, 65.0 and 84.7%	4.5, 6 or 9 g sodium oxybate or placebo for 8 weeks	228 pts, 1 RCT (Ahmed 2005)	⊕⊕⊕⊖ Moderate (risk of bias > high attrition for higher

				dosage; short duration)
	Diary: mean weekly cataplexy attacks reduction > -8.46 (-15.27/ - 1.64)	GHB, 50-60 mg/kg/night; 4 weeks	34 pts, 1 meta-analysis (Boscolo-Berto 2012) including 2 RCTs (Lammers 1993; Scrima 1989)	⊕⊕⊕⊖ Moderate (small sample; short duration)
	Mean daily cataplexy attacks reduction: 1.10; 1.29/0.90, p < 0.00001 Mean weekly cataplexy attacks reduction: 7.04; 95% CI 12.45/1.63, p< 0.01		136 pts, 1 meta-analysis (Boscolo-Berto 2012) including 1 RCT (XyREM 2002)	⊕⊕⊕⊖ Moderate (risk of bias; short duration)
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical		-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.2**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.2** + Ahmed 2005 **:** nausea (14.2%); dizziness (13%); enuresis (11%)			

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Sodium oxybate effective in improving cataplexy Adverse reactions are generally rare although several adverse events (nocturnal confusion, enuresis, nausea, vomiting, dizziness, raised ALT, vertigo causing fall and trauma, headache) can be limiting factors. Very serious AEs (psychosis, death) are very rare but must be considered in selecting patients to be treated
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	□ **X For** □ Against □ No Recommendation
Strength of the Recommendation	□ Weak □ **X Strong**

Question 4.7 - Amphetamines

Studies included: 6.

Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. Sleep 2005;28:667-72

Chen SY, Clift SJ, Dahlitz MJ, Dunn G, Parkes JD. Treatment in the narcoleptic syndrome: self assessment of the action of dexamphetamine and clomipramine. J Sleep Res 1995;4:113-18.

Mitler MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. Sleep 1993;16:306-17.

Parkes JD, Fenton GW. Levo(-) amphetamine and dextro(+) amphetamine in the treatment of narcolepsy. Journal of Neurology Neurosurgery and Psychiatry 1973;36:1076-81.

Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. Br Med J (Clin Res Ed) 1985;290:1167-70.

Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, Steier J, Rosenzweig I, Williams AJ, Leschziner GD, Drakatos P. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. Journal of Sleep Research 2018;27:e12627.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Amphetamines
Comparison: none

Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	-	-	-	-
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	No improvement of cataplexy frequency (No of attacks of cataplexy day)	Dexamphetamine 5-16 mg die	20 pts (12 with cataplexy) (1 study Shindler 1985)	⊕⊖⊖⊖ Very Low
	Significant improvement of atonia total score		60 pts (1 study Chen 1995)	
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - critical	-	-	-	-
Any adverse event of the drugs - critical	Nervousness, sweating, palpitations, headache, Irritability, weight loss and weight gain	l-amphetamine, metamphetamine; Dexedrine; Dexamphetamine	100 pts (4 studies)	⊕⊖⊖⊖ Very Low
	psychosis OR = 12.0 [1.6-92.0] alcohol or polysubstance misuse OR = 4.3 [1.2-15.2] psychiatric hospitalization (odds ratio = 3.2 [1.1-10.0])	Methylphenidate over 120 mg Methamphetamine over 100 mg Dextroamphetamine, over 120 mg Pemoline over 180 mg	116 pts N or IH (1 study Auger 2015)	⊕⊕⊖⊖ Low

	tachyarrhythmias OR = 3.3 [0.92-12.1] anorexia or weight loss OR = 11.0 [1.4-85.2]. The frequency of physician-diagnosed depression, drug-seeking and suicide-related behaviors, hypertension, and cardiovascular disease did not differ significantly between the groups.	Amphetamine over 120 mg		
	Side effects: methylphenidate 37% Most frequent: headache, mood swings, palpitations 30% had side effects that lead to combination therapy	Drug naïve pats were started with modafinil followed by methylphenide, amphetamines or SO, if partial or no response: combinations	72 pts, 1 case series (Thakrar 2018)	

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	very little published evidence and safety concern
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.8 - Methylphenidate

Studies included: 0.

Summary of Findings table

Patients or population Adults with narcolepsy and moderate to severe cataplexy **Intervention: Methylphenidate** **Comparison:** placebo **Outcomes** **subjective measures: Sleep diaries: mean reduction of cataplexy –** Critical **subjective measures: Sleep diaries: percentage of patients with remission of cataplexy –** Critical **subjective measures: Global Clinical Impression: mean cataplexy improvement –** Critical **subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy** - Critical **Adverse events leading to withdrawal from the drugs -** important but not critical **Any adverse event of the drugs -** important but not critical	No study found

VOTE

Direction of the Recommendation	□ For □ **X Against** □ No Recommendation
Strength of the Recommendation	□ Weak □ **X Strong**

Question 4.9 - Solriamfetol

Studies included: 5.

Bogan RK, Feldman N, Emsellem HA, Rosenberg R, Lu Y, Bream G, Khayrallah M, Lankford Da. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. Sleep Med 2015;16:1102-8.

Ruoff C, Swick TJ, Doekel D, Emsellem HA, Feldman NT, Rosenberg R, Bream G, Khayrallah MA, Lu Y, Black J. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: a Phase 2b Study. Sleep 2016;39:1379-87.

Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y, Black J, Dauvilliers Y. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. Ann Neurol 2019; 85:359-370.

Update searches (October 2019 and July 2020):

Malhotra A, Shapiro C, Pepin JL, Hedner J, Ahmed M, Foldvary-Schaefer N, Strollo PJ, Mayer G, Sarmiento K, Baladi M, Chandler P, Lee L, Schwab R. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep 2020;43(2).

→50-week open-label study (with a nested 2-week withdrawal rct) of patients with narcolepsy and OSAS: it does not modify the main findings reported below.

Dauvilliers Y, Shapiro C, Mayer G, et al. Solriamfetol for the Treatment of Excessive Daytime Sleepiness in Participants with Narcolepsy with and without Cataplexy: Subgroup Analysis of Efficacy and Safety Data by Cataplexy Status in a Randomized Controlled Trial. CNS Drugs. 2020 34: 773-784.

→Subgroup analyses of data from a previous 12-week randomized, double-blind, placebo-controlled, phase III trial of solriamfetol for EDS in narcolepsy evaluated the efficacy and safety of solriamfetol by cataplexy status: it does not modify the main findings reported below.

Summary of Findings table

Patients or population Adults with narcolepsy and moderate to severe cataplexy
Intervention: Solriamfetol
Comparison: placebo

Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	No significant difference in number of weekly cataplexy attacks (JZP-110 −1.0; placebo, 0) in the 33 patients -	110 up to 300 mg JZP110-solriamfetol	93 pts (33 NwC) (1 RCT Ruoff 2016)	⊕⊕⊕⊖ Moderate
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	-			
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	-			
Adverse events leading to withdrawal from the drugs - important but not critical	TEAE leading to study drug discontinuation Plac 1 (1.7%) All doses 9 (5.1%) 75 mg 1 (1.7%) 150 mg 3 (5.1%) 300 mg 5 (8.5%)	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 (3 RCTs Bogan 2015; Ruoff 2016, Thorpy 2019)	⊕⊕⊕⊖ Moderate
Any adverse event of the drugs - important but not critical	most common versus placebo insomnia (23% versus 8%), headache (16%	75 mg, 150 mg, 300 mg JZP110-solriamfetol	357 (3 RCTs Bogan 2015; Ruoff 2016, Thorpy 2019)	⊕⊕⊕⊖ Moderate

	versus 10%), nausea (14% versus 6%), diarrhea (11% versus 6%), decreased appetite (14% versus 0%), and anxiety (11% versus 0%)			

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	No improvement of cataplexy. No major safety concern however long term treatment data not available
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.10 - Mazindol

Studies included: 5.

Alvarez B, Dahlitz M, Grimshaw J, Parkes JD. Mazindol in long-term treatment of narcolepsy. Lancet 1991; 337:1293-4.

Iijima S, Sugita Y, Teshima Y, Hishikawa Y. Therapeutic effects of mazindol on narcolepsy. Sleep 1986;9:265-8.

Nittur N, Konofal E, Dauvilliers Y, Franco P, Leu-Semenescu S, Cock VC, Inocente CO, Bayard S, Scholtz S, Lecendreux M, Arnulf I. Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. Sleep Med 2013;14:30-6.

Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. British medical journal (clinical research ed.) 1985;290:1167-70.

Vespignani H, Barroche G, Escaillas JP, Weber M. Importance of mazindol in the treatment of narcolepsy. Sleep 1984;7:274-5.

Summary of Findings table

Patients or population Adults with narcolepsy and moderate to severe cataplexy **Intervention: Mazindol** **Comparison:** none / placebo				
Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	No of attacks of cataplexy / day: No treatment 2-1 (0 6) Mazindol 1-2 (0-4)	4 mg/day for 12 weeks	20 pts, 1 cross-over RCT (Shindler 1985)	⊕⊕⊖⊖ Low (Risk of bias)
	Reduction from 4.6 ± 3.1 to 2 ± 2.8 cataplexy episodes per week	3.4 ± 1.3 mg/day, 1–6 mg) for an average of 30 months	62 pts (1 study; Nittur 2013)	⊕⊖⊖⊖ Very Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	Cataplexy was eliminated in 14.5% of patients, improved in 27.5%, and	3.4 ± 1.3 mg/day, 1–6 mg) for an average of 30 months	62 pts, 1 before/after study (Nittur 2013)	⊕⊖⊖⊖ Very Low

	unchanged in 29% (missing data in 29%).			
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	Efficacy (excellent to good effect): 50%	0.5-4 mg for 4 weeks	8 pts, 1 case series (Iijima 1986)	⊕⊖⊖⊖ Very Low
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	(Cataplectic attacks disappeared in six of seven patients, 1 patient received additional clomipramine)	2-4 mg/day (28 mo mean duration of treatment)	7 pts, 2 case series (Vespignani 1984; Alvarez 1991)	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	22% stopped due to lack of efficacy	Mean dose 3.4 ± 1.3 mg for about 30 months	62 pts, 1 before/after study (Nittur 2013)	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical	Headache, insomnia, decreased appetite, tolerance; urinary retention, restlessness, dry mouth, constipation; palpitation	0.5-4 mg / day	81 pts, 4 studies; (Vespignani 1984; Shindler 1985; Iijima 1986; Alvarez 1991)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Absence of enough good benefit-risk ratio evaluation
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No** **Recommendation** because the drug is out of market

Question 4.11 - Modafinil

Studies included: 15.

Studies on effectiveness and safety (10)

Besset A, Tafti M, Villemin E, Billiard M. [The effects of modafinil (300mg) on sleep, sleepiness and arousal in narcoleptic patients]. Neurophysiol Clin 1993;23: 47-60.

Billiard M, Besset A, Montplaisir J, Laffont F, Goldenberg F, Weill JS, Lubin S. Modafinil: a double-blind multicentric study. Sleep 1994;17:S107-12.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Boivin DB, Montplaisir J, Petit D, Lambert C, Lubin S. Effects of modafinil on symptomatology of human narcolepsy. Clinical neuropharmacology 1993;16:46-53.

Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, Montplaisir JY, Morehouse RL, Moscovitch A, Murphy WF. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997;49:444-51.

Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. Med Sci Monit 2010;16: Ra177-86.
Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med 2000;1:109-16.
Saletu M, Anderer P, Saletu-Zyhlarz GM, Mandl M, Arnold O, Nosiska D, Zeitlhofer J, Saletu B. EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil. Eur Arch Psychiatry Clin Neurosci 2005;255:20-32.
US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97.
US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000;54:1166-75.
Studies on safety (5)
Prince V, Philippidou M, Walsh S, Creamer D. Stevens-Johnson syndrome induced by modafinil. Clin Exp Dermatol 2018:43:191-192.
Sanyal D, Ghosh M. A case of modafinil induced mania in a child suffering from Narcolepsy. Bengal Journal of Private Psychiatry 2017;8:14-15.
Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry 2005;162:813–14.
Wu P, Jones S, Ryan CJ, Michail D, Robinson TD. Modafinil-induced psychosis. Intern Med J. 2008;38:677-8.
Yasui-Furukori N, Kusunoki M, Kaneko S. Hallucinations associated with modafinil treatment for narcolepsy. J Clin Psychopharmacol 2009;29:408.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Modafinil
Comparison: placebo

Outcomes →improvement or remission of cataplexy	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Number of cataplexy attacks per day: Mean difference 0.02 (95% CI -0.27-0.31)	200-400 mg per day FU 2 weeks	Meta-analysis (Golicki 2010) of 317 pts from 4 RCTs (3 cross-over: 1 parallel; Boivin, Billiard, Broughton; Moldofsky)	⊕⊕⊖⊖ Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.7**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.7**			

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall moderate quality of evidence

Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Modafinil is not effective in improving cataplexy. No major concern on safety Headache, nausea, dry mouth; nervousness, dyspepsia, pain, and vomiting, increased blood pressure
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.12 - Armodafinil

Studies included: 3.

Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. J Clin Sleep Med 2010;6:458-66.

Harsh JR, Hayduk R, Rosenberg R, Wesnes KA, Walsh JK, Arora S, Niebler GE, Roth T. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin 2006;22:761-74.

Holfinger S, Roy A, Schmidt M. Stevens-Johnson Syndrome After Armodafinil Use. J Clin Sleep Med 2018;14:885-887. Not a narcolepsy patient

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Armodafinil
Comparison: placebo

Outcomes →improvement or remission of cataplexy	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	There was also no change in the incidence of selfreported cataplexy (mean ± SD change from baseline to final visit, armodafinil 150 mg, 0.0 ± 1.14; armodafinil 250 mg, –0.2 ± 0.66; armodafinil combined group, –0.1 ± 0.93; placebo, –0.1 ± 0.56).	Armodafinil 150-250 mg; 12 weeks	196 pts (1 study Harsh 2006)	⊕⊕⊕⊕ High
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	-	-	-	-
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	misses/accidents ns reduced in ArM groups	Armodafinil 150-250 mg; 12 weeks	196 pts (1 study Harsh 2006)	⊕⊕⊕⊕ High

Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	Most frequent headache (30%), nasopharyngitis (21%),nausea 15%, insomnia 8%. SAE in 4 NT (coronary artery heart disease (1), hemorrhoidal hemorrhage (1), hypertension (1), dry mouth, dizziness, cough each 8%	Armodafinil 150-250 mg; 12 mo	156 pts (1 study Black 2010)	⊕⊕⊖⊖ Low
	Stevens-Johnson syndrome: 1 case	Armodafinil	1 pt (NOT with narcolepsy), 1 case report (Holfinger 2018)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Armodafinil is not effective in improving cataplexy. No major concern on safety
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.13 - Pitolisant

Studies included: 2.

Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding CL, Lecomte JM, Schwartz JC. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol 2013;12:1068-75.

Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, Sonka K, Lehert P, Lecomte I, Lecomte JM, Schwartz JC. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:200-07.

After update search (October 2019):

Dauvilliers Y, Arnulf I, Szakacs Z, Leu-Semenescu S, Lecomte I, Scart-Gres C, Lecomte JM, Schwartz JC. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep 2019;42(11).

→12-month open-label study: it does not modify the main findings reported below, except for **1 possibly related miscarriage**, as serious adverse effect.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Pitolisant
Comparison: placebo

Outcomes →improvement or remission of cataplexy	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Changes in daily rates of cataplexy from Baseline (between visits V2 and V3) to Final (between V6 and V7) periods in the "exposed" population: Plac 0.9 vs 1.5	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg; FU 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate (Attrition bias; short duration)

	Pit: 1.25 vs 0.4 Mod 1.0 vs 0.9 Pit vs Plac p=0.034 Mod vs Plac p=0.396 Mod vs Pit p=0.138 WRC=weekly rate of cataplexies. Pit Baseline 9.15 Final 2.27 Change 0.25 Plac Baseline 7.31 Final 4.52 Change 0.62 Treatment effect 0.51 (0.43–0.60) p<0.0001 WRC >15 (n/N [%]) Pit Baseline 15/54 (28%) Final 4/54 (7%) Plac Baseline 9/51 (18%) Final 12/51 (24%) Treatment effect 0.05 (0.01–0.40) p<0.005			
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	CGI-C cataplexy improved (n/N [%]) Placebo 6/25 (24%) Pitolisant 9/26 (35%) Modafinil 8/28 (29%) Ns Improvement in CGI cataplexy (n/N [%]) PIT 36/54 (67%) Plac 17/51 (33%) Treatment effect 4.00 (1.54–10.38) p=0.004	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg; FU 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	ns reduced in Pit groups	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	more AEs for Pitolisant 35% vs placebo 31%); sig more TEAs for Pitolisant 28% vs 6%; 1 SAE with severe nausea Most frequent: headache 35%, insomnia 10%, abdominal discomfort, nausea each 6%; irritability, anxiety; 1 SAE due to abdominal discomfort	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg 7-8 weeks	199 pts, 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖

	Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Moderate improvement of cataplexy. Not major concern on AEs
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 4.14 - Selegiline

Studies included: 3.

Hublin C, Partinen M, Heinonen EH, Puukka P, Salmi T. Selegiline in the treatment of narcolepsy. Neurology 1994;44:2095-101.
Mayer G, Ewert Meier K, Hephata K. Selegeline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. Clin Neuropharmacol 1995;18:306-19.
Reinish LW, MacFarlane JG, Sandor P, Shapiro CM. REM changes in narcolepsy with selegiline. Sleep 1995;18:362-7.

Summary of Findings table

Patients or population Adults with narcolepsy and moderate to severe cataplexy
Intervention: Selegiline
Comparison: placebo / none

Outcomes →improvement or remission of cataplexy	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Dose dependent up to 89% reduction cataplexy > median number of cataplectc attacks = 0 with the 20-40 doses (6-8 in plac and sel 10 mg dose) up to 50% significant with higher dose (2x10 mg).	10,20,30,40 mg (3tbl./d); 4 wks 10, 20 mg; 2 weeks,	47 pts, 2 RCTs; (Hublin 1994; Mayer 1995)	⊕⊕⊖⊖ Low (fixed sequence; small sample)
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	-	-	-	-
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	-
Any adverse event of the drugs - important but not critical	Slight increase of alanine aminotransferase in 2 NT1; Most common side effects:	10,20,30,40 mg (3tbl./d); 4 wks 10, 20 mg; 2 weeks,	58 pts (3 studies; Hublin 1994; Mayer 1995; Reinish)	⊕⊕⊖⊖ Low

	dry mouth, headache, insomnia, sweating			

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Improvement of cataplexy at higher doses. Safety concern at higher doses
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.15 - Tricyclic Antidepressants

Studie included: 6.

Chen SY, Clift SJ, Dahlitz MJ, Dunn G, Parkes JD. Treatment in the narcoleptic syndrome: Self assessment of the action of dexamphetamine and clomipramine. Journal of Sleep Research 1995;4:113-18.

Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. Acta Neurol Scand 1976;54:71-87.

Parkes JD. Clomipramine (Anafranil) in the treatment of cataplexy. Journal of International Medical Research 1973;1:427-31.

Parkes JD, Schachter M. Clomipramine and clonazepam in cataplexy. Lancet 1979;2:1085-6.

Ristanovic RK, Liang H, Hornfeldt CS, Lai C. Exacerbation of cataplexy following gradual withdrawal of antidepressants: manifestation of probable protracted rebound cataplexy. Sleep Med 2009;10: 416-21.

Schachter M, Parkes JD. Fluvoxamine and clomipramine in the treatment of cataplexy. J Neurol Neurosurg Psychiatry 1980;43:171-4.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Tricyclic Antidepressants
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Significant reduction of cataplexy from the drug withdrawal evaluation (mean 24.0 SD 23.6) to first (mean 0.8 SD 2.1, p<0.01) and second (mean 6.4, SD 10.4, p<0.05) clomipramine evaluation Reduction of cataplexy by more than 50%according to simple subjective report, at the short-term follow up. Five	Clomipramine 75 mg; up to 3 weeks to years FU Clomipramine; Protriptyline; Imipramine; Desipramine; Doxepin; Nortriptyline	66 pts, 3 studies (Guilleminault 1976; Schachter 1980; Ristanovic 2009)	⊕⊕⊖⊖ Low

	participants out of 11 had reduction of cataplexy in the fluvoxamine period versus 7 participants out of 11 in the clomipramine period. Among the patients who were and were not withdrawn from antidepressants treatment, the median frequency of baseline weekly cataplexy was similar (17.5 vs. 14.0, respectively). Significant between-group differences emerged by the end of the washout period (52.04 vs. 15.25, respectively; $p < 0.05$)			
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy **-** Critical	Elimination of cataplexy according to subjective report: 3 participants out of 11 were free from attacks in the fluvoxamine period versus 4 participants out of 11 in the clomipramine period.	Clomipramine50 – 200 mg mean 60 mg; For 3 wks	18 pts, 1 study (Schachter 1980)	⊕⊕⊖⊖ Low
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	cataplexy was reduced by 23%	Clomipramine, mean dosage 64 mg/24 h, range 25-125: mean treatment period 14 years, range 1-24	148 pts 1 study (Chen 1995)	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical	weight gain (1/7) 11/11 dry mouth 7 /11 : nocturnal myoclonus, sexual complaints (mainly males), digestive problems Rebound after withdrawal Weight gain, sexual side effects, nausea and one a rash 2/18 dry mouth 2/18 delayed ejaculation 63% Weight gain 19% Sexual dysfunction Constipation 25%, dry mouth 38%, impaired sexual function 19%	-	70 pts, 5 studies (Parkes 1973; Guilleminault 1976; Parkes 1979; Schachter 1980; Chen 1995)	⊕⊕⊖⊖ Low

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Tricyclic antidepressants are effective in improving cataplexy. Due to possible tolerance and frequent AEs (weight gain, sexual dysfunction, constipation, dry mouth) the balance of benefits versus harms could be uncertain for some patients
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	

AFTER TWO ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.16 - SSRI – NSRI - Other Antidepressants

Eligible studies proposed to experts: 8.

Guilleminault C, Mancuso J, Salva MA, Hayes B, Mitler M, Poirier G, Montplaisir J. Viloxazine hydrochloride in narcolepsy: a preliminary report. Sleep 1986;9:275-9.

Jin L, Shi L, Zhang Y, Chen BB, Wang XL, Liu YH. Antidepressants for the treatment of narcolepsy: A prospective study of 148 patients in northern China. J Clin Neurosci 2019;63:27-31.

Larrosa O, de la Llave Y, Bario S, Granizo JJ, Garcia-Borreguero D. Stimulant and anticataplectic effects of reboxetine in patients with narcolepsy: a pilot study. Sleep 2001;24:282-5.

Mitler MM, Hajdukovic R, Erman M, Koziol JA. Narcolepsy. Journal of Clinical Neurophysiology 1990;7:93–118.

Salin-Pascual RJ. Improvement in cataplexy and daytime somnolence in narcoleptic patients with venlafaxine XR administration. Sleep and Hypnosis 2002;4:22-25.

Schachter M, Parkes JD. Fluvoxamine and clomipramine in the treatment of cataplexy. J Neurol Neurosurg Psychiatry 1980;43:171-4.

Schrader H, Kayed K, Bendixen Markset AC, Treidene HE. The treatment of accessory symptoms in narcolepsy: a double-blind cross-over study of a selective serotonin re-uptake inhibitor (femoxetine) versus placebo. Acta Neurol Scand 1986;74:297-303.

Wang J, Greenberg H. Status cataplecticus precipitated by abrupt withdrawal of venlafaxine. J Clin Sleep Med 2013;9:715-6.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: SSRI – NSRI - Other Antidepressants
Comparison: none / placebo / other antidepressant

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	Reduction of cataplexy by more than 50%: 5 out of 11 had reduction of cataplexy in the fluvoxamine period versus 7 participants out of 11 in the clomipramine period.	fluvoxamine 50-200 mg, mean 75 mg, for 3 weeks	18 pts, 1 cross-over RCT (Schachter 1980)	⊕⊕⊖⊖ Low

	The frequency of cataplectic attacks, according to an ordinal scale (range of values 0-9) was 1.77 during the viloxazine period and 2.94 during the placebo period. (P value = 0.0001).	Viloxazine100 mg; 6 weeks FU	23 pts, 1 RCT (Guilleminault 1986 / Mitler 1990)	
	Within patient differences in frequency of cataplectic attacks per day reduced: mean 1.29, p= 0.03 Severity score per day not reduced → Several pts prefered clomipramine which they had used before, because of better efficacy.	Femoxetine 600 mg; 4 weeks FU	10 pts, 1 RCT (Schrader 1986)	
	UNS Cataplexy subscore from 5,85±2,67 to 1,71±1,60, p<0.05	Reboxetine 10 mg Follow up 14 days	12 pts, 1 before/after study (Larrosa 2001)	
	Significant reduction was observed since the first week. 7 attacks /wk at baseline; less than 1/wk at 8wk), p<0.05 vs.	Venlafaxine XR 300 mg	6 pts, 1 before/after study (Salin-Pascual 2002)	
	SSRI: median number of cataplexy episodes from 21 times per week to 2 times per week in 76 patients (p < 0.001) NSRI: median number of cataplexy episodes from 28 times per week to 1 per week in 44 patients (p < 0.001)	SSRI (100; sertraline, paroxetine, fluoxetine) NSRI (48 venlafaxine)	148 pts, 1 before/after study (Jin 2019)	
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	Elimination of cataplexy: 3 out of 11 free from attacks in fluvoxamine versus 4 out of 11 in clomipramine	fluvoxamine 50-200 mg, mean 75 mg, for 3 weeks	18 pts, 1 1 cross-over RCT (Schachter 1980)	⊕⊕⊖⊖ Low
Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	Viloxazine 1/23 subject discontinued because of nausea and headache	-	23 pts, 1 RCT (Guilleminault 1986 / Mitler 1990)	⊕⊕⊖⊖ Low
Any adverse event of the drugs - important but not critical	Transient nausea in 2/10 patients „dry mouth, hyperhidrosis, constipation, restlessness 4/6: nausea, anorexia and anxiety, > mild,	Femoxetine Reboxetine Venlafaxine XR 300 mg venlafaxine 75 mg	10 pts, 1 RCT Schrader 1986 12 pts Larrosa 2001 6 pts Salin-Pascual 2002	⊕⊕⊖⊖ Low

	and disappeared after one or two weeks of treatment. Status cataplecticus within 48 hrs after withdrawal early awakening and dry mouth for all three groups; fluoxetine: dizziness, nausea, decreased appetite; sertraline: irritability, insomnia, weight gain, nausea, hyperhidrosis, diarrhea; venlafaxine: irritability, insomnia, weight gain, nausea, constipation, decreased appetite	SSRI (100; sertraline, paroxetine, fluoxetine) NSRI (48 venlafaxine)	1 Wang 2013 148 Jin 2019	

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	SSRI/NSRI/other antidepressants are effective in improving cataplexy. Due to possible tolerance and frequent AEs (nausea, dizziness, decreased appetite; irritability, insomnia, weight gain, hyperhidrosis, diarrhea; constipation) the balance of benefits versus harms could be uncertain for some patients
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	

AFTER 2 ROUND OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 4.17 - Baclofen

Studies included: 1.

Lee EK, Douglass AB. Baclofen for narcolepsy with cataplexy: two cases. Nat Sci Sleep 2015;7:81-3.

After update search (October 2019):

Morse AM, Kelly-Pieper K, Kothare SV. Management of Excessive Daytime Sleepiness in Narcolepsy With Baclofen. Pediatr Neurol 2019;93:39-42.

→1 case series (5 pts): it does not modify the main findings reported below.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe cataplexy
Intervention: Baclofen
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical				
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Non validated tools to assess cataplexy - important but not critical	Remission of cataplexy	Baclofen 20-30 every night FU 8 mo-3yrs	2 pts (Lee 2015)	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical				
Any adverse event of the drugs - important but not critical	1/2 : mild daytime sleepiness	Baclofen 20-30 every night FU 8 mo-3yrs	2 pts (Lee 2015)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	very little published evidence
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**

Group 3 - Symptomatic treatment, pharmacological management, Adults

Treatment of moderate to severe night-time disturbed sleep

Question 5.1 - Hypocretin/Orexin

Studies included: 2.

Baier PC, Hallschmid M, Seeck-Hirschner M, Weinhold SL, Burkert S, Diessner N, Goder R, Aldenhoff JB, Hinze-Selch D. Effects of intranasal hypocretin-1 (orexin A) on sleep in narcolepsy with cataplexy. Sleep Med 2011;12:941-6.

Weinhold SL, Seeck-Hirschner M, Nowak A, Hallschmid M, Goder R, Baier PC.The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. Behav Brain Res 2014:262:8-13.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep
Intervention: Hypocretin/Orexin
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	No data	-	-	-
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	no difference compared to placebo	intra-nasal hypocretin before bed in 2 separate nights of assessment	8 narcolepsy patients (type 1), 1 RCT (Baier 2011)	⊕⊕⊖⊖ Low
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	no difference compared to placebo only REM sleep slightly decreased with treatment as were shifts from wake to REM only N2 sleep slightly increased	intra-nasal hypocretin before bed or in morning in 2 separate nights of assessment	16 narcolepsy patients (type 1), 2 RCTs (Baier 2011, Weinhold 2014)	⊕⊕⊖⊖ Low
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	-
Any adverse event of the drugs - important but not critical	No data	-	-	-

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	no difference compared to placebo unknown adverse events
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For **X Against** ☐ No Recommendation
Strength of the Recommendation	Weak

	X **Strong**

Question 5.2 - Sodium Oxybate

Studies included: 22.

Studies on effectiveness and safety (8)

Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. Sleep Med 2009;10:829-35.

Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010;6:596-602.

Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431-43.

Dauvilliers Y, Roth T, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate, modafinil, and their combination on disrupted nighttime sleep in narcolepsy. Sleep Med 2017;40:53-57.

Lammers, G. J., J. Arends, A. C. Declerck, M. D. Ferrari, G. Schouwink, and J. Troost. 1993. 'Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study', Sleep, 16: 216-20.

Roth T, Dauvilliers Y, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate on disrupted nighttime sleep in patients with narcolepsy. J Sleep Res 2017;26:407-14.

Scrima L., Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study. Sleep 1990;13:479-90.

Scrima L., Hartman PG, Johnson FH, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. Biol Psychiatry 1989;26:331-43.

Studies on safety (14)

Akins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). J Forensic Sci 2009;54:495-6.

Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451-8.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med 2015;11:427-32.

Drakatos P, Lykouras D, D'Ancona G, Higgins S, Gildeh N, Macavei R, Rosenzweig I, Steier J, Williams AJ, Muza R, Kent BD, Leschziner G. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. Sleep Med 2017;35:80-84.

Langford J, Gross WL. Psychosis in the context of sodium oxybate therapy. J Clin Sleep Med 2011;7:665-6.

Mamelak M, Swick T, Emsellem H, Montplaisir J, Lai C, Black J. A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy. Sleep Med 2015;16: 52-8.

Mayer G, Plazzi G, Iranzo A, Ortega-Albas J, Quinnell T, Pesch H, Serralheiro P, Schlit AF, Wuiame D, Bentz JWG. Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Post-Authorization, Non-Interventional Surveillance Study. Sleep 2018;41(9).

Ortega-Albas JJ, Lopez-Bernabe R, Garcia AL, Gomez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci 2010;22:352r.e26-52.e26.

Poryazova R, Tartarotti S, Khatami R, Baumann CR, Valko P, Kallweit U, Werth E, Bassetti CL. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. Eur Neurol 2011;65:175-82.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol 2014;5:136.

The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.

The Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.

Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. Sleep Med 2009;10:490-3.

After update search (October 2019):

Buckley PJ, Wolf CT. Psychosis in a 22-Year-Old Woman With Narcolepsy After Restarting Sodium Oxybate. Psychosomatics 2018;59:298-301.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Noujaim MG, Mourad A, Clough JD. Sodium Oxybate: A Cause of Extreme Involuntary Weight Loss in a Young Lady. Case Rep Med 2019;2019:6537815.

→ case report of 1 patient on safety: it does not modify the main findings reported below.

Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczek R, Lammers GJ. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. J Sleep Res 2019;28:e12684.

→2-year before-after study: treatment with sodium oxybate is associated with a body mass index reduction in narcolepsy type 1,

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep
Intervention: Sodium Oxybate (SO) / Gamma Hydroxybutyrate (GHB)
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence

Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	subjective nocturnal awakenings: mean reduction of 1 awakening per night (WMD 1.33; 95% CI 1.78/0.88, p < 0.00001)	4 weeks of SO (4 gr)	44 narcolepsy patients (mixed types) 1 metanalysis of 2 RCTs (Boscolo-Berto 2012; 2 RCTs Scrima 1989/1990, Lammers 1993)	⊕⊕⊕⊖ Moderate
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	-	-	-	-
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	Objective measures of nocturnal awakenings improved with GHB - sleep stage shifts: mean reduction of 9.69 shift per night (WMD 9.69; 95% CI 17.14/2.24, p = 0.01). - increased sleep stages 3-4 of a mean of 4% of the total sleep time (WMD 4.11; 95% CI 0.07/8.16, p = 0.05)	4 weeks of SO (4 gr)	44 narcolepsy patients (mixed types) 1 metanalysis of 2 RCTs (Boscolo-Berto 2012; 2 RCTs Scrima 1989/1990, Lammers 1993)	⊕⊕⊕⊖ Moderate
	Total sleep time increased of mean 18 min at 8 weeks at 9g Nocturnal awakenings reduced (from 7.5 to 15.0 per night) in all treatment groups at 4 weeks dose-dependent effects on reduced Wake After Sleep Onset (WASO) in 9 gr group (-22 min) Slow wave sleep increased (+ 3 min) 3 gr, (+21 min) 6g, (+52.50) 9g groups at 8 weeks Stage 1 sleep decreased at 4 weeks; No change in sleep latency No effects on stage 2 or REM sleep	8 week treatment (4.5 / 6 / 9 gr) with titration up to 9g/day over 4 weeks	228 pts; 1 RCT (Black 2010)	
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.2**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.2**			

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep
Intervention: Sodium Oxybate
Comparison: Modafinil

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	Oxybate groups improved subjective sleep quality on	At 8 weeks Placebo SO	232 pts (all taking modafinil before trial). 1 RCT (Black	⊕⊕⊕⊖ Moderate

	PQSI compared to placebo and modafinil alone	Modafinil SO + Modafinil SO dose increased from 6 to 9g after 4 weeks for a total of 8 week treatment	2009; Dauvilliers 2017; Roth 2017)	
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	No data	-	-	-
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	both oxybate groups increased total non-REM sleep time and slow wave sleep (also reduced REM sleep time); no change in total sleep time; modafinil alone group had no changes	At 8 weeks Placebo SO Modafinil SO + Modafinil SO dose increased from 6 to 9g after 4 weeks for a total of 8 week treatment	232 pts (all taking modafinil before trial). 1 RCT (Black 2009; Dauvilliers 2017; Roth 2017)	⊕⊕⊕⊖ Moderate
Adverse events leading to withdrawal from the drugs - important but not critical	No data	-	-	
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	Nausea and vomiting highest frequency in oxybate groups; dizziness highest in oxybate/modafinil group; Tremor (4%) and paraesthesiae (2.6%) higher in oxybate group; One event of psychosis linked to oxybate	At 8 weeks Placebo SO Modafinil SO + Modafinil oxybate dose increased from 6 to 9g after 4 weeks for a total of 8 week treatment	2 RCTs (Black 2010; The U.S. Xyrem. Multicenter Study Group 2002	⊕⊕⊕⊖ Moderate

Overall quality of evidence across all critical outcomes	⊕⊕⊕⊖ Moderate

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ Yes ☐ **X No**	Overall moderate quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Sodium oxybate effective in improving nocturnal sleep maintenance and quality Adverse reactions are generally rare although several adverse events (nocturnal confusion, enuresis, nausea, vomiting, raised ALT, vertigo causing fall and trauma, headache) can be limiting factors.
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	**X For** ☐ Against

	☐ No Recommendation
Strength of the Recommendation	Weak **X Strong**

Question 5.3 - Benzodiazepines

Study included: 1.

Thorpy MJ, Snyder M, Aloe FS, Ledereich PS, Starz KE. Short-term triazolam use improves nocturnal sleep of narcoleptics. Sleep 1992;15:212-6.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep
Intervention: Benzodiazepines
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	-	-	-	-
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	-			
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	Total sleep time (392 v 346 mins) and sleep efficiency (87 v 77%) increased in treated group; No effects on other parameters or tests of daytime sleepiness	Single-blind trial of triazolam (0.25mg) versus placebo, used for 2 consecutive nights in a 6 night study	10 pts patients 1 RCT (Thorpy 1992)	⊕⊕⊖⊖ Low
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	-
Any adverse event of the drugs - important but not critical	-	-	-	-

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Modest effect on outcome
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ **X Against** No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 5.4 - Baclofen

Included studies: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep **Intervention: Baclofen** **Comparison:** - **Outcomes** **Sleep diaries: mean improvement of nighttime disturbed sleep –** Critical **Global Clinical Impression: mean improvement of nighttime disturbed sleep –** Critical **PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts –** Critical **Adverse events leading to withdrawal from the drugs -** important but not critical **Any adverse event of the drugs -** important but not critical	No study found on adults 1 study on children Huang YS, Guilleminault C. Narcolepsy: action of two gamma-aminobutyric acid type B agonists, baclofen and sodium oxybate. Pediatr Neurol 2009; 41:9-16. Low quality

AFTER 2 ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 5.5 / 5.6 / 5.7 - Gabapentin / Pregabalin / Melatonin

Included studies: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe night-time disturbed sleep **Intervention: Gabapentin / Pregabalin / Melatonin** **Comparison:** - **Outcomes** **Sleep diaries: mean improvement of nighttime disturbed sleep –** Critical **Global Clinical Impression: mean improvement of nighttime disturbed sleep –** Critical **PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts –** Critical **Adverse events leading to withdrawal from the drugs -** important but not critical **Any adverse event of the drugs -** important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Group 3 - Symptomatic treatment, pharmacological management, Adults

Treatment of moderate to severe sleep paralysis/sleep-related hallucinations

Question 6.1 - Hypocretin/Orexin

Included studies: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations **Intervention: Hypocretin/Orexin** **Comparison:** - **Outcomes** Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ X **No Recommendation**

Question 6.2 - Sodium Oxybate

Studies included: 18.

Studies on effectiveness and safety (4)

Lammers, G. J., J. Arends, A. C. Declerck, M. D. Ferrari, G. Schouwink, and J. Troost. 1993. 'Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study', Sleep, 16: 216-20.

The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.

The Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.

U.S. Xyrem. Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep 2003;26:31-5.

Studies on safety (14)

Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451-8.

Akins BE, Miranda E, Lacy JM, Logan BK. A multi-drug intoxication fatality involving Xyrem (GHB). J Forensic Sci 2009;54:495-6.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010;6:596-602.

Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med 2015;11:427-32.

Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431-43.

Drakatos P, Lykouras D, D'Ancona G, Higgins S, Gildeh N, Macavei R, Rosenzweig I, Steier J, Williams AJ, Muza R, Kent BD, Leschziner G. Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice. Sleep Med 2017;35:80-84.

Langford J, Gross WL. Psychosis in the context of sodium oxybate therapy. J Clin Sleep Med 2011;7:665-6.

Mamelak M, Swick T, Emsellem H, Montplaisir J, Lai C, Black J. A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy. Sleep Med 2015;16: 52-8.

Mayer G, Plazzi G, Iranzo A, Ortega-Albas J, Quinnell T, Pesch H, Serralheiro P, Schlit AF, Wuiame D, Bentz JWG. Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Post-Authorization, Non-Interventional Surveillance Study. Sleep 2018;41(9).

Ortega-Albas JJ, Lopez-Bernabe R, Garcia AL, Gomez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci 2010;22:352r.e26-52.e26.

Poryazova R, Tartarotti S, Khatami R, Baumann CR, Valko P, Kallweit U, Werth E, Bassetti CL. Sodium oxybate in narcolepsy with cataplexy: Zurich sleep center experience. Eur Neurol 2011;65:175-82.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol 2014;5:136.

Zvosec DL, Smith SW, Hall BJ. Three deaths associated with use of Xyrem. Sleep Med 2009;10:490-3.

After update search (October 2019):

Studies on safety (3)

Buckley PJ, Wolf CT. Psychosis in a 22-Year-Old Woman With Narcolepsy After Restarting Sodium Oxybate. Psychosomatics 2018;59:298-301.
→ case report of 1 patient on safety: it does not modify the main findings reported below.
Noujaim MG, Mourad A, Clough JD. Sodium Oxybate: A Cause of Extreme Involuntary Weight Loss in a Young Lady. Case Rep Med 2019;2019:6537815.
→ case report of 1 patient on safety: it does not modify the main findings reported below.
Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczek R, Lammers GJ. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. J Sleep Res 2019;28:e12684.
→2-year before-after study: treatment with sodium oxybate is associated with a body mass index reduction in narcolepsy type 1,

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations
Intervention: Sodium Oxybate
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations - Critical	GHB reduced the daily number of hypnagogic hallucinations (n = 12) from 0.87 ± 0.58 to 0.28 ± 0.40 vs placebo 0.88 ± 0.77-0.95 ± 0.86; p = 0.008 The effect on sleep paralysis could not be assessed because of the low incidence of this item during the baseline weeks (n = 4)	4 weeks of SO (4 gr)	24 pts, 1 RCT (Lammers 1993)	⊕⊕⊖⊖ Low
	Improvement N.S. compared to placebo	4 weeks of SO (3-6-9 gr)	364 pts, 2 RCTs (U.S. Xyrem. Multicenter Study Group 2002; Xyrem® International Study Group 2005	
	a nonsignificant decrease in the frequency of episodes of both phenomena in the long term	12 mo	118 pts, 1 open study (The U.S. Xyrem Multicenter Study Group 2003 A 12 month)	
Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations Critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.2**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.2**			

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation

Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Overall low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	It is uncertain whether Sodium oxybate is effective in improving sleep paralysis/sleep-related hallucinations Adverse reactions are generally rare although several adverse events (nocturnal confusion, enuresis, nausea, vomiting, raised ALT, vertigo causing fall and trauma, headache) can be limiting factors.
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	It is unknown whether sleep paralysis/sleep-related hallucinations alone have an impact on patients It is possible a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 6.3 - Antidepressants

Studies included: 5

Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. Acta Neurol Scand 1976;54:71-87.

Guilleminault C, Mancuso J, Salva MA, Hayes B, Mitler M, Poirier G, Montplaisir J. Viloxazine hydrochloride in narcolepsy: a preliminary report. Sleep 1986;9:275-9.

Hishikawa Y, Ida H, Nakai K, Kaneko Z. Treatment of narcolepsy with imipramine (tofranil) and desmethylimipramine (pertofran). J Neurol Sci 1966;3:453-61.

Mitler MM, Hajdukovic R, Erman M, Koziol JA. Narcolepsy. Journal of Clinical Neurophysiology 1990;7:93–118.

Parkes JD, Schachter M. Clomipramine and clonazepam in cataplexy. Lancet 1979;2:1085-6.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations
Intervention: Antidepressants
Comparison: none / placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations - Critical	No effect on self reported HH and SP SP abolished usually	Clomipramine 10 – 150 mg; weeks to years FU	82 pts, 2 open studies (Guilleminault 1976; Parkes 1979)	⊕⊕⊖⊖ Low
	HH and SP improved when compared with entry, placebo, and withdrawal (n = 22,P < 0.05).	Viloxazine100 mg; 6 weeks FU	23 pts, 1 RCT (Guilleminault 1986 / Mitler 1990)	
	Less attacs of SP (p<0,02); Effect on HH number was n.s.	Femoxetine 600 mg; 4 weeks FU	10 pts, 1 RCT Schrader 1986	

Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - **Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations** Critical	SP: excellent results in 9 out of 11 patients treated with desmethylimipramine, and by 7 out of 8 patients with imipramine- HH: desmethylimipramine as well as imipramine produced good results in 4 patients	Desmethylimipramine; imipramine; 1-12 mo FU	17 pts, 1 open study (Hishikawa 1966)	⊕⊕⊖⊖ Low
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Questions 4.15 and 4.16**			
Any adverse event of the drugs - important but not critical	**See above Questions 4.15 and 4.16**			

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	It is uncertain whether Antidepressants are effective in improving sleep paralysis/sleep-related hallucinations
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	It is unknown whether sleep paralysis/sleep-related hallucinations alone have an impact on patients It is possible a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 6.4 - Pitolisant

Studies included: 1

Dauvilliers Y, Arnulf I, Szakacs Z, Leu-Semenescu S, Lecomte I, Scart-Gres C, Lecomte JM, Schwartz JC; HARMONY III study group. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep 2019;42:zsz174.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations
Intervention: Pitolisant
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - **Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations -** Critical	Mean frequency of HH decreased by 54% between baseline and 12 months (from 0.13 ± 0.06 to 0.06 ± 0.03 per day; change −0.06; 95% CI [−0.14; 0.01]).	Pitolisant 40 mg; 1 yr FU	76 pts, 1 open studies (Dauvilliers 2019)	⊕⊕⊖⊖ Low

	Mean frequency of SP reduced by 63% (from 0.16 ± 0.06 to 0.06 ± 0.04, change −0.10; 95% CI [−0.21; 0.00] p = 0.023)			
Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations Critical				
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Questions 3.9**			
Any adverse event of the drugs - important but not critical	**See above Questions 4.15 and 4.16**			

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Possibile improvement of sleep paralysis/sleep-related hallucinations
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	It is unknown whether sleep paralysis/sleep-related hallucinations alone have an impact on patients It is possible a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 6.5 - Benzodiazepines

Studies included: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations **Intervention: Benzodiazepines** **Comparison:** any **Outcomes** Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Question 6.6 - Baclofen

Studies included: 1.

Lee EK, Douglass AB. Baclofen for narcolepsy with cataplexy: two cases. Nat Sci Sleep 2015;7:81-3.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations **Intervention: Baclofen** **Comparison:** - **Outcomes** Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Question 6.7/6.8/6.9 - Gabapentin / Pregabalin / Melatonin

Studies included: 0.

Summary of Findings table

Patients or population: Adults with narcolepsy and moderate to severe sleep paralysis/sleep-related hallucinations **Intervention: Gabapentin / Pregabalin / Melatonin** **Comparison:** - **Outcomes** Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Sleep diaries: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Global Clinical Impression: mean reduction of sleep paralysis/sleep-related hallucinations - Global Clinical Impression: percentage of patients with remission of sleep paralysis/sleep-related hallucinations – Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Group 4 - Non- pharmacological and pharmacological management for co-morbidities

Question 7 – Any treatment for psychiatric symptoms

Studies included: 2.

Becker PM, Schwartz JR, Feldman NT, Hughes RJ. Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. Psychopharmacology (Berl) 2004;171:133-9.

Rye DB, Dihenia B, Bliwise DL. Reversal of atypical depression, sleepiness, and REM-sleep propensity in narcolepsy with bupropion. Depress Anxiety 1998;7:92-5.

Summary of Findings table

Patients or population: People with narcolepsy (any age) and **psychiatric symptoms**
Intervention: Any psychiatric treatment
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Mood: mean improvement of mood scales - critical	improvement in depressive symptoms (BDI)	buproprione hydrocloride 100 mg, 16 months	1 pt, 1 case report ; Rye 1998)	⊕⊖⊖⊖ Very Low
	reduced fatigue and improved vigor and cognition on POMS	modafinil 200-400mg/day week 2-6	151 pt, 1 open label study; Becker 2004)	⊕⊕⊖⊖ Low
Anxiety scales: mean improvement of anxiety scales - important but not critical	-	-	-	-
Insomnia: mean improvement of insomnia scales - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	-	-	-	-
Any adverse event of the drugs - important but not critical	-	-	-	-

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Uncertain effect
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 8.1 – CPAP for SDB

Studies included: 2.

Inoue Y, Nanba K, Higami S, Honda Y, Takahashi Y, Arai H. Clinical significance of sleep-related breathing disorder in narcolepsy. Psychiatry Clin Neurosci 2002;56:269-70.
Pataka AD, Frangulyan RR, Mackay TW, Douglas NJ, Riha RL. Narcolepsy and sleep-disordered breathing. Eur J Neurol 2012;19:696-702.

Summary of Findings table

Patients or population: People with narcolepsy (adults) and SDB
Intervention: CPAP
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)** - Critical	ESS improved (19 ± 3.6 vs. 15.8 ± 4.5, p = 0.006)	CPAP use follow up, up to max 24 months after diagnosis	26 narcolepsy pts with OSAHS, 1 case series (Pataka 2012)	⊕⊖⊖⊖ Very Low
Subjective measures: Global Clinical Impression: mean EDS improvement **percentage of patients with EDS improvement** - Critical	-	-	-	-
Objective measures: MWT: **mean EDS improvement** - Critical	-	-	-	-
Sleep diaries: mean improvement of nighttime disturbed sleep - critical	-	-	-	-
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	-	-	-	-
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	-	-	-	-
objective measures: MSLT: **mean EDS improvement** **percentage of patients with remission of EDS (according to normative values)** - Important but not Critical	MSLT did not corellate with AHI No improvement of MSLT on CPAP	CPAP-control after 2 weeks (with CPAP and AHI<5)	10 NC type 1 pts with OSAHS(+AHI>5) 12 controls-NC without OSAHS, 1 study (Inoue 2002)	⊕⊕⊖⊖ Low
Adverse events leading to withdrawal from the intervention - important but not critical	Long term adherence to CPAP is poor (only 13 out of 26 p uses CPAP after 12-24 months)	CPAP use follow up	26 narcolepsy pts with OSAHS, 1 case series (Pataka 2012)	⊕⊖⊖⊖ Very Low
Any adverse event of the intervention - important but not critical	-	-	-	-

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Not clear improvement of EDS despite using CPAP

Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 8.2 – Any drug treatment for RBD

Studies included: 3.

Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. J Sleep Res 2010;19:591–6

Ferri R, Zucconi M, Marelli S, Plazzi P, Schenck CH, Ferini-Strambi L. Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder. Sleep Med 2013;14:399-406

Mayer G. Efficacy of sodium oxybate on REM sleep behavior disorder in a patient with narcolepsy type 1. Neurology 2016;87:2594-95.

Summary of Findings table

Patients or population: People with narcolepsy (adults) and RBD
Intervention: Any (found studies on Melatonin / Clonazepam / Sodium oxybate)
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)** - Critical				
Subjective measures: Global Clinical Impression: mean EDS improvement **percentage of patients with EDS improvement** - Critical				
Objective measures: MWT: **mean EDS improvement** - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - critical	-	-	-	-
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical	**Melatonin** improves CGI severity (-2.157 point score; p= 0.031)	3mg melatonin, cross over design with placebo	8 pts with RBD; 1 cross over RCT (Kunz 2010)	⊕⊕⊖⊖ Low
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	**Clonazepam** reduced WASO, REM latency and %stage 2 were increased. Stage 1 and 2 instability and duration of EEG transients decreased	1 year, 0,5-1 mg clonazepam	46pts: 15 iRBD, 13 NC+RBD, 18 controls; 1 before-after study (Ferri 2013)	⊕⊖⊖⊖ Very Low
	Sodium oxybate SO decreased muscle activity in REM from 12% to 0%	Sodium oxybate (2x4,5g)	1 NC1 patient +RBD; 1 case report (Mayer 2016)	⊕⊖⊖⊖ Very Low
objective measures: MSLT: **mean EDS improvement**				

percentage of patients with remission of EDS (according to normative values) - Important but not Critical				
Adverse events leading to withdrawal from the drugs **-** important but not critical				-
Any adverse event of the drugs - important but not critical	**Melatonin** No side effects reported	3mg melatonin, cross over design with placebo	8 pts with RBD; 1 cross over RCT (Kunz 2010)	⊕⊕⊖⊖ Low
	Clonazepam No side effects reported	1 year, 0,5-1 mg clonazepam	46pts: 15 iRBD, 13 NC+RBD, 18 controls; 1 before-after study (Ferri 2013)	⊕⊖⊖⊖ Very Low
	Sodium oxybate SO increased PLM and nocturnal moaning	Sodium oxybate (2x4,5g)	1 NC1 patient +RBD; 1 case report (Mayer 2016)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Not clear improvement of outcomes
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No Recommendation**

Question 8.3 - Any drug treatment for RLS/PLM

Studies included: 6.

Bedard MA, Montplaisir J, Godbout R. Effect of Ldopa on periodic movements in sleep in narcolepsy. European Neurology 1987;27: 35–38.

Bedard MA, Montplaisir J, Godbout R, Lapierre O. Nocturnal gamma-hydroxybutyrate. Effect on periodic leg movements and sleep organization of narcoleptic patients. Clinical Neuropharmacology 1989;12: 29–36.

Boivin DB, Montplaisir J, Poirier G. The effects of Ldopa on periodic leg movements and sleep organization in narcolepsy. Clinical Neuropharmacology 1989;12:339–345.

Boivin DB, Lorrain D, Montplaisir M. Effects of bromocriptine on periodic limb movements in human narcolepsy. Neurology 1993;43:2134-6.

Boivin DB, Montplaisir J, Lambert C. Effects of bromocriptine in human narcolepsy. Clin Neuropharmacol 1993; 16: 120-6.

Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, Montplaisir JY, Morehouse RL, Moscovitch A, Murphy WF. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 1997;49:444-51.

Summary of Findings table

Patients or population: People with narcolepsy (adults) and RLS/PLM
Intervention: Any (found studies on L-Dopa / Zimelidine / GHB / Bromocriptine)
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence

subjective measures: Epworth Sleepiness Scale: mean improvement of EDS **percentage of patients with remission of EDS (according to normative values)** **-** Critical				
subjective measures: Global Clinical Impression: mean EDS improvement **percentage of patients with EDS improvement** **-** Critical	-	-	-	-
objective measures: MWT: **mean EDS improvement** **-** Critical	**Bromocriptine** no changes	4 weeks of treatment (Bromocriptine 7.5 mg or placebo)	6 pts; 3 with PLMS >10 (Boivin 1993)	⊕⊕⊖⊖ Low
Sleep diaries: mean improvement of nighttime disturbed sleep - critical	-	-	-	-
Global Clinical Impression: mean improvement of nighttime disturbed sleep **-** Critical	-	-	-	-
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts **-** Critical	**L-dopa** decreased Stage 1 and REM fragmentation and increased SWS and REM.	L-Dopa+ benserazide for 1 month	5 pts; 2 also RLS, all PLMS on PSG (PLMS>10) (Bedard 1987)	⊕⊖⊖⊖ Very Low
	L-dopa reduced WASO	Levodopa 2 weeks, 1 week wash out, 2 weeks placebo/reversible protocol in ½ of patients	6 pts (Boivin 1989)	
	Zimelidine No effect on sleep variables	Zimelidine for 1 month	No=1 NC and PLMS (Bedard 1987)	⊕⊖⊖⊖ Very Low
	GHB No effect on sleep variables Decreased REM sleep latency. Increase REM efficiency. No change in total REM sleep	GHB for 1 month	1 pt with PLMS (Bedard 1987) 12 pts: 6 NC and 6 NC+PLMS (Bedard 1989)	⊕⊖⊖⊖ Very Low
	Bromocriptine no changes in sleep architecture on PSG no changes were observed in sleep structure or symptoms	Bromocriptine 7,5mg, 4 weeks 4 weeks of treatment Bromocriptine 7.5 mg or placebo	8 pts+PLMS (PLMS>5), (Boivin 1993) 6 pts, 3 with PLMS >10 (Boivin 1993)	⊕⊕⊖⊖ Low
objective measures: MSLT: **mean EDS improvement** **percentage of patients with remission of EDS (according to normative values)** - Important but not Critical				
Adverse events leading to withdrawal from the drugs **-** important but not critical				-
Any adverse event of the drugs important but not critical	-	-	-	-

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation

Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Very Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Not clear improvement of outcomes
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ For ☐ Against **X No recommendation**

Question 9

No specific recommendations were provided. CGI, QoL and prevention of everyday life risks were considered to substantiate the recommendations on symptomatic treatments. The synthesis of effect on these outcomes is reported by single drugs in the Synopsis below.

Synopsis of Summary of Findings

Drug	N. of studies	Quality of Evidence	Effect
Immunoglobulins children and adults	3	Very Low	**CGI: no effect** QoL: no data prevention of everyday life risks: no data
Sodium Oxybate adults	6	Moderate	**CGI: improvement** **QoL: improvement** **prevention of everyday life risks: reduction of error rate in driving test**
Sodium Oxybate children	2	Low	CGI: no data **QoL: contrasting results** prevention of everyday life risks: no data
Methamphetamine adults	1	Very Low	CGI: no data QoL: no data **prevention of everyday life risks: reduction of error rate in driving test**
Solriamfetol adults	3	Moderate	**CGI: improvement** **QoL: improvement** **prevention of everyday life risks: improved work productivity**
Modafinil adults	7	Moderate	**CGI: improvement** **QoL: improvement** **prevention of everyday life risks: improvement of driving performance in driving test**
Armodafinil adults	1	Moderate	**CGI: improvement** QoL: no data prevention of everyday life risks: no data
Pitolisant adults	2	Moderate	**CGI: improvement** **QoL: no improvement (EQ-5D)** prevention of everyday life risks: no data
All other treatments children and adults	0	na	CGI: no data QoL: no data prevention of everyday life risks: no data

Immunoglobulins

Studies included: 3.

Knudsen S, Biering-Sorensen B, Kornum BR, et al. Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. Neurology 2012;79:102–103.

Lecendreux M, Berthier J, Corny J, Bourdon O, Dossier C, Delclaux C. Intravenous Immunoglobulin Therapy in Pediatric Narcolepsy: A Nonrandomized, Open-Label, Controlled, Longitudinal Observational Study. J Clin Sleep Med 2017,13:441-53.

Plazzi G, Poli F, Franceschini C, Parmeggiani A, Pirazzoli P, Bernardi F, Mignot E, Cicognani A, Montagna P. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. J Neurol 2008;255:1549-54.

Summary of Findings table

Patients or population: People with narcolepsy (any age)
Intervention: Immunoglobulins
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Global Clinical Impression (overall): mean improvement - Critical	No effect in CGI	IVIg perfusion at: 0.4 g/kg per day for five days, repeated monthly for three months and followed by the same single day dose every month for the following six months.	4 NC pts (children), 1 case series (Plazzi 2008)	⨁⊖⊖⊖ Very Low

	No effect were observed on clinical outcome measures: Ullanlinna Narcolepsy Scale (UNS)	IVIg w 1 g/kg as three separate infusions at monthly intervals	56 pts, 1 open label study (Lecendreux 2017)	⊕⊕⊖⊖ Low
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical	-	-	-	-
Psychosocial implication (school): mean difference of school years loss Psychosocial implication (school): difference of percentage of early school leaving Psychosocial implication (job): difference of percentage of job loss Psychosocial implication (car): difference of percentage of stop driving Psychosocial implication (car): difference of percentage of traffic accidents Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls) - important but not critical	-	-	-	-
Adverse events leading to withdrawal from the drugs - important but not critical	**See above question 1.2**			
Any adverse event of the drugs - important but not critical	**See above question 1.2**			

Sodium Oxybate - Adults

Studies included: 6.

Alshaikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451-8.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431-43.

The U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.

The Xyrem® International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.

Update search (October 2019):

Liakoni E, Dempsey DA, Meyers M, et al. Effect of gamma-hydroxybutyrate (GHB) on driving as measured by a driving simulator. Psychopharmacology (Berl) 2018;235:3223-3232.

→1 cross-over RCT (16 pts) assessing effects of oral sodium oxybate upon driving as measured by a driving simulator**:** sodium oxybate in doses used to treat narcolepsy resulted in severe driving impairment at one hour post dosing. After three to six hours there was full recovery.

Summary of Findings table

Patients or population: **ADULT** Patients with narcolepsy
Intervention: Sodium Oxybate
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Global Clinical Impression (overall): mean improvement - Critical	Sodium oxybate increasing Clinical Global Impression scores, OR 3.45; 95% CI 2.47-4.80, p < 0.00001)		Meta-analysis by 1 SR (Boscolo 2012) with 3 RCTs, 655 pts (XyREM 2002, XyREM	⊕⊕⊕⊖ Moderate

			2005, Black 2006)	
	RR (Proportion of patients "much improved" or "very much improved"): 2.42, 95% CI: 1.77-3.32	3, 4.5, 6 or 9 g sodium oxybate or placebo for 8 weeks	Meta-analysis by 1 SR (Alshaikh 2012) with 3 RCTs, 280 pts (XyREM 2002, XyREM 2005, Black 2006)	
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical	Functional Outcomes of Sleep Questionnaire: dose-related improvements in the Total Functional Outcomes of Sleep Questionnaire score, as well as in the Activity Level, General Productivity, Vigilance, and Social Outcomes subscales Small to medium effect at 6.0 g dose; Large effect at 9.0 gr	4.5, 6 or 9 g sodium oxybate or placebo for 8 weeks	285 pts, 1RCT (Xyrem group 2005)	⊕⊕⊕⊖ Moderate
	Improvement from baseline on the Physical Component Summary (PCS) significantly greater with SXB 9 g/night than placebo (6.3 ± 9.1 vs. 1.5 ± 6.2; p = 0.005) with moderate effect size No significant difference between the SXB and placebo groups on the Mental Component Summary. SXB 9 g/night significantly (p\0.05) greater improvements than placebo in Physical Functioning (4.4 ± 9.2 vs. 1.0 ± 8.0), General Health (GH; 3.1 ± 7.0 vs. 0.4 ± 6.8), and Social Functioning (6.8 ± 16.8 vs. 1.1 ± 9.6). All SXB significant improvement (p\0.05) relative to placebo for Vitality, with moderate effect size. No significant differences versus placebo were observed for Role–Physical, Role–Emotional, or Mental Health domains.			
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical				

Adverse events leading to withdrawal from the drugs - important but not critical	**See above question 3.2**
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above question 3.2**

Sodium Oxybate - Children

Studies included: 2.

Nordstrand SH, Hansen BH, Kamaleri Y, Nilsen KB, Rootwelt T, Karlsen TI, Knudsen S. Changes in quality of life in individuals with narcolepsy type 1 after the H1N1-influenza epidemic and vaccination campaign in Norway: a two-year prospective cohort study. Sleep Med 2018;50:175-80.

Plazzi G, Ruoff C, Lecendreux M, Dauvilliers Y, Rosen CL, Black J, Parvataneni R, Guinta D, Wang YG, Mignot E. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. The Lancet Child and Adolescent Health 2018;2:483-94.

Summary of Findings table

Patients or population: **Children** Patients with narcolepsy
Intervention: Sodium Oxybate
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Global Clinical Impression (overall): mean improvement - Critical				
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical	No significant difference on the SF-10	The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label; patients aged 7–16 years; RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low
	Treatment at follow up positively associated with changes in PedsQL Total Health Summary score, after adjusting for age and gender, p = 0.027	Sodium Oxybate (among other treatments); 1 yr FU	31 patients, 1 open study (Nordstrand 2018)	⊕⊕⊖⊖ Low
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical				
Adverse events leading to withdrawal from the drugs	**See below Question 10.1**			

- important but not critical	
Any adverse event of the drugs - important but not critical	**See below Question 10.1**

Methamphetamine - Adults

Studies included: 1.

Mitler MM, Hajdukovic R, Erman MK. Treatment of narcolepsy with methamphetamine. Sleep 1993;16:306-17.

Summary of Findings table

Patients or population: **Adult** Patients with narcolepsy
Intervention: Methamphetamine
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Global Clinical Impression (overall): mean improvement - Critical				
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical				
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical	Narcoleptics' error rate on the driving task decreased from 2.53% on placebo to 0.33% on high dose, compared with a decrease from 0.22% to 0.16% for controls.	Methamphetamine 0, 20, or 40-60 mg to narcoleptics and 0, 5 or 10 mg to controls	8 pts (Mitler 1993)	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - critical	**See above Question 3.3**			
Any adverse event of the drugs - critical	**See above Question 3.3**			

Solriamfetol - Adults

Studies included: 3.

Bogan RK, Feldman N, Emsellem HA, Rosenberg R, Lu Y, Bream G, Khayrallah M, Lankford Da. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. Sleep Med 2015;16:1102-8.

Ruoff C, Swick TJ, Doekel D, Emsellem HA, Feldman NT, Rosenberg R, Bream G, Khayrallah MA, Lu Y, Black J. Effect of Oral JZP-110 (ADX-N05) on Wakefulness and Sleepiness in Adults with Narcolepsy: a Phase 2b Study. Sleep 2016;39:1379-87.

Update search (July 2020):

Emsellem HA, Thorpy MJ, Lammers GJ, et al. Measures of functional outcomes, work productivity, and quality of life from a randomized, phase 3 study of solriamfetol in participants with narcolepsy. Sleep Med. 2020 67: 128-136.

→ Solriamfetol improved measures of functional status, HRQoL, and work productivity, particularly at the 150- and 300-mg doses.

Summary of Findings table

Patients or population Adult Patients with narcolepsy **Intervention: Solriamfetol** **Comparison:** placebo				
Outcomes	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Global Clinical Impression (overall): mean improvement - Critical	Clinical Global Impression of Change: .87.9% of patients at least minimal improvement with 150 mg/day, compared with 27.3% with placebo (P < 0.0001).	JZP-110 at 150 mg/day (weeks 1 and 3) increased to 300 mg/day (weeks 2 and 4).	33 pts, 1 cross-over RCT (Bogan 2015)	⨁⨁⨁⊖ Moderate
	CGI-C improvement (at least minimal improvement) percentage of patients: 4 w, 80% versus 51%, P = 0.0066; 12 w, 86% versus 38%, P < 0.0001).	110 up to 300 mg JZP110-solriamfetol, 12 weeks	93 pts, 1 RCT (Ruoff 2016)	
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical	-	-	-	-
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical				
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.5**			
Any adverse event of the drugs - important but not critical	**See above Question 3.5**			

Modafinil - Adults

Studies included: 7.

Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L,Goswami M, Steinwald B. Health-related quality of life effects of modafinil for treatment of narcolepsy. Sleep 1999;22:757-65.

Billiard M, Besset A, Montplaisir J, Laffont F, Goldenberg F, Weill JS, Lubin S. Modafinil: a double-blind multicentric study. Sleep 1994;17:S107-12.

Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29: 939-46.

Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. Med Sci Monit 2010;16: Ra177-86.

US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97.

US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 2000;54:1166-75.

Philip P, Chaufton C, Taillard J, Capelli A, Coste O, Léger D, Moore N, Sagaspe P. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep 2014;37:483-7.

Summary of Findings table

Patients or population: **Adult** Patients with narcolepsy **Intervention: Modafinil** **Comparison:** placebo				
Outcomes	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Global Clinical Impression (overall): mean improvement - Critical	CGI percentages of patient with improvement: RR 1.6, 95% CI 1.32 to 1.95), moderate heterogeneity (I2=46%) RR 2.83, 95% CI 1.90 to 4.20; I2=0%) including only high quality RTCs	200 mg modafinil; or 400 mg modafinil; 40 weeks	Meta-analysis of 724 pts from 4 RCTs (1 cross-over: 3 parallel; Billiard, Black; US Modafinil study group 1998, 2000)	⊕⊕⊕⊖ Moderate
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical	SF 36 tool: 400 mg modafinil group significantly higher scores than placebo for 10 of the 17 HQL scales. More energy, fewer difficulties performing usual activities, fewer interferences with social activities, improved psychological well-being and higher productivity, attention and self-esteem compared to placebo subjects (p<.05).	200 mg modafinil; or 400 mg modafinil; 40 weeks	Pooled analysis of 481 pts from 2 parallel RCTs (Beusterien 1999)	⊕⊕⊕⊖ Moderate
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical	Reduction of the mean number of Inappropriate Line Crossings and Standard Deviation of Lateral Position of the vehicle compared to placebo ($F(1,25) = 4.88$, $P < 0.05$ and $F(1,25) = 3.87$, $P = 0.06$ tendency).	modafinil (400 mg) or placebo for 5 days prior to the driving test	27 pts (13 narcolepsy, 14 idiopatic hypersomnia) from 1 RCT (Philip 2014)	⊕⊕⊕⊖ Moderate
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.7**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.7**			

Armodafinil - Adults

Studies included: 1.

Harsh JR, Hayduk R, Rosenberg R, Wesnes KA, Walsh JK, Arora S, Niebler GE, Roth T. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin 2006;22:761-74.

Summary of Findings table

Patients or population: **Adult** Patients with narcolepsy **Intervention: Armodafinil** **Comparison:** placebo				
Outcomes	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**
Global Clinical Impression (overall): mean improvement - Critical	proportions of patients with at least minimal improvement in the CGIC rating from baseline to final visit in the armodafinil 150-mg, 250-mg, and combined groups were 69%, 73%, and 71%, respectively, compared with 33% for placebo (p < 0.0001).	Armodafinil 150-250 mg; 12 weeks	196 pts (1 RCT Harsh 2006)	⊕⊕⊕⊕ High
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales - Critical				
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** - important but not critical				
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.8**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.8**			

Pitolisant - Adults

Studies included: 2.

Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding CL, Lecomte JM, Schwartz JC. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol 2013;12:1068-75.

Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, Sonka K, Lehert P, Lecomte I, Lecomte JM, Schwartz JC. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:200-07.

Summary of Findings table

Patients or population: **Adult** Patients with narcolepsy **Intervention: Pitolisant** **Comparison:** placebo				
Outcomes	**Impact**	**Intervention**	**Participants (Studies)**	**Quality of the evidence**

Global Clinical Impression (overall): mean improvement **-** Critical	Patient global opinion improved (n/N [%]) plac 14/25 (56%); Pitolisant 24/28 (81%); Modafinil 24/28 (86%) Patient global opinion Improvement (score <3, n/N [%]) Pitolisant 43/54 (79%) ; Placebo 22/51 (43%)	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg; FU 7-8 weeks	199 pts; 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate
Health related QoL: mean improvement of HRQoL according to generic or disease specific scales **-** Critical	No difference in EQ-5D	mod 100,200, 400 mg, pit 5, 10, 20, 40 mg; FU 7-8 weeks	199 pts; 2 RCTs (Dauvilliers 2013; Szakacs 2017)	⊕⊕⊕⊖ Moderate
Psychosocial implication (school): mean difference of school years loss **Psychosocial implication (school): difference of percentage of early school leaving** **Psychosocial implication (job): difference of percentage of job loss** **Psychosocial implication (car): difference of percentage of stop driving** **Psychosocial implication (car): difference of percentage of traffic accidents** **Psychosocial implication (other accidents): difference of percentage of any accident (home, fires, occupational, drowning, falls)** **-** important but not critical				
Adverse events leading to withdrawal from the drugs - important but not critical	**See above Question 3.9**			
Any adverse event of the drugs - important but not critical (focus on: death, suicidal thoughts, psychosis, mood instability, sleep apnea, nREM parasomnia, nocturnal confusion, dramatic weight loss, dizziness, nausea)	**See above Question 3.9**			

Group 5 - Symptomatic treatment, pharmacological management, Children

Question 10.1 - Sodium Oxybate

Studies included: 7.

Lecendreux M, Poli F, Oudiette D, Benazzouz F, Donjacour CE, Franceschini C, Finotti E, Pizza F, Bruni O, Plazzi G. Tolerance and efficacy of sodium oxybate in childhood narcolepsy with cataplexy: a retrospective study. Sleep 2012;35:709-11.

Mansukhani MP, Kotagal S. Sodium oxybate in the treatment of childhood narcolepsy-cataplexy: a retrospective study. Sleep Med 2012;13:606-10.

Murali H, Kotagal S. Off-label treatment of severe childhood narcolepsy-cataplexy with sodium oxybate. Sleep 2006;29:1025-9.

Plazzi G, Ruoff C, Lecendreux M, Dauvilliers Y, Rosen CL, Black J, Parvataneni R, Guinta D, Wang YG, Mignot E. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. The Lancet Child and Adolescent Health 2018;2:483-94.

Poli F, Ricotta L, Vandi S, Franceschini C, Pizza F, Palaia V, Moghadam KK, Banal D, Vetrugno R, Thorpy MJ, Plazzi G. Catathrenia under sodium oxybate in narcolepsy with cataplexy. Sleep Breath 2012;16:427-34.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol 2014;5:136.

After update search (October 2019):

Filardi M, Pizza F, Antelmi E, Ferri R, Natale V, Plazzi G. In-field assessment of sodium oxybate effect in pediatric type 1 narcolepsy: an actigraphic study. Sleep 2018;41(6). →1 before-after study (24 pts)**:** Actigraphy objectively documented changes in nocturnal sleep quality and diurnal napping behavior after 1 year of sodium oxybate treatment.

Summary of Findings table

Patients or population: Children with narcolepsy (<18 yrs)
Intervention: Sodium Oxybate
Comparison: placebo

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
Subjective measures: Pediatric Daytime Sleepiness Scale (PDSS) / ESS-CHADS: mean improvement of EDS - Critical	Change in median ESS Score (modified) from 19 (range 13-23, SD 3.4) to 12.5 (range 9-22, SD 4.27, p = 0.02).	Sodium oxybate treatment ranged from 3 to 7 gm per day duration : mean 11.4 mths(sd 8.6) range 3-28 months.	8 subjects narcolepsy with cataplexy; 1 case series (Murali 2006)	⊕⊖⊖⊖ Very Low
	Daytime sleepiness improved in 13/15 patients. The median ESS scores (10 patients) from 18 (range 15–23) to 12 (range 5–17). In 2 subjects PDSS Scores: decreased from 25 to 19 in one patient and 19–8 in the other.	SO mean maintenance dose 5 g (range 3–9, SD 2) Average duration of treatment 33 months (range: 3–90 months, SD 29.8)	15 children and adolescents narcolepsy with cataplexy; case series (Mansukhani 2012)	⊕⊖⊖⊖ Very Low
	ESS-CHAD scores median change from baseline greater in the placebo group: 3.0 [Q1, Q3=1.0, 5.0] compared with the sodium oxybate group: 0.0 [–1.0, 2.0]; p=0.0004;	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low 1. Concern of Generalizability (withdrawal design including only responders; short on treatment FU time [2 weeks]) 2. Possible bias due to possible rebound effect (document by EMA). 3. Stopping trial early for benefit (after interim analysis): large

				overestimates are likely in trials with fewer than 200 events (GRADEhanbook)
Subjective measures: Pediatric Daytime Sleepiness Scale (PDSS) / ESS-CHADS: percentage of patients with remission of EDS (according to normative values) - Critical				
Subjective measures: Global Clinical Impression: mean EDS improvement - Critical		-	-	-
Subjective measures: percentage of patients with EDS improvement - Critical				
Subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	The median change from baseline in the weekly number of cataplexy attacks was 12.7 (Q1, Q3=3.4, 19.8) for placebo and 0.3 (–1.0, 2.5) for continue treatment with sodium oxybate (p<0.0001)	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low See above for Reasons
	Change in median number of cataplexy attacks from 38.5 (range 3-700, SD 237), to 4.5 (range < 1-35, SD 12.4, p = 0.0078). The mean severity of cataplexy decreased from 2.75 (range 2-3) to 1.75 (range 1-3, p = 0.06).	Sodium oxybate treatment ranged from 3 to 7 gm per day duration : mean 11.4 mths(sd 8.6) range 3-28 months.	8 subjects narcolepsy with cataplexy; 1 case series (Murali 2006)	⊕⊖⊖⊖ Very Low
	Cataplexy frequency improved in all patients. The median number of estimated cataplexy episodes fell from 38.5 per week (range 0.5–700) to 0.5 per week (range 0–21) (p < 0.001). Cataplexy severity improved in 13 patients (87%), decreasing from a mean of 3 (severe) to 1 (mild) on the arbitrary scale described previously (p < 0.001).	SO mean maintenance dose 5 g (range 3–9, SD 2) Average duration of treatment 33 months (range: 3–90 months, SD 29.8)	15 children and adolescents narcolepsy with cataplexy; case series (Mansukhani 2012)	⊕⊖⊖⊖ Very Low
Subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				

Subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical	The mean change for the placebo group was –1.5 (SD 1.2) versus –0.4 (1.1) for the sodium oxybate group (p=0.0006).	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low
Subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical	the percentage of participants with worsening CGI-C scores for cataplexy severity was significantly higher for the placebo group (66%) than for the sodium oxybate group (17.2%; p=0.0001)	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical				
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical				
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Critical				
Weight: mean reduction of weight - Critical	no significant change in the median percentile of weight before and after treatment with sodium oxybate, (70th and 75th percentiles, respectively (n = 14, p = 0.70)).	SO mean maintenance dose 5 g (range 3–9, SD 2) Average duration of treatment 33 months (range: 3–90 months, SD 29.8)	15 children and adolescents narcolepsy with cataplexy; case series (Mansukhani 2012)	⊕⊖⊖⊖ Very Low
Adverse events leading to withdrawal from the drugs - important but not critical	Two serious adverse events (one event of severe acute psychosis and one event of moderate suicidal ideation) were reported Other four discontinued (affect lability, sleep apnea, weight decrease,	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low

	tactile hallucinations)	treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).		
	increased nightmares and suicidal ideation; dissociated feelings	Sodium oxybate treatment ranged from 3 to 7 gm per day duration : mean 11.4 mths(sd 8.6) range 3-28 months Associated or not with other treatments for sleepiness or cataplexy	8 subjects narcolepsy with cataplexy; 1 case series (Murali 2006)	⊕⊖⊖⊖ Very Low
	1 pt for persistent Nausea	SO at 4 and 9 g/night for 2 months	9 patients with NC enrolled at SO treatment (Poli 2012)	⊕⊖⊖⊖ Very Low
	4 patients (14.8%) because of important side effects (sleep loss, n = 2; persistent nausea, n = 2)	The mean duration of SXB treatment : 22.1 ± 16.9 months SO in combination with modafinil (52%), venlafaxine and modafinil (9%), or venlafaxine only (4%); 35% are taking SXB in monotherapy.	27 children with Narcolepsy with cataplexy; 1 case series (Lecendreux 2012)	⊕⊖⊖⊖ Very Low
	One patient for nausea, constipation, and dissociative feelings	SO mean maintenance dose 5 g (range 3–9, SD 2) Average duration of treatment 33 months (range: 3–90 months, SD 29.8)	15 children and adolescents narcolepsy with cataplexy; case series (Mansukhani 2012)	⊕⊖⊖⊖ Very Low
Any adverse event of the drugs - important but not critical	75 (72%) of 104 participants reported adverse events. Commonly reported (>5%): enuresis (15 [21%] of 72 sodium oxybate-naive participants vs four [13%] of 32 participants taking sodium oxybate at study entry), nausea (16 [22%] vs 2 [6%]), vomiting (15 [21%] vs 2 [6%]), headache (13 [18%] vs 4 [13%]), decreased weight (11 [15%] vs 1 [3%]), decreased appetite (8[11%] vs none), nasopharyngitis (7 [10%] vs none), and dizziness (5 [7%] vs 1 [3%]).	Double-blind, placebo-controlled, randomised-withdrawal: assigned to receive placebo or to remain on sodium oxybate for 2 weeks; then an open-label sodium oxybate treatment period for up to 1 year The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range 3.0–9.0 g per night).	63 randomized and 33 open label pts; 1 RCT withdrawal design (Plazzi 2018-)	⊕⊕⊖⊖ Low

	Terminal insomnia; tremors and constipation	Sodium oxybate treatment ranged from 3 to 7 gm per day duration : mean 11.4 mths(sd 8.6) range 3-28 months Associated or not with other treatments for sleepiness or cataplexy	8 subjects narcolepsy with cataplexy; 1 case series (Murali 2006)	⊕⊖⊖⊖ Very Low
	Irritability, night cold sweat Groaning (4), daily drunkeness, sleep walking	SO at 4 and 9 g/night for 2 months	9 patients with NC enrolled at SO treatment. (Poli 2012)	⊕⊖⊖⊖ Very Low
	Weight loss ; Headache ; Nausea; Disrupted nocturnal sleep ; Irritability ; Parasomnias (sleepwalking, sleep talking, enuresis); Daily episodes of sleep drunkenness	The mean duration of SXB treatment : 22.1 ± 16.9 months SO in combination with modafinil (52%), venlafaxine and modafinil (9%), or venlafaxine only (4%); 35% are taking SXB in monotherapy.	27 children with Narcolepsy with cataplexy; 1 case series (Lecendreux 2012)	⊕⊖⊖⊖ Very Low
	Side effects in four patients included tremor, blurring of vision, nocturnal awakenings, and increased nightmares, dizziness, body aches	SO mean maintenance dose 5 g (range 3–9, SD 2) Average duration of treatment 33 months (range: 3–90 months, SD 29.8)	15 children and adolescents narcolepsy with cataplexy; case series (Mansukhani 2012)	⊕⊖⊖⊖ Very Low
	hallucinations, voices in her head (psychotic symptoms)	SO 7 g per night	One patient 17 years withNC type 1; 1 case report (Sarkanen 2014)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊕⊖⊖ Low

Judgment

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Evidence of efficacy. Not negligible side effects
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ Weak ☐ **X Strong**

Question 10.2 - Amphetamines

Studies included: 0.

Summary of Findings table

Patients or population: Patients with narcolepsy (children and adolescents <18) **Intervention: Amphetamines** **Comparison:** - **Outcomes** subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - - Critical subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - - Critical subjective measures: Global Clinical Impression: mean EDS improvement – Critical subjective measures: percentage of patients with EDS improvement – Critical subjective measures: Sleep diaries: mean reduction of cataplexy -- Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep - Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight - - Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

AFTER TWO ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 10.3 - Methylphenidate

Studies included: 1.

Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep 2010;33:1457-64.

Summary of Findings table

Patients or population Children and adolescents (<18 yrs) with narcolepsy
Intervention: Methylphenidate
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - Critical				
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - Critical				
subjective measures: Global Clinical Impression: mean EDS improvement - Critical				
subjective measures: percentage of patients with EDS improvement - Critical				
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	0.2 ± 0.1 (18) (Ritalin) 0.0 ± 0.0 (8) (Concerta)	Methylphenidate (Ritalin or Concerta) ± other(SO, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low

		other drugs		
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	Insomnia -0.1 ± 0.1 (14) (Ritalin) 0.0 ± 0.0 (7) (Concerta)	Methylphenidate (Ritalin or Concerts) ± other(SO, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical				
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Critical	Hypnagogic hallucinations: 0.1 ± 0.2 (10) (Ritalin) 0.0 ± 0.0 (4) (Concerta) Sleep paralysis 0.0 ± 0.0 (5) (Ritalin) 0.0 ± 0.0 (4) (Concerta)	Methylphenidate (Ritalin or Concerts) ± other(SO, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Weight: mean reduction of weight - Critical				
Adverse events leading to withdrawal from the drugs **-** important but not critical				
Any adverse event of the drugs - important but not critical	81% (16) (Ritalin) 50% (6) (Concerta)	Methylphenidate (Ritalin or Concerts) ± other(SO, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgment

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	Low quality of evidence

Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	No evidence of efficacy. Not negligible side effects
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	Not probable a difference in values

AFTER TWO ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 10.4 - Solriamfetol

Studies included: 0.

Summary of Findings table

Patients or population Children and adolescents (<18 yrs) with narcolepsy **Intervention: Solriamfetol** **Comparison:** - **Outcomes:** subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - - Critical subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - - Critical subjective measures: Global Clinical Impression: mean EDS improvement – Critical subjective measures: percentage of patients with EDS improvement – Critical subjective measures: Sleep diaries: mean reduction of cataplexy -- Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep - Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight - - Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**

Question 10.5 - Modafinil

Studies included: 6.

Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep 2010;33:1457-64.

Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med 2003;4:579-82.

Lecendreux M, Bruni O, Franco P, Gringras P, Konofal E, Nevsimalova S, Paiva T, Partinen M, Peeters E, Peraita-Adrados R, Plazzi G, Poli F. Clinical experience suggests that modafinil is an effective and safe treatment for paediatric narcolepsy. J Sleep Res 2012;21:481-3.

Prince V, Philippidou M, Walsh S, Creamer D. Stevens-Johnson syndrome induced by modafinil. Clin Exp Dermatol 2018:43:191-192.

Sanyal D, Ghosh M. A case of modafinil induced mania in a child suffering from Narcolepsy. Bengal Journal of Private Psychiatry 2017;8:14-15.

Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry 2005;162: 813–14.

Summary of Findings table

Patients or population: Children and adolescents (<18 yrs) with narcolepsy **Intervention: Modafinil** **Comparison:** none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - Critical				
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - Critical				
subjective measures: Global Clinical Impression: mean EDS improvement - Critical				
subjective measures: percentage of patients with EDS improvement - Critical				
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	0.2 ± 0.1 (33)	Modafinil ± other(SO, venlafaxine, fluoxetine, atomoxetine, clomipramine. Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical				
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	Insomnia: 0.0 ± 0.1 (31)	Modafinil ± other(SO, venlafaxine, fluoxetine, atomoxetine, clomipramine. Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	7 patients underwent repeated NPSG and MSLT during treatment. No significant differences in sleep characteristics, but a trend towards decreased total amount of REM sleep and prolongation of REM sleep latency.	average daily effective dose of modafinil 346 ± 120 mg ranging from 200 to 600 mg daily. The average duration in clinical follow-up was 15:6 ^ 7:8 month	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low

	Significant prolongation of mean MSLT from 6.6 ±3.7 to 10.2±4.8 min (p=0.02). 5 out of 7 children showed no SOREMs on the follow-up MSLT.			
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Critical	Hypnagogic hallucinations: 0.1 ± 0.1 (22) Sleep paralysis: 0 ± 0 (22)	Modafinil ± other(SO, venlafaxine, fluoxetine, atomoxetine, clomipramine. Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Weight: mean reduction of weight - Critical				
Adverse events leading to withdrawal from the drugs **-** important but not critical				
Any adverse event of the drugs - important but not critical	Headhache (13,7%), nervousness and irritability (6,5%), loss of appetite (2,2%), no severe reactions.	modafinil varied from 50 to 600 mg, treated for more than 10 years	205 patients with narcolepsy (4–18 years); 1 case series (Lecendreux 2012)	⊕⊖⊖⊖ Very Low
	developed mania with modafinil 400mg and depression at withdrawal.	Modafinil 400 mg/day for 1 year, switched to methylphenidate 40 mg/day for 2 years, then returned to modafinil, 400 mg/day.	17 yo boy with narcolepsy; 1 case report (Vorspan 2005)	⊕⊖⊖⊖ Very Low
	developed mania (irritability, hypersexuality)	initially 200 mg and gradually increased up to 300mg +imipramine 75 mg	14 yo boy with narcolepsy; 1 case report (Sanyal 2017**)**	⊕⊖⊖⊖ Very Low
	39% (36)	Modafinil ± other(SO, venlafaxine, fluoxetine, atomoxetine, clomipramine. Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
	Stevens-Johnson syndrome: 1 case	Modafinil	1 pt (NOT with narcolepsy), 1 case report (Prince 2018)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	**Decision**	**Explanation**
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Concern of mania in adolescent and Steven-Johnson syndrome

Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 10.6 - Armodafinil

Studies included: 0.

Summary of Findings table

Patients or population Children and adolescents (<18 yrs) with narcolepsy **Intervention: Armodafinil** **Comparison:** - **Outcomes:** subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - - Critical subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - - Critical subjective measures: Global Clinical Impression: mean EDS improvement – Critical subjective measures: percentage of patients with EDS improvement – Critical subjective measures: Sleep diaries: mean reduction of cataplexy -- Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep - Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight - - Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No Recommendation**

Question 10.7 - Pitolisant

Studies included: 1.

Inocente C, Arnulf I, Bastuji H, Thibault-Stoll A, Raoux A, Reimao R, Lin JS, Franco P. Pitolisant, an inverse agonist of the histamine H3 receptor: an alternative stimulant for narcolepsy-cataplexy in teenagers with refractory sleepiness. Clin Neuropharmacol 2012;35:55-60.

Summary of Findings table

Patients or population: Children and adolescents (<18 yrs) with narcolepsy
Intervention: Pitolisant
Comparison: none

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - Critical	The adapted Epworth Sleepiness Score decreased from 14.3 T 0.9 to 9.5 T 2.9 (P = 0.03) with pitolisant alone.	pitolisant 10-40 mg. follow-up period 13.5 months All cases refractory to modafinil, methylphenidate, mazindol, sodium oxybate, D-amphetamine	4 pts with narcolepsy with cataplexy, 1 case series (Inocente 2012)	⨁⊖⊖⊖ Very Low

subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - Critical				
subjective measures: Global Clinical Impression: mean EDS improvement - Critical				
subjective measures: percentage of patients with EDS improvement - Critical				
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical				
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	the intensity of cataplexy attacks decreased in 2 teenagers and changed from complete falls to partial cataplexy in one patient and were unchanged in the last patient	pitolisant 10-40 mg. follow-up period 13.5 months All cases refractory to modafinil, methylphenidate, mazindol, sodium oxybate, D-amphetamine	4 pts with narcolepsy with cataplexy, 1 case series (Inocente 2012)	⊕⊖⊖⊖ Very Low
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical				
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical	trends toward a lighter and shorter night-time sleep, with increased sleep latency and arousal index and decreased sleep time. Mean± SD sleep onset latency increased from 31±14 minutes to 36±8 minutes (P = 0.21) on the maintenance of wakefulness test.	pitolisant 10-40 mg. follow-up period 13.5 months All cases refractory to modafinil, methylphenidate, mazindol, sodium oxybate, D-amphetamine	4 pts with narcolepsy with cataplexy, 1 case series (Inocente 2012)	⊕⊖⊖⊖ Very Low
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Critical				
Weight: mean reduction of weight - Critical				
Adverse events leading to withdrawal from the drugs **-** important but not critical				

Any adverse event of the drugs - important but not critical	insomnia, headache, hot flushes, leg pain, and hallucinations.	pitolisant 10-40 mg. follow-up period 13.5 months All cases refractory to modafinil, methylphenidate, mazindol, sodium oxybate, D-amphetamine	4 pts with narcolepsy with cataplexy, 1 case series (Inocente 2012)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence [The higher the quality of evidence, the more likely is a strong recommendation.]	☐ **X Yes** ☐ No	
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	

AFTER TWO ROUNDS OF VOTE (2 votes against the final decision)

Direction of the Recommendation	☐ **X** For ☐ Against ☐ No recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

Question 10.8 - Selegiline

Studies included: 0.

Summary of Findings table

Patients or population Children and adolescents (<18 yrs) with narcolepsy **Intervention: Selegiline** **Comparison:** - **Outcomes:** subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - - Critical subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - - Critical subjective measures: Global Clinical Impression: mean EDS improvement – Critical subjective measures: percentage of patients with EDS improvement – Critical subjective measures: Sleep diaries: mean reduction of cataplexy -- Critical subjective measures: Sleep diaries: percentage of patients with remission of cataplexy – Critical subjective measures: Global Clinical Impression: mean cataplexy improvement – Critical subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy – Critical Sleep diaries: mean improvement of nighttime disturbed sleep - Critical Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts – Critical Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations – Critical Weight: mean reduction of weight - - Critical Adverse events leading to withdrawal from the drugs - important but not critical Any adverse event of the drugs - important but not critical	No study found

VOTE

Direction of the Recommendation	☐ For ☐ Against ☐ **X No recommendation**

Question 10.9 - Any Antidepressant Drug

Studies included: 3.

Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep 2010;33:1457-64.

Moller LR, Ostergaard JR. Treatment with venlafaxine in six cases of children with narcolepsy and with cataplexy and hypnagogic hallucinations. J Child Adolesc Psychopharmacol 2009;19:197-201.

Ratkiewicz M, Splaingard M. Treatment of cataplexy in a three-year-old using venlafaxine. J Clin Sleep Med 2013;9:1341-2.

Summary of Findings table

Patients or population: Children and adolescents (<18 yrs) with narcolepsy
Intervention: Any Antidepressant Drug
Comparison: -

Outcomes	Impact	Intervention	Participants (Studies)	Quality of the evidence
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): mean improvement of EDS - Critical				
subjective measures: Pediatric Daytime Sleepiness Scale (PDSS): percentage of patients with remission of EDS (according to normative values) - Critical				
subjective measures: Global Clinical Impression: mean EDS improvement - Critical				
subjective measures: percentage of patients with EDS improvement* - Critical				
subjective measures: Sleep diaries: mean reduction of cataplexy - Critical	2.1 ± 0.1 (26)	Venlafaxine ± other(SO, modafinil, methylphenidate) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
	0.9 ± 0.2 (11)	Fluoxetine ± other (SO, modafinil, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
subjective measures: Sleep diaries: percentage of patients with remission of cataplexy - Critical	At subsequent clinic visits over the following 2 years, continued to do well without any episodes of cataplexy	Venlafaxine 0.4 mg/kg/Day for cataplexy - 2 years follow up	3-year-old boy; 1 case report- (Ratkiewicz 2013)	⊕⊖⊖⊖ Very Low
subjective measures: Global Clinical Impression: mean cataplexy improvement - Critical				
subjective measures: Global Clinical Impression: percentage of patients with remission of cataplexy - Critical				
Sleep diaries: mean improvement of nighttime disturbed sleep - Critical	Insomnia: 0.0 ± 0.1 (24)	Venlafaxine ± other(SO, modafinil, methylphenidate) Not clear how many subjects were under	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low

		treatment and for how long. Combination with other drugs		
	Insomnia: -0.1 ± 0.1 (8)	Fluoxetine ± other (SO, modafinil, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Global Clinical Impression: mean improvement of nighttime disturbed sleep - Critical				
PSG parameters: mean improvement in WASO, n° awakenings, SWS, stage shifts - Critical				
Sleep diaries: mean reduction of sleep paralysis/sleep-related hallucinations - Critical	Hypnagogic hallucinations: 0.5 ± 0.3 (15) Sleep paralysis: 0.6 ± 0.3 (11)	Venlafaxine ± other(SO, modafinil, methylphenidate) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
	Hypnagogic hallucinations: 0.0 ± 0.0 (5) Sleep paralysis: 0.0 ± 0.0 (4)	Fluoxetine ± other (SO, modafinil, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
Weight: mean reduction of weight - Critical				
Adverse events leading to withdrawal from the drugs - important but not critical				
Any adverse event of the drugs - important but not critical	Increase in disturbed sleep if taken after 2 pm	Venlafaxine For 11 to 60 months	6 pts;1 case series- (Moller 2009)	⊕⊖⊖⊖ Very Low
	48% (25)	Venlafaxine ± other(SO, modafinil, methylphenidate) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low
	70% (10)	Fluoxetine ± other (SO, modafinil, venlafaxine) Not clear how many subjects were under treatment and for how long. Combination with other drugs	40 pts; 1 case series (Aran 2010)	⊕⊖⊖⊖ Very Low

Overall quality of evidence across all critical outcomes	⊕⊖⊖⊖ Very Low

Judgments about the strength of a recommendation

Factors that can weaken the strength of a recommendation [Instructions]	Decision	Explanation
Lower quality evidence	☐ **X Yes** ☐ No	Very Low quality of evidence

[The higher the quality of evidence, the more likely is a strong recommendation.]		
Uncertainty about the balance of benefits versus harms and burdens [The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely is a weak/conditional recommendation warranted.]	☐ **X Yes** ☐ No	Tricyclic antidepressants might be effective in improving cataplexy. Due to possible tolerance and frequent AEs (weight gain, sexual dysfunction, constipation, dry mouth) the balance of benefits versus harms could be uncertain for some patients
Uncertainty or differences in values [The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak/conditional recommendation warranted.]	☐ Yes ☐ **X No**	

VOTE

Direction of the Recommendation	☐ **X For** ☐ Against ☐ No Recommendation
Strength of the Recommendation	☐ **X Weak** ☐ Strong

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