Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Network meta-analysis of the efficacy and safety of drugs, psychotherapy and other treatments for elderly people with insomnia

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/02/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/07/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Myrto Samara

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Samara

7. * Named contact email.

Give the electronic mail address of the named contact.

samaramyrto@gmail.com

8. Named contact address

Give the full postal address for the named contact.

Klinik für Psychiatrie und Psychotherapie der TU-München Klinikum rechts der Isar Ismaningerstr. 22

81675 München Germany

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+498941406466

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Klinik für Psychiatrie und Psychotherapie der TU-München Klinikum rechts der Isar

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Myrto Samara. Klinik für Psychiatrie und Psychotherapie der TU-München, Klinikum rechts der Isar
Dr Maximilian Huhn. Klinik für Psychiatrie und Psychotherapie der TU-München, Klinikum rechts der Isar
Dr Johannes Schneider. Klinik für Psychiatrie und Psychotherapie der TU-München, Klinikum rechts der Isar
Dr Adriani Nikolakopoulou. Institute of Social and Preventive Medicine (ISPM), University of Bern
Professor Georgia Salanti. Institute of Social and Preventive Medicine (ISPM), University of Bern
Professor Stefan Leucht. Klinik für Psychiatrie und Psychotherapie der TU-München, Klinikum rechts der Isar

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Grant from the Bundesministerium für Bildung und Forschung (BMBF), Grant number: 01GL1731

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Yes

Maximilian Huhn has received lecture honoraria from Lundbeck Institute and Johnson&Johnson, Stefan Leucht has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, TEVA, LTS Lohmann, Geodon Richter, Recordati, BoehringerIngelheim, and for lectures from Janssen, Lilly, Lundbeck, Otsuka, SanofiAventis and Servier. The other authors have no conflicts of interest.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

Mrs Sarah Dawson. Senior Research Associate in Information Retrieval, Bristol Medical School, University of Bristol
Mrs Catharina Azarm. Patient representative from a Munich self-help group for people with insomnia
Mrs Name undisclosed Name undisclosed. Patient representative from a Munich self-help group for people with insomnia

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

To examine the comparative efficacy and tolerability of all drugs, various types of psychotherapy and other interventions for elderly patients with insomnia by pairwise and network meta-analysis (NMA).

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following sources will be searched without restrictions for language or publication period:1. Electronic

databases: Multiple systematic searches will be conducted using the database of the Cochrane group “Common mental disorders”, EMBASE, MEDLINE, PsycINFO, and the clinical trials registers Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP).2. Previous reviews: we will search previous reviews concerning pharmacological and non-pharmacological treatments for elderly patients with major depressive disorder.3. Reference searching: we will inspect the references of all identified studies for more trials.

Search 1 (conditions, age, group)

#1 MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees

#2 insomni*:ti (Word variations have been searched)

#3 insomni*:ab (Word variations have been searched)

#4 insomni*:kw (Word variations have been searched)

#5 (sleep* or wake*):ti, ab, kw (Word variations have been searched)

#6 (#3 or #4) and #5

#7 #1 or #2 or #6

#8 MeSH descriptor: [Aged] explode all trees

#9 MeSH descriptor: [Aging] this term only

#10 MeSH descriptor: [Health Services for the Aged] this term only

#11 MeSH descriptor: [Geriatric Psychiatry] this term only

#12 MeSH descriptor: [Geriatrics] this term only

#13 (aging or ageing or elder* or frail or geriatri* or geronto* or psychoger* or geropsych* or seniors or "late* life*" or "late* adulthood" or "old* adult*" or "old* age*" or "old* people*" or "old* person*" or "old* citizen*" or "old* men" or "old* women" or "old* male*" or "old* female*" or "old* patient*" or "old* population*" or "old old" or "very old" or "senior citizen*" or pensioner* or retired or retirement or "care home*" or "nursing home*")

#14 ("55 years" or "60 years" or "64 years" or "65 years" or "70 years" or "75 years" or "79 years" or "80 years" or "85 years" or "90 years" or "95 years" or "older than 55" or "older than 60" or "older than 65" or "older than 70" or "older than 75" or "older than 80" or "older than 85" or "older than 90" or "older than 95")

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #7 and #15

#17 ((sleep* or wake*) and (elder* or geriatri* or geronto* or psychoger* or geropsych* or seniors or ((late* or old*) and (adult* or age* or people* or person* or citizen* or men or women or male* or female* or patient* or population*)) or "old old" or "very old" or "senior citizen*" or pensioner* or retired or retirement or "care home*" or "nursing home*")):ti

#18 #16 or #17

#19 sleep*:ti (Word variations have been searched)

#20 sleep next (hygiene or onset or quality or stage*):ab (Word variations have been searched)

#21 #15 and (#19 and #20)

#22 #21 not #18

[Embase search strategy]

1 randomized controlled trial.de. (939601)

2 controlled clinical trial/ and (Disease Management or Drug Therapy or Prevention or Rehabilitation or Therapy).fs.

(292788)

3 randomization.de. (76774)

4 placebo.de. (318130)

5 placebo.ti, ab. (456490)

6 (randomi#ed or randomi#ation).ti, ab, kw. (1268572)

7 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*))).ti, ab, kw. (1020308)

8 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).mp. (483196)

9 ((animal or nonhuman) not (human and (animal or nonhuman))).de. (5451842)

10 (or/1-8) not 9 (2186561)

11 primary insomnia/ (11595)

12 *insomnia/ (21716)

13 insomnia/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy] (9191)

14 insomnia severity index/ (1399)

15 (sleep initiation adj2 maintenance).ti, ab, kw. (362)

16 insomni*.ti, kw. (18684)

17 insomni*.ab. /freq=2 (18256)

18 (insomni* and (sleep* or wake*)).ti, ab, kw. (26315)

19 or/11-18 (44935)

20 aged/ or aged hospital patient/ or frail elderly/ or institutionalized elderly/ or very elderly/ (5401858)

21 exp geriatric care/ (26000)

22 elderly care/ or nursing home/ (92736)

23 home for the aged/ (11535)

24 aging/ (448216)

25 (aging or ageing or elder* or frail or geriatri* or geronto* or psychoger* or geropsych* or seniors or (late* adj

(life* or adulthood)) or (old* adj (adult? or age? or people? or person? or citizen? or men or women or male? or female?

or patient? or population?)) or old old or very old or senior citizen? or pensioner? or retired or retirement or care

home? or nursing home?).ti, ab, kw. (1801455)

26 (("55" or "60" or "65" or "70" or "75" or "79" or "80" or "85" or "90" or "95") adj years).ti, ab. (587686)

27 (("55" or "60" or "65" or "70" or "75" or "79" or "80" or "85" or "90" or "95") adj2 old*).ti, ab. (255111)

28 or/20-27 (6817119)

29 10 and 19 and 28 (2467)

30 29 use oemez (1429) [Records from Embase 1974 to present]

[MEDLINE search strategy]

31 controlled clinical trial.pt. (92150)

32 randomized controlled trial.pt. (453387)

33 (randomi#ed or randomi#ation).ab, ti, kf. (1266362)

34 randomly.ab. (653902)

35 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or

divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*))).ti, ab, kf. (1017397)

36 placebo*.ab, ti. (459312)

37 trial.ab, ti. (1182732)

38 groups.ab. (4143545)

39 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. (483196)

40 exp animals/ not (humans.sh. and exp animals/) (28279169)

41 or/31-39 (6090815)

42 41 not 40 (2709873)

43 *"Sleep Initiation and Maintenance Disorders"/ (14100)

44 "Sleep Initiation and Maintenance Disorders"/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy] (5454)

45 insomni*.ti, kf. (16434)

46 insomni*.ab. /freq=2 (18256)

47 (insomni* and (sleep* or wake*)).ti, ab, kf. (25406)

48 or/43-47 (37899)

49 aged/ or "aged, 80 and over"/ or frail elderly/ (5430902)

50 AGED/ or HEALTH SERVICES FOR THE AGED/ or HOMES FOR THE AGED/ (5411172)

51 (aging or ageing or elder* or frail or geriatri* or geronto* or psychoger* or geropsych* or seniors or (late* adj

(life* or adulthood)) or (old* adj (adult? or age? or people? or person? or citizen? or men or women or male? or female?

or patient? or population?)) or old old or very old or senior citizen? or pensioner? or retired or retirement or care

home? or nursing home?).ti, ab, kf. (1785345)

52 (("55" or "60" or "65" or "70" or "75" or "79" or "80" or "85" or "90" or "95") adj years).ti, ab. (587686)

53 (("55" or "60" or "65" or "70" or "75" or "79" or "80" or "85" or "90" or "95") adj2 old*).ti, ab. (255111)

54 or/49-53 (6686953)

55 42 and 48 and 54 (1638)

56 55 use ppez (1528) [Records from Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 to Present)]

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Elderly patients with insomnia will be included in the analysis based on the following criteria: For the age criterion we will accept the criteria of the authors of the individual studies. However we set as a minimum criterion that participants in the study must be at least 65 years old by inclusion criteria. If only the mean age

is presented, this should be at least 70 years old. Regarding the definition of insomnia, we will include studies whose definition of insomnia is comparable to primary insomnia according to DSM-IV or non-organic insomnia according to ICD-10. This limitation is necessary because until now most of the studies have been conducted on a population with primary/non-organic insomnia and because the compilation of a network meta-analysis requires comparable study populations (principle of transitivity). However, in light of recent understanding that the relationship between cause and effect between sleep disorders and concurrent medical conditions can often not be clearly defined, studies that include up to 20% patients with secondary insomnia or other serious illnesses will be included. Studies without clear inclusion criteria (e.g., clinical diagnosis of sleep disorder without further specification) will also be included. In addition, studies involving patients with secondary insomnia and severe comorbidities of different types will be included in the network meta-analysis as part of a sensitivity analysis. In principle, only studies that examine specific secondary insomnia forms are excluded, e.g. studies in which all patients had insomnia associated with parkinson disease. If further substantial differences between the included studies are found, we will evaluate these in additional subgroup examinations.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: Elderly patients with insomnia. Minimum age is defined at 65 years old, or, if only mean age is presented, this should be at least 70 years old. There will be no restrictions in terms of gender, ethnicity, or settings. We will exclude studies in which all patients had the same somatic or psychiatric disease. We will also exclude studies that included only patients with a psychiatric disease other than insomnia.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

We plan to conduct a comprehensive analysis of all currently available interventions that are used to treat sleep disorders in elderly people. Interventions identified by a review of existing reviews and guidelines are listed below. The literature search may yield further therapeutic options and these will be included as well. Pharmacotherapy and other substances (daily or as interval-therapy):1. Benzodiazepines: Short, medium and long-acting substance e.g. triazolam, lormetazepam, flurazepam 2. Benzodiazepine-receptor-agonists (“Z-Drugs”): Zopiclone, eszopiclone, zolpideme, zaleplon

3. Sedating antidepressants: Tricyclic antidepressants e.g. trimipramin, doxepine, amitryptilin, opipramol 4. Sedating antipsychotics: First generation antipsychotics, e.g. pipamperon, melperon, promethazine or

chlorprothixene, or second generation antipsychotics, e.g. quetiapine, olanzapine or risperidone 5. Melatonin or melatonin- receptor-agonists: Ramelteon, agomelatonin, tasimelteon 6. Orexin-receptor-antagonists e.g. suvorexant 7. Pregabalin 8. Gabapentin 9. Antihistamines e.g. diphenhydramine, doxylamine, hydroxyzine 10. Chloralhydrate 11. Chlormethiazole
12. Beta-receptor-blockers 13. Herbal preparations: Valerian, chamomile, hops, kava-kava, passionflower, St. John's wort, oat, melissa/lemon balm, skullcap, gui pi 14. Nutrients e.g. L-tryptophan, magnesium 15.Homeopathy e.g. viburcol 16. Other interventions.Cognitive and behavioural therapy and related approaches (as single method or in combination)1. Psychoeducation: Structured education of patients about sleep and sleep disorders 2. Sleep Hygiene Methods: Education of patients about the impact of habits and environmental factors on sleep 3. Stimulus control: Aims to psychologically reconnect (conditioning) the sleep environment, bed time and bed time stimuli with sleep. Basically patients are asked to leave their bed after 10-15 minutes of insomnia and only return when they feel really tired again 4. Sleep restriction or compression: Time spent in bed is limited to the total sleep time as judged from sleep diaries or reduced to 6-7 hours per night respectively 5. Cognitive therapy: Negative thoughts and feelings and related dysfunctional beliefs concerning sleep and impairment in day time functioning are identified and modified 6. Problem solving strategies: Reduction of general stress level due to improved problem solving strategies 7. Paradoxical intention: Patient is asked to intentionally try not to sleep while lying in bed at sleep time 8. Relaxation methods e.g. Progressive Muscle Relaxation, Meditation, Mindfulness Exercise, Biofeedback or imaginary techniques 9. Other interventionsOther approaches:1. Bright light therapy to restore the physiological circadian rhythm 2. Day time activity and physical exercise to increase physical sleep pressure 3. Electric stimulation techniques 4.Magnetic stimulation techniques 5.Hypnosis 6.Acupuncture, auricular therapy, acupressure 7.Music-therapy 8.Yoga 9.Tai Chi 10. Footbath
11. Aromatherapy 12. Other interventions.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

We will include studies where an intervention to improve sleep disorders is compared to a non-active intervention like no-treatment, waiting list, sham intervention or placebo-pill-administration, but also to any other pharmacological or non-pharmacological intervention for insomnia since every comparator can be helpful to create and strengthen the evidence in network-meta-analysis. For presentation of the relative results of the different interventions a reference intervention has to be chosen. We will use drug placebo as the reference standard since it can be expected that it will be the control group in many of the

pharmacological trials. Furthermore it is a natural comparator that can be understood intuitively and which is used in many network-meta-analyses. Other controls will be integrated independently in the network and presented in comparison to placebo, too. Special attention will be on waiting-list-controls, since they may act as nocebos in psychotherapy trials. Their role will be examined in a sensitivity analysis (see Statistical Method below).

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will only include randomized controlled trials in people with insomnia without a specific organic or psychiatric cause. We will only include studies with adequate randomization or if the details of randomization are unclear as described in the Cochrane Handbook. We will also exclude quasi-randomised studies. We will include blinded and unblinded trials, but we will exclude open studies in a sensitivity analysis. Both, studies that compared active interventions with inactive comparators (e.g. drug- or psychological placebo) and head-to-head comparisons of two active interventions can be used in network meta-analysis and will thus be included. Unlike most of the existing meta-analysis in this field, there will be no language restriction to avoid the problem of language bias. Furthermore, this procedure will allow us to include further studies. We will exclude cluster randomized trials due to the unit-of-analysis-problems associated with this design. The reason is that, as we will apply a network meta-analysis, the assumption of transitivity will be easily violated. 5 days is set as the minimum duration of drug treatment in drug trials. For non-pharmacological interventions, no minimum duration will apply.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

1. Nocturnal sleep time total: Total amount of time participants perceive that they slept in minutes. Reduced total sleep time is the core symptom of insomnia and “nocturnal sleep time total” is a comprehensive outcome for several phenotypes of sleep disorders. 2. Sleep quality: Subjective judgement of soundness of sleep or satisfaction with sleep as assessed by any validated self-rating scale e.g. the Pittsburgh Sleep Quality Index or the Insomnia Severity Index. This is a comprehensive parameter for any changes in different aspects of sleep. Furthermore this outcome plays an important role in clinical routine, because the subjective appraisal of the success of a method typically determines the continuation of and the compliance with an

intervention.

Timing and effect measures

All outcomes will be categorized into short-term (immediately post-treatment) and long-term follow-up. Short-term will be the primary outcome.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

1. Sleep onset latency: The time taken to fall asleep is a natural measure for sleep onset insomnia. 2. Number of nocturnal awakenings is a natural parameter for disturbances in sleep continuity. 3. Nocturnal time awake after sleep onset is a quantitative measure of sleep maintenance disorders 4. Daytime impairment as measured by performance tasks and self-reports such as the Epworth Sleepiness Scale or the Stanford Sleepiness Scale. This outcome can be patient relevant, because it is not always the amount of sleep, but rather the daytime impairment which leads to altered quality of life 5. Patients subjective well-being/Quality of life (e.g. SF-36, EURO-Quol) is a patient relevant and comprehensive outcome that somehow combines efficacy and side effects.6. Polysomnographic or actigraphic recordings of the primary outcome "Nocturnal sleep time total" to control for the differences in subjective and objective perception of insomnia. 7. Dropouts due to any reason is a global outcome that combines efficacy and safety (the main reasons why patients discontinue trials). It has therefore been used as a measure for the acceptability of treatment 8. Total number of adverse events is a global measure of tolerability 9. Number of dropouts for adverse events: The rate of study discontinuations due to intolerability is a global parameter for safety frequently applied in studies and meta-analysis. A particular focus will lie on separating dropouts due to real side effects from drop outs due to adverse events related to the treated disease.10. Individual Adverse Events (AEs) based on the specific side-effect profile of European Medicines Agency and includes AEs related to sedation and subsequent impaired daytime-functioning, risk of falls, paradoxical drug reactions, dependency (analyzed from long-term follow up), cardiovascular AEs, haematological AEs and endocrinologic AEs.

Timing and effect measures

All outcomes will be categorized into short-term (immediately post-treatment) and long-term follow-up. Short-term will be the primary outcome.

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of

researchers involved and how discrepancies will be resolved. List the data to be extracted.

1. Selection of trials: Two reviewers will independently inspect all abstracts identified in the literature searches in Rayyan https://rayyan.qcri.org/welcome. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection. At least two reviewers will independently decide whether the studies meet the review criteria. If disagreement cannot be clarified by discussion, we will resolve it with a third reviewer or seek further information from the study authors.2. Data extraction: At least two reviewers will independently extract data from all selected trials on data entry forms into an Microsoft Access Database. The data will be checked="checked" value="1"="checked="checked" value="1"" value="1" by an algorithm. Inconsistencies between the reviewers will be resolved by discussion with a third reviewer. Where this is not possible we will contact the study authors.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Again working independently, two reviewers will assess risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions. This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding, the completeness of outcome data, selective reporting, and other biases. We will not include studies in the data-analyses whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week).

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

1. A comprehensive network-meta-analysis of all interventions is the proposed strategy for information synthesis. Although successful examples for the inclusion of both drug and psychotherapy trials in network meta-analysis exist, we are well aware that transitivity and heterogeneity might pose a problem in our review, because we aim to include quite different interventions. Therefore, if it turns out that the trials are too different to make a network meta-analysis reasonable, we will present separate networks for pharmacological treatments and for psychotherapeutic interventions. 2. Conventional pair wise meta-analyses will always precede the network meta-analyses. 3. The effect size measure for dichotomous outcomes will be the relative risk (RR) and its 95% confidence intervals (CIs) supplemented by numbers needed to treat to benefit/harm with the average occurrence of an outcome as the baseline risk.4. Heterogeneity will be investigated by visual inspection of the forest plots, by applying a $?^2$ test and by calculating the I^2 value. Reasons for heterogeneity will be explored.5. A key assumption is that the network is “transitive”, meaning that direct and indirect evidence on the same comparisons agree. This will be assessed first epidemiologically by comparing the distribution of effect modifiers across studies groups by

comparison. Statistical evaluation of the assumption of transitivity (often termed consistency) will be performed using the design-by-treatment test, and the looped- based approach (where direct and indirect effect sizes are compared within each closed loop of evidence). In case of significant inconsistency we will investigate possible sources of it. Small or moderate amounts of inconsistency will again be further explored by network meta-regression and subgroup analyses using the effect modifiers listed below. But if reasonable transitivity cannot be assumed, we will either do NMAs for drugs and psychotherapy separately or only present pairwise meta-analyses.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Subgroup and meta-regression analyses: a) Percentage of female participants (since prevalence in women is higher), b) baseline severity of the primary outcomes, c) study duration and d) sponsoring of pharmaceutical industry and allegiance bias, i.e. whether the inventors of a psychotherapy are also the authors of a trial, because this could lead to bias, e) setting. Sensitivity analyses: 1) Exclusion of non-double-blind studies (open and single-blind studies), 2) Exclusion of studies that have not used the diagnosis primary or non-organic insomnia as an inclusion criterion or that did not use operationalized criteria, 3) Exclusion of studies that presented only completer analyses, 4) Exclusion of studies with high risk of bias, 5) Fixed effects instead of random effects model, 6) If the main analysis will not provide major efficacy differences between the individual interventions, we will undertake an additional analysis in which the interventions will be compared as groups (drug groups e.g. benzodiazepines, sedating antipsychotics, sedating antidepressants etc. and non-pharmacological approaches which will be categorized according to their main therapeutic concept. Interventions that cannot be assigned to specific groups are included as individual interventions, and 7) additional inclusion of studies involving patients with secondary insomnia or patients with severe somatic or psychiatric conditions, as long as not all patients had the same underlying disorder.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
Yes

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
Yes

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Germany

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The review will be published in open access journal which will allow for a rapid dissemination of the findings.

Additionally we will, together with our patient representatives, prepare a lay version of the results. This presentation will be disseminated by our cooperating insomnia-self-help group and other mental-health patient organizations such as “BASTA Bündnis für psychischerkrankte Menschen” und “Bündnis gegen

Depression". The hierarchical ranking of all available interventions for efficacy and safety outcomes – provided by network-meta-analysis – can be understood intuitively and will help both, clinicians and patients to decide based upon the current evidence.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

insomnia; elderly; treatment; network meta-analysis

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.