**TITLE: Initial treatment choices for long term remission of chronic insomnia disorder in adults: a systematic review and network meta-analysis**

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# **1. PROTOCOL**

The protocol was prospectively registered in PROSPERO (CRD42023450720). Below is the protocol as of 20 January 2024.

First draft: 20 September 2023

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**Title: Initial treatment choices for insomnia disorder in adults: a protocol for a systematic review and network meta-analysis**

**REVIEW QUESTION**

What are the long-term comparative efficacy and acceptability of cognitive behavioral therapy for insomnia, pharmacotherapy, and their combination when used as the initial treatment for insomnia disorder in adults?

**BACKGROUND**

Insomnia is common and disabling.(Roth et al., 2011) Meta-analyses of randomized controlled trials have shown the effectiveness of cognitive behavioral therapy for insomnia(Furukawa et al., 2024) and some pharmacotherapies.(De\_Crescenzo et al., 2022) A recent network meta-analysis (NMA) suggested potential superiority of CBT-I over pharmacotherapies and their combination over pharmacotherapies both at the end of the acute phase treatment and at follow-up(Zhang et al., 2022) However, the NMA included hypnotic-resistant insomniacs and this does not answer the clinical question of which treatment strategy to choose when starting to treat medication-naïve insomnia. In this study, we will explore the relative efficacy and acceptability of CBT-I, pharmacotherapy, and their combination as the initial treatment choice with the use of NMA, focusing on trials that randomized treatment-naïve insomniacs only.

**METHODS**

We will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline extension for NMA.(Hutton et al., 2015) We will register the study protocol on PROSPERO.

**Data sources**

**Criteria for considering studies for this review**

***Study design***

We will include all randomized controlled trials that compared CBT-I, pharmacotherapies, or their combination against each other in the treatment of hypnotic-free adults with chronic insomnia.

***Participants***

We will include studies of patients of both genders aged 18 years or older with insomnia either diagnosed according to formal diagnostic criteria (such as the Diagnostic and Statistical Manual of Mental Disorders, the International Classification of Diseases or the International Classification of Sleep Disorders) or judged so by clinical experts (e.g. presence of significant symptoms). The criteria need to include significant distress or daytime impairment. The effect of including studies without a formal diagnosis of insomnia will be tested in a sensitivity analysis. We will include patients with psychiatric or physical comorbidities. The effect of including such studies will be examined in a sensitivity analysis.

We will exclude trials if patients currently using prescription or over-the-counter sleep medications were included. We will include studies if patients discontinued the medications for a certain period before randomization.

***Interventions and controls***

We regard CBT-I as a psychotherapy involving any one of the following effective components: cognitive restructuring for insomnia, third wave components for insomnia(mindfulness and acceptance and commitment therapy), sleep restriction or stimulus control.(Furukawa et al., 2024) We will include drugs that were proven to be effective in the recent NMA. (benzodiazepines, doxylamine, eszopiclone, lemborexant, seltorexant, suvorexant, trazodone, zaleplon, zolpidem, zopiclone) (De\_Crescenzo et al., 2022) Where multiple arms are reported in a single trial, we will include only the relevant arms.

**Search methods for identification of studies**

We will carry out a comprehensive literature search in PubMed, Cochrane Central Register of Controlled Trials and PsycINFO. We will use a combination of index and free terms of psychological treatments and insomnia with filters for randomized clinical trials. We will also search WHO International Clinical Trials Registry Platform. We will impose no date, language or publication status restriction. We will check the reference lists of identified studies and review articles for additional potentially eligible records.

**TABLE 3 Search strings for PubMed, Cochrane Central Register of Controlled Trials and PsycINFO**

| Database | Search strings |
| --- | --- |
| PubMed | ( "psychotherapy"[Mesh] OR "psychotherap\*"[All Fields] OR "cognitive behavioural therapy"[All Fields] OR "cognitive behavioral therapy"[All Fields] OR "CBT"[All Fields] OR "CBTI"[All Fields] OR "CBT-I"[All Fields] OR "cognitive therapy"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioral therapy"[All Fields] OR "cognitive restructuring"[All Fields] OR "third wave"[All Fields] OR "mindfulness"[All Fields] OR "acceptance and commitment"[All Fields] OR "sleep restriction"[All Fields] OR "stimulus control"[All Fields] )  AND  ("hypnotic"[All Fields] OR "sleep medication"[All Fields] OR "benzodiazepines"[Mesh] OR "benzodiazepine"[All Fields] OR "brotizolam"[All Fields] OR "diazepam"[All Fields] OR "estazolam"[All Fields] OR "flunitrazepam"[All Fields] OR "flurazepam"[All Fields] OR "haloxazolam"[All Fields] OR "loprazolam"[All Fields] OR "lorazepam"[All Fields] OR "lormetazepam"[All Fields] OR "nimetazepam"[All Fields] OR "nitrazepam"[All Fields] OR "quazepam"[All Fields] OR "rilmazafone"[All Fields] OR "temazepam"[All Fields] OR "triazolam"[All Fields] OR "trazodone"[All Fields] OR "eszopiclone"[All Fields] OR "zopiclone"[All Fields] OR "doxylamine"[All Fields] OR "zolpidem"[All Fields] OR "seltorexant"[All Fields] OR "lemborexant"[All Fields] OR "suvorexant"[All Fields] OR "zaleplon"[All Fields] )  AND  ("sleep initiation and maintenance disorders"[Mesh] OR "insomnia"[All Fields] )  AND  ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[ti] NOT (animals[Mesh] NOT humans[Mesh])) |
| Cochrane Central Register of Controlled Trials | ([mh psychotherapy] OR psychotherap\* OR "cognitive behavioural therapy" OR "cognitive behavioral therapy" OR CBT OR CBTI OR CBT-I OR "cognitive therapy" OR "behavioural therapy" OR "behavioral therapy" OR "cognitive restructuring" OR "third wave" OR mindfulness OR "acceptance and commitment" OR "sleep restriction" OR "stimulus control")  AND  (hypnotic OR "sleep medication" OR [mh benzodiazepines] OR benzodiazepine OR brotizolam OR diazepam OR estazolam OR flunitrazepam OR flurazepam OR haloxazolam OR loprazolam OR lorazepam OR lormetazepam OR nimetazepam OR nitrazepam OR quazepam OR rilmazafone OR temazepam OR triazolam OR trazodone OR eszopiclone OR zopiclone OR doxylamine OR zolpidem OR seltorexant OR lemborexant OR suvorexant OR zaleplon)  AND  ([mh "sleep initiation and maintenance disorders"] OR insomnia) |
| PsycINFO via Ebsco | ((MH psychotherapy+) OR psychotherap\* OR "cognitive behavioural therapy" OR "cognitive behavioral therapy" OR CBT OR CBTI OR CBT-I OR "cognitive therapy" OR "behavioural therapy" OR "behavioral therapy" OR "cognitive restructuring" OR "third wave" OR mindfulness OR "acceptance and commitment" OR "sleep restriction" OR "stimulus control")  AND  (hypnotic OR "sleep medication" OR (MH benzodiazepines+) OR benzodiazepine OR brotizolam OR diazepam OR estazolam OR flunitrazepam OR flurazepam OR haloxazolam OR loprazolam OR lorazepam OR lormetazepam OR nimetazepam OR nitrazepam OR quazepam OR rilmazafone OR temazepam OR triazolam OR trazodone OR eszopiclone OR zopiclone OR doxylamine OR zolpidem OR seltorexant OR lemborexant OR suvorexant OR zaleplon)  AND  ((MH "sleep initiation and maintenance disorders+") OR insomnia)  AND  (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR TI (randomised OR randomized) OR AB (random\*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR MH (crossover design) OR MH (comparative studies) OR AB (cluster W3 RCT)) NOT ((MH animals+ OR MH animal studies OR TI (animal model\*)) NOT MH human) |
| WHO International Clinical Trials Registry Platform | (psychotherap\* OR "cognitive behavioural therapy" OR "cognitive behavioral therapy" OR "CBT" OR "CBTI" OR "CBT-I" OR "cognitive therapy" OR "behavioural therapy" OR "behavioral therapy" OR "cognitive restructuring" OR "third wave" OR mindfulness OR "acceptance and commitment" OR "sleep restriction" OR "stimulus control")  AND  (hypnotic OR "sleep medication" OR benzodiazepines OR benzodiazepine OR brotizolam OR diazepam OR estazolam OR flunitrazepam OR flurazepam OR haloxazolam OR loprazolam OR lorazepam OR lormetazepam OR nimetazepam OR nitrazepam OR quazepam OR rilmazafone OR temazepam OR triazolam OR trazodone OR eszopiclone OR zopiclone OR doxylamine OR zolpidem OR seltorexant OR lemborexant OR suvorexant OR zaleplon)  AND  ("sleep initiation and maintenance disorders " OR insomnia) |

**Data collection and analysis**

**Selection of studies**

Two review authors will independently screen titles and abstracts of all the potential studies we identify as a result of the search and code them as ‘retrieve’ or ‘do not retrieve’. We will retrieve the full text study reports/publications and two review authors will independently screen the full text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third reviewer. We will identify publications from the same study so that each study rather than each report is the unit of analysis in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram.

**Data items**

Two review authors will extract independently data from the included studies. Any disagreement will be resolved through discussion, or discussed with a third person if necessary. We will abstract the following information.

***1. Characteristics of the studies***

Name of the study, year of publication, country, study site (single or multi-center), recruitment, population characteristics (mean age, number of women, definition of insomnia), intervention, outcomes (scale used for the primary outcome)

***2. Risk of bias***

We will use Cochrane Risk of Bias 2.0 tool (RoB2) (Sterne et al., 2019) to assess the risk of bias of the primary outcome. We will report the inter-rater agreement in terms of percentage agreement and kappa.

***3. Data to calculate effect sizes***

We will extract data to calculate effect sizes (the number of patients randomized to each arm, the number of patients assessed, the number of remitters, the scale used, the mean, standard deviation and the number assessed for continuous outcomes) When only change from baseline to endpoint is reported for continuous outcomes, we will use it instead of endpoint mean.

**Primary outcome and secondary outcomes**

The primary outcome

1. Efficacy at long-term follow-up. (Remission defined as reaching a satisfactory state at endpoint measured by any validated self-reported scale. Dichotomous. Longest follow-up between 3 to 12 months)

Secondary outcomes are as follows;

2. Acceptability: dropouts for any reason at long-term follow-up (dichotomous)

3. Sleep diary measures at long-term follow-up (continuous)

3.1. Sleep efficiency at long-term follow-up (%)

3.2. Total sleep time at long-term follow-up (minutes)

3.3. Sleep latency at long-term follow-up (minutes)

3.4. Wake after sleep onset at long-term follow-up (minutes)

4. Efficacy at long-term follow-up (continuous)

5. Efficacy at post-treatment: remission defined as reaching a satisfactory state at endpoint measured by any validated self-reported scale (dichotomous)

6. Acceptability: dropouts for any reason at post-treatment (dichotomous)

7. Sleep diary measures at post-treatment (continuous)

7.1. Sleep efficiency at post-treatment (%)

7.2. Total sleep time at post-treatment (minutes)

7.3. Sleep latency at post-treatment (minutes)

7.4. Wake after sleep onset at post-treatment (minutes)

8. Efficacy at post-treatment (continuous)

Intention-to-treat analysis will be prioritized whenever available. We will use the number of participants randomized as the denominator for dichotomous outcomes. We will use odds ratio for dichotomous outcomes, mean difference for continuous outcomes expressed in minutes and percent.

**Hierarchy of outcome measures**

For efficacy, we will prioritize the remission using the Insomnia Severity Index (7 or less points at endpoint) and its imputed number. If it is not reported, we will use the following scales in this order: the remission using the Sleep Condition Indicator (17 or more points at endpoint); the remission using the Functional Outcomes of Sleep Questionnaire-10 (18 or more points at endpoint), and then its imputed number; remission using the Epworth Sleepiness Scale (10 or less points at endpoint), and then its imputed number; remission using the Pittsburgh Sleep Quality Index (5 or less points at endpoint), and then its imputed number; remission using the Athens Insomnia Scale (5 or less points at endpoint), and then its imputed number; remission using any other validated self-reported scales; remission using sleep diary measures (SE larger than 85% at endpoint; WASO less than 30 minutes at endpoint; SL less than 30 minutes at endpoint) and its imputed number.

When any of the measure is reported using another definition of remission than stated above, we will use the definition stated by the authors. When any of the measure is reported only in continuous values, we will impute remission using mean and standard deviation.

**Statistical analysis**

We will examine transitivity, an important underlying assumption of the network meta-analysis model, by creating a table of important trial and patient characteristics to see if potential effect modifiers (publication year, mean age, baseline severity) are similarly distributed among treatment comparisons. If we deem transitivity to be a plausible assumption, we will proceed with performing a network meta-analysis. Given the expected clinical and methodological heterogeneity of treatment effects among the studies, we will use the random-effects model, assuming a common heterogeneity parameter across the network.

Lack of transitivity may manifest as inconsistency in the network, in case there are closed loops. We will check for consistency using by comparing direct and indirect estimates and using global consistency test (design-by-treatment)(White et al., 2012). If the prerequisites of network meta-analysis are not met, or in case of large unexplained inconsistency, we will only present direct (i.e. from pairwise meta-analyses) and indirect evidence for each treatment comparison.

We will perform all analyses in R using *netmeta* package(Rücker et al., 2020) to conduct network meta-analysis and *meta* package(Balduzzi et al., 2019) to assess the reporting bias.

**Certainty of evidence**

We will assess the certainty of evidence in network estimates of the primary outcome using CINeMA.(Nikolakopoulou et al., 2020)

**Publication bias**

We will assess the presence of small study effects, including publication bias, in the evidence set with ten or more trials by examining asymmetry in the contour-enhanced funnel plots.

**Sensitivity analyses**

1. Excluding studies without formal diagnosis of insomnia

2. Excluding studies focusing on patients with comorbidities (both physical and psychological)

3. Excluding studies with overall high dropout rate (20% or more)

4. Excluding studies at high overall risk of bias

**Patient and public involvement**

There was no patient or public involvement in the development of this manuscript.

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**Declaration of interests**

YF has received consultancy fee from Panasonic outside the submitted work.

MS reports personal fees from SONY outside the submitted work.

TAF reports personal fees from Boehringer-Ingelheim, DT Axis, Kyoto University Original, Shionogi and SONY, and a grant from Shionogi, outside the submitted work; In addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe.

MP wrote treatment manuals and books for CBT-I, teaches CBT-I, and is a founder of Hypknowledge LLC.

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The views expressed are those of the authors and not necessarily those of affiliated organizations.

**Registration**

We will register the study protocol on PROSPERO.

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**Amendments**

April 10, 2024. We decided to conduct two post-hoc sensitivity analyses to test the influence of arm definitions.

**Additional table. Interventions**

| Intervention | Description |
| --- | --- |
| Cognitive components | |
| Cognitive restructuring | Skills to identify, challenge and change unrealistic beliefs about sleep that may disturb sleep. Sometimes simply called cognitive therapy. |
| Third wave components | Mindfulness and acceptance and commitment therapy. Mindfulness is a form of meditation emphasizing a non-judgmental state of heightened or complete awareness of one’s thoughts, emotions, or experiences on a moment-to-moment basis. Acceptance and commitment therapy focuses on accepting the feelings and thoughts associated with insomnia through value-based behaviors. |
| Behavioral components | |
| Sleep restriction | Skills to improve sleep by limiting time in bed. First, time in bed is restricted to the average sleep duration and then it is increased or decreased depending on sleep efficiency. |
| Stimulus control | Skills to re-associate the bed with sleep. Patients are instructed to; wake up at the same time every morning, refrain from daytime napping, go to bed only when sleepy, get out of bed when unable to sleep, and use the bed/bedroom for sleep and sex only. |