

BMJ Open Effectiveness of low-dose amitriptyline and mirtazapine for insomnia disorder: study protocol of a randomised, double-blind, placebo-controlled trial in general practice (the DREAMING study)

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ABSTRACT

Introduction For over more than a decade, low-dose amitriptyline and mirtazapine are prescribed off-label for insomnia. However, placebo-controlled evidence on these antidepressants for insomnia is still lacking. Therefore, the present trial aims to assess the effectiveness of low-dose amitriptyline (10–20 mg/day) and mirtazapine (7.5–15 mg/day) in patients with insomnia disorder with difficulty maintaining sleep or early-morning awakening problems in general practice.

Methods and analysis The Drug REDiscovery: low-dose Amitriptyline and Mirtazapine for INSomnia disorder in General practice (DREAMING) study is a randomised, double-blind, placebo-controlled trial in about 50 general practices. Adults (18–85 years) with insomnia disorder (Diagnostic and Statistical Manual of Mental Disorders-5) who ask their general practitioner (GP) for sleep medication when non-pharmacological treatment is deemed not effective, are eligible. Exclusion criteria: isolated sleep initiation problem, contraindications for or drug–drug interactions with either amitriptyline or mirtazapine. Participants (n=156) will be randomly assigned to three parallel treatment groups of 16-week treatment with either amitriptyline (one or two tablets of 10 mg/day) or mirtazapine (one or two tablets of 7.5 mg/day) or placebo (one or two tablets) alongside usual GP care. All participants start and end with single dose, but dose can be doubled following GP consultation in week 3. Questionnaire assessments will be conducted at baseline, week 6, 12, 20 and 52. The primary study outcome is self-reported insomnia severity at 6 weeks, measured with the Insomnia Severity Index (ISI) in an intention to treat analysis. Secondary outcomes include subjective sleep quality quantified by sleep indices, daytime functioning and symptoms, safety and treatment evaluation and other sleep care consumption.

Ethics and dissemination The Medical Ethics Committee of the VU Medical Centre Amsterdam approved this trial. The results of this trial will be published in peer-reviewed scientific journals and presented at relevant academic conferences and to key stakeholders.

Trial registration number NTR7449.

Strengths and limitations of this study

- The study addresses an internationally recognised research question on the effectiveness of treatment with low-dose antidepressants for insomnia disorder.
- The pragmatic design ensures the external generalisability of study results to general practice care.
- In addition to short term effects on sleep, day time functioning and long-term effects up to 1 year of the 16-week trial treatment will be assessed.
- The study includes two different types of well-known antidepressants that are relevant for general practice care, that is, amitriptyline and mirtazapine versus placebo.
- A pragmatic low-risk drug trial in general practice comes with practical and logistical challenges, including patient inclusion rates.

INTRODUCTION Background

Insomnia disorder is a prevalent condition affecting sleep and the daily lives of about 6% of the population.¹ According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), the diagnosis insomnia disorder is based on the clinical assessment of a predominant complaint of dissatisfaction with sleep quantity or quality for three or more days a week during more than 3 months, resulting in significant daytime impairment despite sufficient opportunity to sleep.² Patients may experience difficulty initiating sleep, maintaining sleep and early-morning awakening with inability to return to sleep again. Apart from being difficult to treat, insomnia is associated with various major physical and mental health consequences such as an increased risk of cardiovascular diseases and depression.^{3 4} In Europe, the

indirect costs for insomnia disorder are being estimated at €1472 per patient per year, mainly because of loss of work productivity.^{5 6}

Cognitive-behavioural therapy for insomnia (CBT-I) is internationally considered the first-choice therapy for insomnia disorder,^{7–10} since its long-term effectiveness has been shown to be larger with fewer side effects compared with pharmacological therapy.^{11 12} CBT-I consists of a combination of stimulus-control, sleep restriction, relaxation and structured exercise and shows moderate to large effects on sleep efficiency and insomnia severity.^{13 14} In spite of this, many insomnia patients are treated with sleep medication. Reasons for this discrepancy include the limited availability and use of CBT-I, the lack of knowledge and confidence by general practitioners (GPs) in the provision and use of CBT-I and patient pressure to prescribe medication.¹⁵ Moreover, CBT-I is not effective in all patients, as it has been reported that nearly 40% of patients do not achieve remission after treatment¹¹ and some patients may still need sleep medication for remaining insomnia symptoms.¹⁶

Pharmacotherapy for insomnia classically consists of benzodiazepine receptor agonists (BZRAs) (ie, benzodiazepines and so-called ‘z drugs’). These hypnotics induce sleep by enhancing the inhibitory effect of gamma-aminobutyric acid in the central nervous system. Although BZRAs have a short-term efficacy, their use may result in serious adverse effects, that is, non-restorative sleep and side effects like drowsiness, nocturnal confusion, memory loss, falls, rapid development of tolerance, dependence and rebound effects.^{10 17 18}

For over more than a decade, clinicians prescribe various antidepressants with sedative effects in low dose (ie, lower than the dosage for antidepressant efficacy) as an alternative to BZRAs.^{15 19–23} Based on their pharmacological mechanism of action (ie, in low-dose antagonising the wake promoting activities of the central nervous system mediated by histamine H1-receptors) these antidepressants might be especially effective in treating sleep maintenance problems.²⁴ However, most of the generally prescribed antidepressants are not licensed for insomnia treatment nor is their use substantiated with scientific evidence. In the Netherlands as well as internationally, particularly low-dose amitriptyline and mirtazapine are prescribed on a large scale off-label.^{15 19 25} A Cochrane review from 2018 on the use of antidepressants in the treatment of insomnia in adults called for high-quality trials of antidepressants for insomnia to provide better evidence to inform clinical practice.²⁶ In this review, small positive effects on sleep quality and sleep maintenance on the short-term were found for doxepin, which was in 2010 approved by the Food and Drug Administration for the treatment of insomnia with sleep maintenance problems in the USA,^{27–30} and possibly trazodone.²⁶ Es-mirtazapine, the left-enantiomer of mirtazapine, was more recently studied for insomnia in randomised placebo-controlled industry-funded trials.³¹ However, up to the present day, despite their common usage, there is no evidence from

placebo-controlled trials on the effectiveness of low-dose amitriptyline and mirtazapine for insomnia disorder.

We, therefore, designed the Drug REdiscovery: low-dose Amitriptyline and Mirtazapine for INsomnia disorder in General practice (DREAMING) study; a randomised, double-blind, placebo-controlled pragmatic trial. The results of this trial will be of clinical relevance since they will either support or discourage the use of these agents as an effective, safe and generic alternative pharmacological treatment for (primary care) patients with insomnia disorder in case non-pharmacological approaches alone are insufficient.

Objectives

The primary study objective is to assess the effectiveness of low-dose amitriptyline and mirtazapine, respectively, as compared with placebo in patients in general practice with insomnia disorder (DSM-5) with difficulty maintaining sleep or early-morning awakening problems on (1) self-reported insomnia severity. Secondary objectives are to assess (2) the effectiveness during and after treatment on self-reported sleep quality and on sleep (diary) indices, (3) effectiveness with regard to daytime symptoms and functioning both during and after treatment, (4) treatment tolerability (side effects, discontinuation symptoms, evaluation) and (5) whether the treatment is sufficient or that additional sleep medication is requested during or after treatment (up to 1 year).

METHODS AND ANALYSIS

Study design

The DREAMING study is an investigator-initiated, randomised, double-blind, placebo-controlled, multi-centre, phase III trial with three parallel treatment groups in a primary care setting (general practice) comparing amitriptyline and mirtazapine with placebo.

The DREAMING study is pragmatically designed. First, clinical eligibility is assessed by the patient’s own GP and selection criteria of patients resembles as much as possible the target population for off-label low-dose amitriptyline and mirtazapine in daily practice. Second, participating patients remain under care in their own general practice for both trial and non-pharmacological insomnia treatment. Third, our intervention reflects current practice with regard to dosage (10–20 mg amitriptyline or 7, 5–15 mg mirtazapine), usual period of prescribing (around 16 weeks aiming to achieve sustained sleep improvement) and doubling the doses after about 3 weeks if the desired effect has not yet been reached. This pragmatic design not only contributes to the generalisability of the results, but supposedly also to the acceptability of the study medication and will result in a low study drop-out. The DREAMING study is coordinated by the Department of General Practice of the Amsterdam University Medical Centers (UMC), location VUmc, Amsterdam, The Netherlands and will be conducted in over 50 general practices in the Amsterdam region. The trial is conducted in

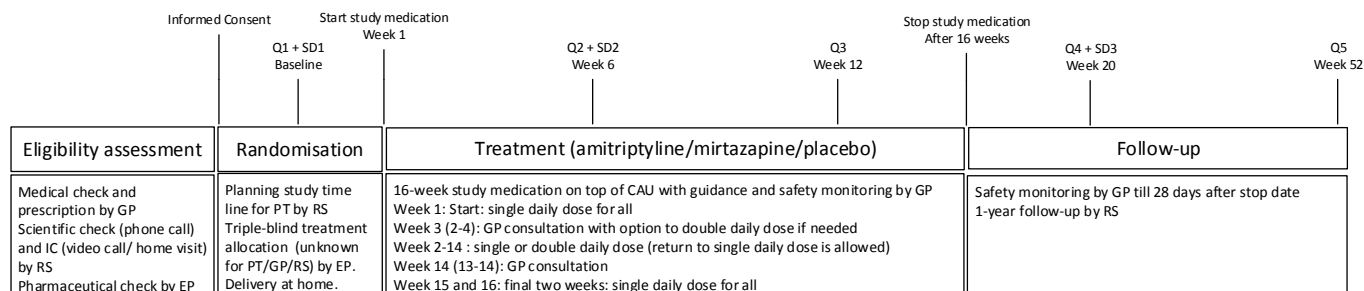


Figure 1 Participant time line. Questionnaires (Q) are filled out about the past 2 weeks. Sleep diaries (SD) are filled out for 1 week prospectively. CAU, care as usual; EP, experimental pharmacy VUmc; GP, general practitioner; RS, researchers; coordination researcher or dedicated research assistant; PT, participant.

accordance to the International Conference on Harmonization Good Clinical Practice regulations (ICH-GCP).³² The reporting of the study protocol is in accordance with the Standard Protocol Items for Randomised Trials recommendations and extension on pragmatic trials (Consolidated Standards of Reporting Trials, CONSORT statements).^{33 34} Figure 1 shows the participant time line. The trial will be conducted between January 2019 and Summer 2022; in consultation with the funding agency the planned inclusion is extended with 1 year to Summer 2021.

General practices

In the Netherlands, insomnia care largely takes place in primary care. The vast majority of non-institutionalised citizens are registered with one general practice. GPs work according to national medical guidelines of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG). In the trial instructions for participating GPs we explicitly refer to following the Dutch NHG general practice guideline on sleep problems,³⁵ in which the preferred treatment for long-term sleep problems is non-pharmacological and pharmacological treatment may be considered for short-term (a BZRA prescription up to 10 tablets) in exceptional situations. In this study, GPs from the participating practices assess medical eligibility on consultation for insomnia, prescribe study medication, evaluate trial treatment in two consultations and perform safety monitoring from start date till 28 days after stop date. Furthermore, their usual care continues throughout the study. For logistic reasons only general practices in the Amsterdam region can participate.

Eligibility criteria

Briefly, the target group consists of adults diagnosed with insomnia disorder in general practice, having difficulty maintaining sleep or early-morning awakening problems and for whom non-pharmacological treatment is deemed insufficient by patient and GP. The inclusion and exclusion criteria are listed in box 1.

Recruitment and consent

Recruitment of participants is performed in regular care by the participating GPs during an inclusion period of approximately 2 years. The assessment of eligibility is

performed in three steps consecutively taken by the GP, coordinating researcher or a dedicated research assistant (hereafter ‘researcher’) and the dispensing pharmacist at the Experimental Pharmacy of Amsterdam UMC, location VUmc (hereafter ‘experimental pharmacy’):

1. GP: checks medical eligibility (inclusion and exclusion criteria 1–15) during a regular consultation with an insomnia patient who requests for sleep medication. If applicable, the GP briefly informs the patient about the aim and set-up of the study and asks whether he/she is potentially interested in participation. If this is the case, the patient agrees in writing that the GP shares his/her contact information with the researcher.
2. Researcher: calls the patient (A) to verify (scientific) eligibility (criteria 1, 8 and 13–16) and (B) asks the patients about their main type of sleep problem (ie, frequent waking during the night versus waking up too early in the morning or at night and trouble falling asleep again) for stratification purposes, (C) informs eligible patients about the study setup and provide an opportunity to answer questions, (D) sends an information package (brochure, informed consent form) and schedules a follow-up meeting (at the patients home or, if preferred at another place, eg, at Amsterdam UMC location VUmc or by video call during COVID-19 measures). The meeting serves to answer any remaining questions and obtain informed consent. On written consent, the participant is assigned a study number and provided with the baseline questionnaire and the baseline sleep diary. Researcher and participant agree on the date on which the participant will start taking the study medication* (t=week 1) and a personalised timetable is provided. Finally, the participant fills out a list with the over-the-counter (OTC) medication that he/she uses.
3. Experimental pharmacy: a final double check on a participants’ pharmacological eligibility (exclusion criterion 10) based on the stated use of OTC medication and a list of currently-used prescription medication from the participants’ community pharmacy, for example, medication prescribed by a specialist not yet known to the GP. In case of relevant drug-drug interactions with the study medication, the participant is excluded.

Box 1 Inclusion and exclusion criteria.

Inclusion criteria:

- ▶ Insomnia disorder, clinical assessment based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria, that is, a predominant complaint of dissatisfaction with sleep quantity or quality for three or more days a week during more than 3 months, resulting in significant daytime impairment despite sufficient opportunity to sleep (DSM-5).²
- ▶ Non-pharmacological treatment according to the Dutch general practice guideline (including sleep hygiene advice and cognitive behavioural approaches) is deemed insufficient by patient and general practitioner (GP).
- ▶ Consultation of the GP for a sleep medication request, other than for occasional incidental nights or specific period (eg, travelling).
- ▶ Aged between 18 and 85 years.*
- ▶ Enlisted as patient in one of the participating general practices during the treatment and safety monitoring period.

Exclusion criteria:

- ▶ Insomnia secondary to another medical condition, for example, obstructive sleep apnea syndrome (OSAS), comorbid major depression, chronic pain.
- ▶ Amitriptyline or mirtazapine is contraindicated or would pose additional risks based on information known to the GP in usual care, that is, allergy for amitriptyline or mirtazapine; cardiac arrhythmia/cardiac blockade/long QT syndrome/Brugada syndrome/family history of acute cardiac death/recent myocardial infarction (within the past 90 days)/angina pectoris/coronary insufficiency; severe renal insufficiency (Glomerular Filtration Rate, GFR <10); severe liver dysfunction; epilepsy; ocular hypertension/glaucoma; bipolar affective disorder; concurrent alcohol or drug abuse/addiction; suicide risk; vulnerability due to known unstable health situation, according to GP.
- ▶ Pregnancy, lactation or wish to become pregnant in the next 6 months.†
- ▶ Terminal illness.
- ▶ Potential drug–drug interactions: chronic use of psychotropic drugs (including anxiolytics,‡ antidepressants, antipsychotics and anti-convulsants and stimulants); concurrent use of oral antimycotics; enzyme inductors, antiretroviral drugs, cimetidine and clonidine.
- ▶ Prescription of amitriptyline or mirtazapine for insomnia in the past year.
- ▶ Being unable to follow study instructions and fill out the study questionnaires (in Dutch).
- ▶ Isolated sleep initiation problem (ie, without problems maintaining sleep or early-morning awakening problems).§
- ▶ Doing night shifts on a regular basis.
- ▶ Wish to continue (over-the-counter) sleep aids containing melatonin, St John's worth, cannabis or antihistamines.
- ▶ Concurrent participation in clinical intervention study interfering with the Drug REdiscovery: low-dose Amitriptyline and Mirtazapine for Insomnia disorder in General practice intervention and study procedures.

* Upper age limit is conform the guideline for low-dose amitriptyline treatment of neuropathic pain and the Food and Drug Administration approved use of doxepin, a tricyclic antidepressant, in the treatment of insomnia.²⁷

† This is explicitly mentioned in the patient information brochure and addressed during informed consent procedure.

‡ Incidental use of BZRAs for sleep in the preceding months is allowed.

Continued

Box 1 Continued

§ Sleep maintaining problems or early-morning awakening problems should be present, because beneficial effects are mostly expected via antagonism of wake promoting systems.²⁴

*The GP is responsible for the study medication prescription. When the patient wishes to start study medication later than 1 month after GP consultation, the researcher asks the GP to check medical inclusion and exclusion criteria (1–15) again in the week before start.

Randomisation and blinding

Study participants will be randomly assigned to one of the three study arms: amitriptyline, mirtazapine or placebo (ratio 1:1:1) using random sequence blocks (blocks of 3). Randomisation is stratified by the main type of sleep problem (ie, frequent waking vs waking up too early) to account for potential effect modification. A computer algorithm run by a pharmacist of the experimental pharmacy who is otherwise not involved in the study will perform randomisation. The research team, GPs and participants and the community pharmacy of the participant are blinded to treatment allocation. The community pharmacy of the participant is informed about participation to ensure that new prescriptions are checked for potential drug–drug interactions for either amitriptyline or mirtazapine. The study medication does not contain any reference to the allocation. According to a unblinding protocol, unblinding of the treatment of an individual participant will occur only if this is required on medical grounds, that is, when the nature of the reaction requires certainty on its possible relation with the study medication in view of the safety of this participant and/or other participants. A pharmacist will be available 24/7 for emergency unblinding. The main effect analysis will be performed in a blind way.

Study medication

Manufacturing and handling of study medication will be according to ICH-GCP.³² Identically appearing round, white and film-coated tablets containing amitriptyline 10 mg, mirtazapine 7.5 mg or placebo are manufactured by Tiofarma BV, Oud-Beijerland, the Netherlands. Placebo tablets taste slightly bitter by adding denatonium benzoate. Study medication is provided to the participant by the experimental pharmacy. Participants are instructed to return remaining study medication by mail (free of costs) to the experimental pharmacy for pill count and subsequent destruction.

Intervention

The investigational treatment consists of 16 week amitriptyline (1–2 tablets of 10 mg) or mirtazapine (1–2 tablets of 7.5 mg) or an identically appearing placebo (1–2 tablets). All participants start with one tablet per night 2 hours to 30 min before bedtime (t=week 1). Participants and GPs are instructed to preplan consults in week 3 (week 2–4)

and in week 14 (13–14) to evaluate effects on sleep and side effects of the treatment. In week 3 (week 2–4), the GP and participant may decide to switch to a structural double dosage regime (two tablets per night up to week 14). At the consultation in week 14 (week 13–14), the GP reminds the participant to stop the study medication after 16 weeks and to use single dosage for the final 2 weeks (week 15 and 16) in case of double dosage. GPs are instructed to inform participants about potential short-lived rebound effects stopping study medication. Participants on double dosage regime are allowed to return to a single dose regime at an earlier time point if agreed on with their GP. Participants are informed that in addition to the preplanned consults, they are allowed to consult their GP (for their sleep problem or other reasons) without any restrictions.

Outcomes and timing of measurements

Treatment effect measurement will be based on patient-reported outcome measures (PROMs) related to sleep as well as daytime functioning. Questionnaires (Q) are filled out online or on paper at five points in time: at baseline, during treatment in week 6 and in week 12, and during follow-up in week 20 and week 52. Pen-and-paper sleep diaries are kept for 1 week prospectively at baseline, in week 6 and in week 20. Validated questionnaires are used

when available. The sleep diary and Dutch translations of sleep related questionnaires were based on those used by van der Zweerde *et al.*³⁶ To promote participants to complete follow-up, on non-response to a questionnaire reminders will be send and participants also receive an incentive of 30 euros on completing Q1–4 and another €10 on completion of Q5. Table 1 provides an overview of the outcomes of interest and their timing.

Additional measurements

Additional measurements include pill count of tablets returned to the experimental pharmacy and relevant data from the electronic medical records in general practice. This comprises consultations (frequency of and reason for consultations, diagnoses of somatic and mental health illnesses) and prescriptions of sleep medication during 1 year before and after the date of informed consent. This information will be used to assess the care-as-usual and to evaluate the intervention, for example, effects of additional insomnia treatment such as sleep medication prescriptions.

Primary outcomes

The primary study outcome is the severity of insomnia as measured by the Insomnia Severity Index (ISI) (at 6 weeks treatment vs baseline).³⁷ The ISI is a seven-item

Table 1 Overview of (the timing of) the patient-reported outcome measures (PROMs)

Measurement	Instrument (PROMM)	Timing (Baseline, week 6, 12, 20, 52)
Background characteristics	Study-specific sex, age, body length and weight, highest attained educational level, current work status, smoking status, alcohol consumption, duration of insomnia, sleep treatment history.	Baseline
Sleep—main outcome	Insomnia Severity Index (ISI) ^{*37}	All time points
Sleep—other outcomes	Pittsburgh Sleep Quality Index (PSQI) ^{*50} items 1–4 and the number of nights per week in which the participant experienced sleep problems.	All time points
	Global rate of change ⁵¹ Sleep problem compared with baseline.	Week 6, 12, 20
	Consensus sleep diary, ⁵² pen-and-paper version, prospectively for 1 week.	Baseline, week 6 and 20
Functional impairments due to sleep problem	Work and Social Adjustment Scale (WSAS) ⁵³	All time points
	Glasgow Sleep Impact Index (GSII) ⁴² part 1, 2 and 3.	All time points
Fatigue	Multidimensional Fatigue Inventory (MFI) ^{*54}	Baseline, week 12 and 20
	Flinders Fatigue Scale (FFS) ⁵⁵ items 4 and 6.	Baseline, week 12 and 20
Emotional complaints	Hospital Anxiety and Depression Scale (HADS), ^{*56} validated Dutch version. ⁵⁷	Baseline, week 12 and 20
Side effects	Antidepressant Side-Effect Checklist (ASEC-21), ^{*58} Dutch translation. ⁵⁹ † At baseline symptom rate only. At follow-up in relation to treatment and current dose.	Baseline, week 6 and 12/ in case of treatment discontinuation as soon as possible.
	Bodyweight Self-reported in kg.	All time points
Withdrawal	Discontinuation-Emergent Signs and Symptoms (DESS) checklist, ⁶⁰ Dutch translation. ⁶¹ †	Week 20/in case of treatment discontinuation in combination with the next planned questionnaire.
Treatment evaluation	Study-specific details of usage (dose, timing of taking tablets), adherence and (reasons for) missed tablets and treatment satisfaction.	Week 20/in case of treatment discontinuation in combination with the next planned questionnaire.
Additional measures to improve sleep +life events	Study-specific other measures to improve sleep used by the participant; retrospectively over the intervention period and over the period after the intervention, life-events affecting sleep.	Week 20 and week 52.

*Recall period adapted to past 2 weeks.

†Adapted for self-administration in insomnia disorder patients. The item 'sleep problem' was in the ASEC-21 replaced by the items 'difficulty waking up', 'sleepiness in the morning', 'sleepiness in the afternoon', 'vivid dreams/disturbed sleep' and omitted from the DESS list and evaluated in a separate item.

self-rated questionnaire on a 5-point Likert scale (0=not at all, 4=extremely) with scores ranging from 0 to 28, higher scores indicating more severe insomnia. The ISI assesses the nature, severity and the impact of insomnia night-time and daytime aspects of insomnia as perceived by the patient. The ISI is validated to identify patients with clinically significant insomnia both in the general population³⁸ and in primary care populations.³⁹ It is validated for online use.⁴⁰ It has an adequate internal consistency and is responsive to changes.³⁸ The ISI is also the recommended tool for outcome measurement in insomnia trials.⁴¹

Secondary outcomes

Secondary outcomes are self-reported sleep quality and sleep quantified by sleep indices, daytime functioning and symptoms (fatigue, anxiety and depression), safety and treatment evaluation (side effects, withdrawal symptoms, treatment satisfaction and adherence) and care consumption (based on self-report and medical records). Fatigue is one of the most common daytime consequences of insomnia. Mood symptoms are also commonly associated with insomnia. To evaluate patient self-assessment of overall treatment efficacy, a global rate of change (Visual Analogue Scale score) will be used. Finally, we added a more personalised approach, to assess treatment effect on the participant's own top 3 daytime consequences of insomnia (questionnaire based on the GSII).⁴²

Other study parameters

Other study parameters are: sex, age, body length and weight, highest attained educational level, current work status, smoking status, alcohol consumption.

Patient and public involvement

Study procedures, patient information and outcome measures have been discussed with a panel of insomnia patients to test feasibility, comprehensibility and completeness and relevance, respectively. Study results will also be presented to and discussed with insomnia patients with a view to enhance implementation of the results.

Sample size calculation

The sample size is calculated for the primary outcome (ISI) at 6 weeks assuming a power of 80%, an alpha of 0.05, a study drop-out rate of 25%, and 10% extra to take account of clustering of patients in general practices. Hence, 43–52 patients per group and a total of 156 participants should be included. Effect sizes (varying from 52% to 96% in the active treatment group vs 20% to 40% in the placebo groups) on different sleep quality measures available have been taken from five published studies at the time of funding, which studied low-dose esmirtzapine (up to 4.5 mg/day), amitriptyline (up to 30 mg/day) or mirtazapine (15 mg/day) for 2 up to 13 weeks in various patient samples, that is, patients with primary insomnia, fibromyalgia, ankylosing spondylitis, chronic psychophysiological insomnia either with or without placebo comparison.^{31 43–45} The study drop-out (treatment discontinuation) rate used above (25%) is estimated based on the average of the rates reported in studies on pharmacological

insomnia treatment during 12 weeks to 6 months.^{27 43 46 47} Using the SD scores of the ISI from another trial in a comparable Dutch insomnia patient population¹⁴ between SD 3.5 and 5.5, our minimal detectable change by this sample size will be 3.5–4 points on the ISI score.

Data analysis

In accordance with the CONSORT guidelines,^{33 34} all participant flow will be reported. Baseline data will be presented as well as data on the adherence to the treatment. Standardised questionnaires will be analysed according to their manual or else custom (published) approaches. Amitriptyline and mirtazapine treatment will be compared with placebo in separate analyses.

The main effect analysis, testing the efficacy of the study medications versus placebo at 6 weeks, will be conducted including all participants (intention-to-treat analysis) and in a blinded way. A linear mixed models analysis will be performed and missing data will be dealt with as appropriate, for example, by multiple imputation. Difference between the two study medication groups and placebo will be expressed in effect sizes and a Cohen's *d* will be calculated, which can be interpreted as the number of SD that each of the study treatment groups, respectively, score better than the placebo group.⁴⁸ In addition, both medication groups will be compared with the placebo group with respect to the percentage of participants that improved or recovered. An ISI score of 10 or lower will be considered recovery. Improvement will be defined as an ISI change score >7.³⁸ This information will be used to calculate the relative risk and the number needed to treat. Rates of reported side effects, withdrawal and rebound symptoms as well as treatment evaluation items will be compared with placebo by means of logistic regression models. In addition to the main effect analyses, several secondary (exploratory) analyses will be performed, for example, per-protocol analysis and analysis by dosage.

Data management and confidentiality

Confidentiality of patient information will be secured throughout and after the trial according to Dutch privacy legislation and ICH-GCP regulations.³² Questionnaires will be collected, entered and stored digitally using a structural database (Castor Electronic Data Capture). Original hard copies of sleep diaries and paper questionnaires will be coded in such a way that they cannot directly be traced back to the identity of the participant. Data will be kept for 15 years and after that period the key files will be destroyed.

Patient safety and monitoring

The medical ethical committee VUmc approved the study protocol and has rated DREAMING as a low risk study: well-known generic agents are used in a low dose (ie, lower than the dosage for antidepressant efficacy) in a study population that reflects the current off-label target population in general practice. The Clinical Research Bureau of Amsterdam UMC location VUmc will do on-site monitoring

of both the research activities at location VUmc and the participating sites, that is, general practices. Since this trial is considered a low risk study, a data safety monitoring board/safety committee is not required. Adverse events (AEs) are monitored by the GP from the start of the intervention (i.e. start study medication) till 28 days after taking the last dose of study medication (ie, stop date). GPs are instructed to report serious AEs (SAEs)³² and AEs which are both severe (ie, severe or medically significant requiring medical intervention in line with Common Terminology Criteria for Adverse Events, CTCAE, grade III) and possibly related to the intervention to the coordinating researcher. The coordinating researcher will call participants once during the treatment period (around week 6) and once about 30 days after the last dose of study medication for a final check on events unknown to the GP. All SAE and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported according to our safety reporting protocol to the accredited medical ethical committee.

Potential challenges and limitations

DREAMING is a randomised placebo-controlled trial conducted in over 50 general practices. Its pragmatic design favours the external generalisability of the results. However, some practical barriers needed to be overcome given the strict regulations of (even low risk) drug trials while general practices are not used and organised to act as formal 'participating research sites'. The success of the study further relies on patient inclusion on consultation in general practice, which is known to be notoriously difficult.⁴⁹ A particular difficulty in this specific case is that the investigated treatment is not exclusively available in the trial, but also off-label in routine care. Several activities such as reminders and support will take place to promote patient inclusion.

Another consequence of a pragmatic drug trial among outpatient participants, is that drug adherence monitoring is based on self-report and on returned pills for pill count. This will be taken into account in the per protocol versus intention to treat analyses. In conclusion, CBT-I remains the preferred treatment therapy for insomnia disorder conform international guidelines. In case of insufficient effect of non-pharmacological therapy and a wish for sleep medication, this study will answer whether low-dose amitriptyline and mirtazapine are an effective alternative to BZRAs on short and long term with respect to insomnia and daytime functioning.

ETHICS AND DISSEMINATION

The Medical Ethics Committee of the VU Medical Centre Amsterdam approved this trial (registration number 2017.630a) and it was registered with the Dutch Trial Registry (NTR7449). Any modifications to the study protocol will be submitted for medical ethical clearance before implementation. The results of this trial will be published in peer-reviewed scientific journals and presented at relevant academic conferences and to key stakeholders.

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Contributors PS conceived of the study. All authors (MHB, JGH, AvS, HEVDH and PS) contributed to the trial design from a multidisciplinary perspective (respectively general practice, clinical pharmacology and pharmacy, clinical psychology, general practice and epidemiology). MHB drafted the manuscript, is the coordinating researcher and will conduct the statistical analysis. All authors approved the final manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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