The DREAMING study: Efficacy of low dose amitriptyline and mirtazapine for insomnia disorder: a double-blind, randomized, placebo-controlled trial in general practice.

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to assess the efficacy of a 16-week treatment period of low dose amitriptyline (10-20 mg nightly) or mirtazapine (7.5 - 15 mg nightly) on subjective sleep quality compared to placebo added to usual care in patients with insomnia disorder with sleep...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50436

Source
ToetsingOnline

Brief title
The DREAMING study

Condition

- Other condition

Synonym
insomnia disorder, sleeping disorder

Health condition

slaapstoornissen

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: amitryptiline, Insomnia, mirtazepine, randomised controlled trial

Outcome measures

Primary outcome

the primary study outcome is subjective insomnia severity, measured by the insomnia severity index.

Secondary outcome

Secondary outcomes include subjective sleep quality quantified by sleep indices, daytime functioning and symptoms (fatigue, anxiety and depression), safety and treatment evaluation (side effects, withdrawal symptoms, treatment satisfaction and adherence). Treatment adherence will also be assessed by pill count. Care consumption is based on self-report and medical records in general practice.

Study description

Background summary

insomnia is a major public health issue in general practice because of its high prevalence and substantial impact on patients* well-being and the increased risk of comorbidity and huge (societal) costs associated with it. Insomnia disorder patients often require sleep medication, despite first choice nonpharmacological treatments. These patients are at risk of benzodiazepine misuse and abuse, given the rapid development of tolerance and dependence.

Effective and safe alternatives suitable for general practice are therefore urgently needed. Clinical experience suggests that off-label low dose use of well-known sedating antidepressants such as amitriptyline and mirtazapine, might be effective, non-addictive, and well-tolerated alternatives to treat insomnia disorder in general practice. Yet, evidence from placebo-controlled RCTs is lacking. Hence, this pragmatic trial concerns a phase three study to assess a new indication for well-known medication.

Study objective

to assess the efficacy of a 16-week treatment period of low dose amitriptyline (10-20 mg nightly) or mirtazapine (7.5 - 15 mg nightly) on subjective sleep quality compared to placebo added to usual care in patients with insomnia disorder with sleep maintenance problems in general practice. Secondary objectives include the long-term sleep efficacy (up to 12 months), the effect on daytime symptoms and functioning and whether it is indeed well tolerated (safe) and sufficient in terms of pharmacological insomnia treatment.

Study design

double blind, randomized, placebo-controlled pragmatic trial in general practice with 3 parallel treatment groups (n=3*52) in which patients are randomized using random sequence blocks (blocks of 3) stratified by the self-reported main type of sleep problem (frequent wakening during the night versus waking up too early in the morning or at night and trouble falling asleep again). It is a pragmatic trial, in which the treatment protocol mimics current off label practice, and participants remain with their own general practitioner during treatment and receive this treatment alongside usual general practice care.

Intervention

16-week treatment with either amitriptyline or mirtazapine or placebo, starting at 10 mg amitriptyline and 7.5 mg mirtazapine per day, respectively, with the possibility of doubling of these dosages if necessary following GP consultation at 3 weeks for the period up to 14 weeks, and single dosage for all participants during the final 2 weeks. During treatment and follow-up, usual care by the participant*s GP continues, without restrictions.

Study burden and risks

although mild reversible side effects may be experienced, no major health risks are expected for participants, given the extent of clinical experience with amitriptyline and mirtazapine as antidepressants (i.e. these are generally well-tolerated when used at the authorized, higher dose levels), and given widespread and years of clinical experience with amitriptyline and mirtazapine,

and the exclusion of known risk groups (e.g. contra-indications, drug-drug interactions). The intervention group may benefit from the intervention by improved sleep quality. The placebo group may experience placebo-effects as reported in previous studies. Participants undergo 5 questionnaire assessments: at baseline, during treatment at 6 and 12 weeks, and during follow-up at 20 weeks and 12 months. A one-week sleep diary is requested at baseline, 12 and 20 weeks. During treatment, participants consult their GP at least twice. Both approval and rejection of the hypothesis would contribute to an evidence-based clinical guideline on the use of sleep medication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adults aged 18-85 years and registered as patient in one of the participating

general practices.
- Presence of insomnia disorder conform DSM-5, i.e. sleep problems (including problems maintaining sleep) in at least 3 nights a week during at least 3 months, with consequences for daytime functioning.
- Request for long-term and/or frequent sleep medication put to their GP because non-pharmacological treatment according to the Dutch (NHG) general practice guideline is deemed insufficient by patient and GP.

Exclusion criteria

- Isolated problem falling asleep (without problems maintaining sleep)
- Insomnia secondary to another medical condition, e.g. OSAS, comorbid major depression, chronic pain
- Habitual shift worker doing night shifts
- Wish to continue (over-the-counter) melatonin
- Use of off-label amitriptyline or mirtazapine for insomnia in the past year
- Terminal illness
- Suicide risk
- Pregnancy, lactation or wish to become pregnant in the coming 6 months
- Vulnerability due to unstable health situation according to GP.
- Being unable to follow study instructions and fill out the study questionnaires (in Dutch)
- Participation in other interventional medical scientific studies,
Contra-indications
- Allergy for amitriptyline or mirtazapine
- Cardiac arrhythmia / 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 (GFR < 10)
- Severe liver dysfunction
- Epilepsy
- Ocular Hypertension / Glaucoma
- Bipolar affective disorder
- Current alcohol or drug abuse/addiction, Potential drug-drug interactions
- Current use of psychopharmaceuticals (including anxiolytics as e.g. benzodiazepines, antidepressants including St John*s wort and, anticonvulsants)
- Current use of antimycotics (all types)
- Certain enzyme inductors, antiretroviral drugs, cimetidine and clonidine.
(All of these are not commonly used and will be excluded by the prescription check by the GP and/or the final check by the pharmacist).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2019
Enrollment:	156
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	amitryptiline/mirtazepine
Generic name:	amitryptiline/mirtazepine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-003766-27-NL
CCMO	NL63470.029.17

Study results

Date completed:	28-06-2022
Actual enrolment:	81

Summary results
Trial is onging in other countries