Efficacy of low dose amitriptyline vs. cognitive behavioural therapy for chronic insomnia and medical comorbidity: a randomized controlled non inferiority trial.

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This study has been transitioned to CTIS with ID 2024-518320-71-00 check the CTIS register for the current data. The main objective of the study is to determine whether low dose amitriptyline (10-20 mg nightly) in chronic insomnia coexisting with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55662

Source
ToetsingOnline

Brief title
TIMELAPSE study

Condition

- Other condition

Synonym
Insomnia, sleeplessness

Health condition

insomnia stoornis

Research involving
Human

Sponsors and support

Primary sponsor: Ziekenhuisvoorzieningen Gelderse Vallei
Source(s) of monetary or material Support: geen extra financiering

Intervention

Keyword: amitriptyline, cognitive behavioral therapy for insomnia, insomnia, medical comorbidity

Outcome measures

Primary outcome

The main study parameter is the mean subjective insomnia severity score,

measured by the insomnia severity index (ISI). Primary endpoint is at 12 weeks.

Secondary outcome

During the follow-up period maintenance of the treatment response assessed

operationalized as having a >= 8 point reduction on the ISI Secondary

outcomes include sleep quality quantified by sleep efficiency, questionnaires

on daytime functioning and symptoms (fatigue, emotional complaints, physical

functioning impairment of functioning). Possible moderators are type of

insomnia, dysfunctional attitudes and beliefs about sleep, pre sleep arousal.

Furthermore adverse events and treatment evaluation (side effects, withdrawal

symptoms, and adherence) are assessed.

Study description

Background summary

Insomnia is common in people with medical conditions. Insomnia is related to

increased mortality and morbidity. Cognitive behavioral therapy for insomnia (CBT-I) is first choice of treatment and also effective for people with insomnia and medical conditions. In general CBT-I does not lose its effectiveness when delivered in a less costly format as a group therapy. Despite the evidence that CBT-I is an effective intervention, there can be limitations to CBT-I for patients with medical conditions, requiring a safe alternative.. Preliminary evidence and clinical experience suggests that off-label low dose use of sedating antidepressants such as amitriptyline (AM), might be non-addictive, effective, and well-tolerated alternative to treat insomnia in patients with medical comorbidity.

Study objective

This study has been transitioned to CTIS with ID 2024-518320-71-00 check the CTIS register for the current data.

The main objective of the study is to determine whether low dose amitriptyline (10-20 mg nightly) in chronic insomnia coexisting with medical conditions is as effective as CBT-I in improving subjective sleep.
Secondary objectives include (1) investigating the long-term efficacy of amitriptyline in comparison to CBT-I, (2) determining the effect on daytime symptoms and functioning, (3) determining whether the medication is well tolerated (safe) (4) identifying mediators and moderators of treatment outcome.

Study design

The study is a non-inferiority randomized controlled trial. Participants (n=2*9584) will complete clinical assessments and then will be randomly assigned to (1) Cognitive behavioral therapy (CBT-I), (2) amitriptyline for 12 weeks (AM). Outcomes will be assessed at baseline and after 12 weeks. All treatment responders will be assessed for a period of maximal 12 months after treatment. The score on the Insomnia Severity Index (ISI), a patient-reported outcome, will serve as the primary endpoint for treatment comparisons. All treatment responders will be assessed for a period of maximal 12 months after treatment. Treatment responders are defined as having >= 8 point reduction on ISI (Morin e.a. 2011). Data will be gathered on secondary outcomes, baseline characteristics, and possible moderators and mediators. In both conditions adherence, side effects are assessed and withdrawal in the medication condition.

Intervention

Participants are treated during 12 weeks with either amitriptyline (starting with 10 mg per day, respectively, and, if ineffective, possible doubling of this dose after 3 weeks, and stopping after 12 weeks) or cognitive behavioural therapy 6 weekly sessions and a follow up session after 6 weeks, followed by

usual care by their neurologist-somnologist. Follow up will continue until 12 months after treatment.

Study burden and risks

10 assessments will take place: at baseline, at start treatment, 6, 12 and 14 weeks, and the responders during follow-up (i.e. reduction on ISI <8 until relapse) at 2, 4, 6 , 8 , 10 and 12 months post treatment. A one-week sleep diary is requested at start treatment,12 weeks, and 12 months post treatment. During treatment, patients visit their neurologist at least once. No major health risks are expected for participants in the medication condition, given the level of clinical experience with these antidepressants that are generally well-tolerated, the low dosage in this study, and the exclusion of risk groups. The medication intervention group may benefit from the intervention by improved quality of their sleep and may experience mild reversible side effects. The CBT-I group will benefit by receiving the treatment of first choice. Both groups will benefit from the frequent monitoring (post) treatment and possibility to get access to the other treatment option, when insomnia does not improve or remits after treatment. Both approval or rejection of the hypothesis lead to an evidence based clinical guideline on the use of amitriptyline.

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 older visiting the outpatient clinic department of neurology.
- Presence of insomnia disorder conform DSM-5, i.e. sleep problems in at least 3 nights a week, for at least 3 months with consequences for daytime functioning, the sleep problem cannot be better explained by or occurs exclusively during the course of another sleep disorder (e.g. sleep related breathing disorder, parasomnia)
- Score of >=10 on the Insomnia Severity Index (ISI)
- Have a medical condition and / or chronic pain (> 3 months).

Exclusion criteria

- Habitual night shift worker
- Untreated sleep related breathing disorder
- Wish to continue over-the-counter sleep aids as melatonin and medicinal cannabis
- Use of off-label amitriptyline for insomnia in the past year
- Being unable to follow study instructions and fill out the study questionnaires (in Dutch)
- A known diagnosis of dementia
- History of delirium
- Pregnancy, lactation or wish to become pregnant in the coming 6 months
- Terminal illness (prognosis < 1 year)
- Suicide risk
- Epilepsy
- Ocular Hypertension / Glaucoma
- The presence of a severe psychiatric disorder not in remission or adequately treated.
- Current alcohol or drug abuse/addiction (benzodiazepine excluded).
- Participation in other interventional medical scientific studies
- Current use of psychopharmaceuticals other than benzodiazepine (antidepressants including St John*s wort, anticonvulsants)
- Current use of antimycotica
- Allergy for amitriptyline
- 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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-09-2019
Enrollment:	190
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	amitriptyline
Generic name:	tricyclic antidepressant
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	17-07-2019

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2021
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
EU-CTR	CTIS2024-518320-71-00
EudraCT	EUCTR2019-001520-35-NL
CCMO	NL68611.018.19