

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of E-aid cognitive behavioral therapy for insomnia (eCBTI) to prevent the transition from episodic insomnia to persistent insomnia: study protocol for a randomized controlled trial
AUTHORS	Yang, Yuan; Luo, Xian; Paudel, Dharendra; Zhang, Jihui; Li, Shirley Xin; Zhang, Bin

VERSION 1 – REVIEW

REVIEWER	Christopher Miller Oxford, UK. I am Research Lead of Big Health Inc. and receive a salary from the company behind Sleepio.
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	<p>Background Reference 2 - specify these costs are from Quebec. Reference 3 - does not speak to the preceding statement regarding the risk of various physical disorders. The acronyms STID and CID may be confusing to the reader especially when citing DSM-5 criteria. I suggest using Insomnia Disorder for DSM-5-defined insomnia lasting 3 months or more and acute insomnia for less than this. Further, I am unaware if STID per DSM-5 does not include 'a minimum frequency of more than three nights per week' - my understanding is that only the duration of symptoms is reduced as per the note at the bottom of (https://www.ncbi.nlm.nih.gov/books/NBK519704/table/ch3.t36/)</p> <p>Methods Please include the type of randomization used and the allocation ratio. It may be beneficial to include more information about in what way the intervention was developed and maintained. Where is the clinical trial registered?</p> <p>Discussion The limitations section is missing.</p>
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REVIEWER	Subhajit Chakravorty Perelman Sch of Medicine USA
REVIEW RETURNED	06-Oct-2019

GENERAL COMMENTS	Summary: The authors propose a unique study involving evaluation of the role of a short-term course of internet-based CBT-I for short-term insomnia and its role in prevention of
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	<p>development of insomnia disorder. The aim of this study is to evaluate the feasibility and effectiveness of brief e-aid cognitive behavioral therapy for insomnia (eCBT-I) in treating acute insomnia and preventing transition to insomnia disorder. The study will be a 2-arm, multicenter, randomized control trial, that will compare eCBT-I to Treatment As Usual (TAU). Two hundred subjects with insomnia disorder will be randomized to receive eCBT-I for 1 week via their smartphone or TAU and their outcomes assessed 1 week and 3 months after the intervention. The primary outcome measure is the Insomnia Severity Index (ISI). Secondary outcome measurements include Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Ford Insomnia Response to Stress Test (FIRST), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSAS), and Epworth Sleepiness Scale (ESS). Additionally, Hospital Anxiety and Depression Scale (HADS) and the Short-Form 12-Item Health Survey (SF-12).</p> <p>Comments for the authors. The authors propose a unique study that will evaluate the efficacy of treatment of short-term insomnia and the role of behavioral treatment for short-term insomnia in the prevention of long-term comorbid conditions. I have a few comments for the authors:</p> <ol style="list-style-type: none"> 1. Introduction. <ol style="list-style-type: none"> a. There is a discrepancy in the aims stated in the abstract and the introduction section. Does the primary aim of this study plain to evaluate the effectiveness of eCBT-I (page 2) or is it to evaluate eCBTI as an intervention that will reduce the transition from STID to CID (page 7), or line # 13, page 13? If it is the former, shouldn't the present study be considered an efficacy study (pilot study) in a population of Chinese patients, rather than an effectiveness study? Design. <ol style="list-style-type: none"> a. Subjects – exclusion criteria should include screening for obstructive sleep apnea (OSA), a disorder that may mimic insomnia symptoms. A simple measure such as the STOP-BANG scale may be helpful to screen out clinically significant OSA patients. b. Treatment arms – an education/monitor only such as an insomnia education should be considered instead of TAU (treatment as usual). Subjects in the control group may be given educational information (like reviewing information on the National Sleep Foundation website), but are left to apply it themselves. c. How will the treatment be allocated to the subjects? d. Assessment of safety should include evaluation for suicidal ideation. e. Post-treatment follow up – the assessment measures will be assessed during follow up should be clarified in the text. I only understood this information once I reviewed the flow diagram. Discussion <ol style="list-style-type: none"> a. The possible limitations of this study should be added in the discussion section.
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VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Christopher Miller

Institution and Country: University of Oxford, UK.

Background

Reference 2 - specify these costs are from Quebec.

Re: Thanks for your comments, we have changed the sentence as: On average, the economic burden of insomnia is 5010 US dollars per person per year, comparing with 421 dollars per year in an individual with good sleep, according to a study conducted in Quebec, Canada [2].

Reference 3 - does not speak to the preceding statement regarding the risk of various physical disorders.

Re: Thank you, we have cited another article which could better support our statement: Fernandez-Mendoza, J. and A.N. Vgontzas, *Insomnia and its impact on physical and mental health*. *Curr Psychiatry Rep*, 2013. 15(12): p. 418.

The acronyms STID and CID may be confusing to the reader especially when citing DSM-5 criteria. I suggest using Insomnia Disorder for DSM-5-defined insomnia lasting 3 months or more and acute insomnia for less than this. Further, I am unaware if STID per DSM-5 does not include 'a minimum frequency of more than three nights per week' - my understanding is that only the duration of symptoms is reduced as per the note at the bottom of (<https://www.ncbi.nlm.nih.gov/books/NBK519704/table/ch3.t36/>)

Re: Thanks for your comments. We have rechecked the DSM-5 handbook (page 363, line 2-3), and it specified 'episodic insomnia' as: symptoms last at least 1 month but less than 3 months, while 'persistent insomnia' was defined as: symptoms last 3 months or longer. Therefore, we have replaced 'STID' to 'episodic insomnia' and revised 'CID' as 'persistent insomnia' throughout the manuscript.

Methods

Please include the type of randomization used and the allocation ratio.

Re: Thanks, we have made changes accordingly (see Participant and randomization section).

Participants will be recruited from sleep clinics in 31 hospital sites in mainland China, and will be randomly allocated to two groups at 1:1 ratio, namely, eCBTI (n=100, 50%) or control group (TAU) (n=100, 50%).

It may be beneficial to include more information about in what way the intervention was developed and maintained.

Re: Thanks for your advice, in our study, the E-CBTI will be delivered using the WeChat Mini Program. The program and all tools can be accessed using the WeChat app of any smartphone. With the assistance from professional IT staff and clinical psychologists, the E-CBTI intervention program has been well-developed and tested before the start of our current study. We also have two IT staff

who are responsible for keeping the intervention programme working functionally. Relevant information has been added in the manuscript.

Where is the clinical trial registered?

Re: Thanks, relevant information has been presented on the abstract page: Trial registration: NCT03302455 (clinicaltrials.gov). Date of registration: October 5, 2017.

Discussion

The limitations section is missing.

Re: Thanks, we have acknowledged several limitations in the manuscript: First, double-blinded study design is unable to be fulfilled in the current study, only the onsite-research staff are blinded to the group assignment. Second, the sample size of this study is relatively small, the results might thus not be representative of the general population. Third, sleep measurements in our study are mainly based on self-reports, apart from subjective sleep measurements, objective measurements, such as actigraphy and polysomnography would be beneficial.

Reviewer: 2

Reviewer Name: Subhajit Chakravorty

Institution and Country: Perelman Sch of Medicine, USA

Please state any competing interests or state 'None declared': N/A

Summary: The authors propose a unique study involving evaluation of the role of a short-term course of internet-based CBT-I for short-term insomnia and its role in prevention of development of insomnia disorder. The aim of this study is to evaluate the feasibility and effectiveness of brief e-aid cognitive behavioral therapy for insomnia (eCBT-I) in treating acute insomnia and preventing transition to insomnia disorder. The study will be a 2-arm, multicenter, randomized control trial, that will compare eCBT-I to Treatment as Usual (TAU). Two hundred subjects with insomnia disorder will be randomized to receive eCBT-I for 1 week via their smartphone or TAU and their outcomes assessed 1 week and 3 months after the intervention. The primary outcome measure is the Insomnia Severity Index (ISI). Secondary outcome measurements include Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Ford Insomnia Response to Stress Test (FIRST), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSAS), and Epworth Sleepiness Scale (ESS). Additionally, Hospital Anxiety and Depression Scale (HADS) and the Short-Form 12-Item Health Survey (SF-12).

Comments for the authors. The authors propose a unique study that will evaluate the efficacy of treatment of short-term insomnia and the role of behavioral treatment for short-term insomnia in the prevention of long-term comorbid conditions. I have a few comments for the authors:

1. Introduction

a. There is a discrepancy in the aims stated in the abstract and the introduction section. Does the primary aim of this study plain to evaluate the effectiveness of eCBT-I (page 2) or is it to evaluate eCBTI as an intervention that will reduce the transition from STID to CID (page 7), or line # 13, page 13? If it is the former, shouldn't the present study be considered an efficacy study (pilot study) in a population of Chinese patients, rather than an effectiveness study?

Re: Thanks for your comments and we are sorry for the misunderstanding, we have removed the 'feasibility' description from the manuscript. The current study aims to evaluate the effectiveness of brief e-aid cognitive behavioural therapy for insomnia (eCBTI) in preventing transition from short-term insomnia to chronic insomnia. It is an 'intervention' study rather than a 'feasibility' study. We have made changes accordingly in the manuscript.

Design

a. Subjects – exclusion criteria should include screening for obstructive sleep apnea (OSA), a disorder that may mimic insomnia symptoms. A simple measure such as the STOP-BANG scale may be helpful to screen out clinically significant OSA patients.

Re: Thanks for your comments. Based on the DSM-5 diagnostic criteria, to be diagnosed as insomnia disorder, the insomnia must does not occur exclusively during the course of another sleep-wake disorder (e.g. narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia) (DSM-5, Page 362, Diagnostic Criteria 780.52 (G47.00)). Additionally, in our current study, we exclude participants who have a diagnosis of definite and poor controlled physical diseases, mental disorders and/or sleep disorders requiring immediate attention (see Flowchart). Only participants with a 'pure' insomnia diagnosis will be included in our study (recruited by trained psychiatrists). Therefore, we believe there is no extra need to add another exclusion criterion to rule out OSA particularly.

b. Treatment arms – an education/monitor only such as an insomnia education should be considered instead of TAU (treatment as usual). Subjects in the control group may be given educational information (like reviewing information on the National Sleep Foundation website) but are left to apply it themselves.

Re: Thanks for your comments. We thank the reviewer's suggestion to give education information as a better control. However, in consideration of ethical matters, participants in the control group will be offered eCBTI at week 12. Therefore, we believe that there is no need to provide educational information for the subjects in control group.

c. How will the treatment be allocated to the subjects?

Re: Thank you, under the 'randomization' section, we clarified that: Participants fulfilling the study criteria will be randomly allocated to either eCBTI or Control group using simple randomization (computer-generated random numbers). An independent researcher will implement randomization and treatment allocation, which will be conducted through an online system.

d. Assessment of safety should include evaluation for suicidal ideation.

Re: Thanks for your comments. We have included this evaluation in the manuscript.

e. Post-treatment follow up – the assessment measures will be assessed during follow up should be clarified in the text. I only understood this information once I reviewed the flow diagram.

Re: Thanks for your comments. Please see Page 9, under the subheading named ‘assessment points’, we have mentioned that we will conduct a post treatment assessment at week 2 (one-week post treatment).

Discussion

a. The possible limitations of this study should be added in the discussion section.

Re: Thanks, we have acknowledged several limitations in the manuscript: First, double-blinded study design is unable to be fulfilled in the current study, only the onsite-research staff are blinded to the group assignment. Second, the sample size of this study is relatively small, the results might thus not be representative of the general population. Third, sleep measurements in our study are mainly based on self-reports, apart from subjective sleep measurements, objective measurements, such as actigraphy and polysomnography would be beneficial.

VERSION 2 – REVIEW

REVIEWER	Christopher Miller Oxford, UK. I am Research Lead of Big Health Inc. and receive a salary from the company behind Sleepio.
REVIEW RETURNED	25-Oct-2019

GENERAL COMMENTS	The authors have addressed my points. I would only like to highlight that the blinding procedure appears slightly ambiguous. Can more be done to let readers understand this better. For example, the study appears to be single-blind with onsite-research staff blinded to allocation. In what way will this be achieved and maintained? Which researcher will carry out the randomization procedure and are they independent from the study and what about analysis of data - will the statistician be blinded during this?
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REVIEWER	Subhajt Chakravorty Subhajt Chakravorty Perelman Sch of Medicine, USA
REVIEW RETURNED	17-Oct-2019

GENERAL COMMENTS	No further comments.
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VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Subhajit Chakravorty

Institution and Country:

Subhajit Chakravorty

Perelman Sch of Medicine, USA

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

No further comments.

Reviewer: 1

Reviewer Name: Christopher Miller

Institution and Country: Oxford, UK.

Please state any competing interests or state 'None declared': I am Research Lead of Big Health Inc. and receive a salary from the company behind Sleepio.

Please leave your comments for the authors below

The authors have addressed my points. I would only like to highlight that the blinding procedure appears slightly ambiguous. Can more be done to let readers understand this better. For example, the study appears to be single-blind with onsite-research staff blinded to allocation. In what way will this be achieved and maintained? Which researcher will carry out the randomization procedure and are they independent from the study and what about analysis of data - will the statistician be blinded during this?

Re: Thank you, we have added more information under the randomization and blinding section.

Randomization

We added: An independent researcher from IT department will implement randomization and treatment allocation, which will be conducted through an automated online system. The research team will not be able to influence randomization and have no access to allocations.

Blindness of assessment and analysis

Onsite-research staff will be blinded to the group assignment and study outcomes hypotheses during the trial. The independent researcher from IT department who carries out the randomization and allocation procedure will be blinded to the study protocol. Participants could not be blinded to treatment allocation as participants in blank control group only receive TAU. The research team will have limited contact with both IT staff and study participants therefore will not be able to bias the allocation or the assessments. Statistical analyses will be carried out by an independent researcher

from the Southern Medical University who are not involved in the procedures of randomization and assessment.