Study on the effects of Cognitive Behavioral Therapy on depression-related insomnia and its influence on suicide risk

Dennys Lapenda Fagundes (✉ dennyslapendafagundes@gmail.com)
UFPE: Universidade Federal de Pernambuco
https://orcid.org/0000-0002-6417-980X

Everton Botelho Sougey
UFPE: Universidade Federal de Pernambuco

Tatiana Santana Silva
UFPE: Universidade Federal de Pernambuco

Leia Teixeira Andrade
IMIP: Instituto de Medicina Integral Professor Fernando Figueira

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Abstract

Basis of the study

There is a growing interest in understanding the relationship between sleep and suicide. Although insomnia is commonly cited as a critical risk factor for suicidal thoughts and behavior, evidence on the treatment and management of insomnia and its effects on reducing risk and/or suicidal thinking remains unclear. In this sense, this is the first trial to test the effectiveness of CBTI in reducing suicidal behavior over a long period (8 weeks), associated with improvement in depressive symptoms.

Methods

Double-blind, randomized, controlled clinical trial, conducted over 8 weeks, to be constructed in accordance with the SPIRIT, and registered on the national clinical trials platform, with a duly calculated sample. Individuals aged 18 to 60 years will be included, who are diagnosed with depression according to DSM-V criteria and with symptoms of insomnia, and who report suicidal ideation with intent to die in the last week and/or suicide attempt in the last month. Randomized into 2 intervention groups, namely: Group A: therapeutic protocol including only Amitriptyline medication at a dosage of 25 mg for insomnia; Group B: therapeutic protocol including Amitriptyline medication at a dosage of 25 mg for insomnia and intervention with CBTI, with a protocol lasting 8 sessions. Primary outcomes will include assessment of insomnia severity (Insomnia Severity Index - ISI) and suicide risk (Columbia Suicide Risk Assessment Scale - C-SSRS); the secondary outcome will include severity of depressive symptoms (Montgomery-Asberg Depression Scale). Primary and secondary outcome measures will be collected at weeks 0, 2, 4, 6 and 8 of the intervention. And the follow up will be carried out for up to three months after the intervention with biweekly periodicity.

Discussion

To the best of our knowledge, this will be the first clinical trial to test the effectiveness of CBTI in reducing the risk of suicide in patients with depression and insomnia. The findings will contribute to the understanding of the therapeutic effects in the management of depression and insomnia, as well as risk behaviors, and may help guide the development of new care protocols aimed at clinical and pharmacological support in reducing the risk of suicide.

Trial registration:


Basis of the study

Suicide has become one of the leading causes of death worldwide ((WHO, 2018). In Brazil alone, in 2016, the WHO registered 6.1 suicides per 100,000 inhabitants, equivalent to 62,804 deaths that year, a number
which has increased almost sevenfold since 2010.

A substantial body of evidence demonstrates that sleep disturbance is a significant risk factor for suicidal behavior (LAVIGNE et al., 2019; WANG, CHENG, XU, 2019; DOLSEN et al., 2020; LAU et al., 2020; SHER, 2020; HARRIS et al., 2020).

Insomnia, including difficulties falling asleep, staying asleep or returning to sleep, is associated with suicidal ideation, especially among patients with depression, alcohol abuse or dependence and post-traumatic stress disorder.

Additionally, it is important to highlight that the increased incidence of suicide emphasizes the need to identify and treat associated factors. Suicidal ideation is a precursor of the sort of suicide which has been associated with sleep disorders and insomnia. (PIGEON, PINQUART, CONNER et al., 2012; MCCAL, BLACK et al., 2013; ZUROMSKI, CERO, WITTE, 2017).

Although depression is the main target for identifying suicide, symptoms of insomnia may outperform depression in predicting suicidal ideation (RIBEIRO et al., 2012; SHER, 2020; WANG, CHENG, XU, 2019; HARRIS et al., 2020). Additional evidence suggests that insomnia may be a potentially modifiable risk factor, and can become a target for suicide prevention (MCCAL et al., 2019; SIMMONS et al., 2020; SHER, 2020; HARRIS et al., 2020).

In this context, treatments for insomnia could be essential for reducing suicidal behavior. An example is Cognitive-Behavioral Therapy for Insomnia (CBTI), which is an effective non-pharmacological treatment for primary insomnia. CBTI has behavioral components, such as stimulus control instructions, sleep restriction therapy and relaxation training; as well as cognitive components, such as the restructuring of cognitions that interfere with sleep, psychoeducation and sleep hygiene. For this reason, psychotherapeutic intervention has been recognized as a first-line treatment for insomnia by the National Institute of Health (NIH), Consensus Statement 2, and the British Association of Psychopharmacology (NIH, 2005).

Historically, CBTI research has focused on individuals with primary insomnia and excluded people with comorbidity. However, a growing body of research has now established that CBTI can indeed be effective for patients with insomnia and comorbidity (BROWN, ROGERS, LIU, 2015; SADLER et al., 2018). Despite these results, clinical trials related to CBTI with community patients who have important psychiatric comorbidities, such as depression and suicidal behavior, have been underrepresented in the literature. Thus, conducting a randomized controlled clinical trial is necessary in this scenario, because promising evidence indicates that CBTI not only improves insomnia, but has the potential to also reduce depression and consequently suicidal behavior. For this reason, CBTI can influence the future direction of risk behavior prevention strategies, making it possible to include this safe and relatively inexpensive treatment as a relevant strategy for the prevention of deaths by suicide.
This article presents the protocol of a randomized clinical trial, with the objective of evaluating the therapeutic effects of Cognitive-Behavioral Therapy for Insomnia, related to depression and suicidal ideation, in patients with depression and insomnia, attended at the psychiatric outpatient clinic of the Instituto Materno Infantil de Pernambuco, located in northeastern Brazil – in comparison with a control group (Daily Drug Administration for 8 Weeks). The hypothesis is that CBTI improves depressive symptoms and decreases both insomnia and the risk of suicide in patients with depression.

**Methods**

This study protocol was guided by the SPIRIT recommendations (Fig. 1 – study flowchart). The proposed prospective randomized study was duly registered at http://www.ensaiosclinicos.gov.br/org – Number: RBR-10b889rz/ UTN number: U1111-1287-9616 (February 13, 2022).

The clinical trial will be conducted in accordance with the precepts stipulated in the Declaration of Helsinki. The project received approval from the Ethics Committee for Research with Human Beings of the Federal University of Pernambuco (certificate number: 5.167.260 of 12/15/2021) and the Ethics Committee for Research with Human Beings of the Istituto de Medicina Integral Professor Fernando Figueira-IMIP (certificate number: 5.307.597 of 03/23/2022). All participants will be recruited from the psychiatry outpatient clinics of a Brazilian Public Hospital. We will evaluate adults of both genders (18 to 60 years old), with diagnosis of depression, insomnia and a history of suicidal ideation, in routine psychiatric clinic care, for a period of eight weeks.

**Election criteria**

Patients will be considered eligible if they:

- Present minimum age of 18 years and maximum of 60 years;
- Meet the criteria of the Diagnostic and Statistical Manual of Mental Disorders (5th edition, DSM-V Criteria) for Depressive Disorder and Comorbid Insomnia (APA, 2013).
- Present suicidal behavior according to the criteria proposed by the Columbia Suicide Risk Assessment Scale (POSNER et al., 2011);
- Have a total Insomnia Severity Index (ISI) score greater than 15.

Patients may be taking an antidepressant prescribed by their psychiatrist, but the insomnia medication of choice will be added to the study. The level of depression must be considered severe, as assessed by the psychiatrist. Individuals with cognitive impairment (as determined by the Mini-Mental Health Examination), those already under psychotherapeutic treatment or using another antidepressant, those with a history of psychiatric comorbidities, and pregnant or lactating women will be excluded from the study.
Operational procedures

All instructions will be accurate and written in manual form to ensure that all procedures determined for the clinical trial are performed, including patient recruitment, allocation to study groups, administration of the intervention, registration systems, criteria for stopping the intervention, etc. All activities to be carried out during the clinical trial will be previously established in the form of a list of tasks and distributed to the research team.

The initial assessment will consist of completing an identification form, a sociodemographic inventory, compilation of standardized medical records with anamnesis, physical examinations, standardized free and informed consent form, and a structured interview addressing depression using the Montgomery-Asberg Depression Rating Scale – scale that addresses the risk of suicide. The researcher will monitor the application of the depression and suicide risk scales.

Instruments for evaluating the measure of the primary outcomes

Assessment of Insomnia Severity

For this outcome, the Insomnia Severity Index (ISI) will be used, which is a 7-item insomnia measure of self-reported severity, commonly used in research. It has acceptable psychometric properties and is sensitive to treatment response. The questionnaire contains seven questions with scores ranging from zero to four. The specific items assess difficulties such as falling asleep, maintaining sleep, waking up in the morning, among others. The highest total score indicates severe sleep disturbance (Bastien, Vallières, Morin, 2001; SADLER et al., 2018).

Assessment of suicidal behavior and suicide risk

For this outcome, the Columbia Suicide Risk Assessment Scale (C-SSRS) will be used, an instrument designed to assess suicidal behavior, developed by Kelly Posner and collaborators in New York, at Columbia University in 2007. This scale addresses the intensity of suicidal ideation and behavior, differentiating between behaviors with little probability of causing injuries and those with a higher probability of lethality (POSNER et al., 2011).

The instrument has an exclusive version for use in research of clinical trials focused on suicidal behavior outcomes. Currently, the scale is available in 103 languages, including Portuguese. It is one of the few tools which evaluates the entire spectrum of suicidal ideation, based on facts experienced by the individual and behavioral trends (POSNER et al., 2007). The Center for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) recommend the use of this scale (POSNER et al., 2011). In this study, individuals who present a minimum score in any of the five sub-items of the scale during the follow-up period will be considered at risk of suicide.
Instruments for evaluating the measure of the secondary outcome

Assessment of depressive symptom severity

For this outcome, the Montgomery-Asberg Depression Scale, validated in 1979, will be used. The MADRS scale was chosen due to its greater sensitivity to changes in depressive symptomatology (MULDER, JOYCE, FRAMPTON, 2003). On this scale, scores less than or equal to 10 characterize the remission of the depressive episode. Higher MADRS scores indicate more severe depression, and each item yields a score from 0 to 6. The overall score ranges from 0 to 60. The questionnaire includes questions about the following symptoms: a) apparent sadness; b) expressed sadness; c) internal tension; d) reduced sleep; e) reduced appetite; f) concentration difficulties; g) lassitude; h) inability to feel; i) pessimistic thoughts; j) thoughts of suicide (MULDER, JOYCE, FRAMPTON, 2003).

Interventions

Medication Protocol for Insomnia

Both groups (Group A and Group B) will receive a drug protocol for insomnia. This will consist of Amitriptyline at a dosage of 25 mg, because it is a medication indicated for drug treatment in the 2019 Brazilian Consensus on Insomnia, and because of the availability of the medication in the Unified Health System.

CBTI protocol for insomnia

Only Group B will receive the CBTI protocol for insomnia. Cognitive Behavioral Therapy for Insomnia (CBTI) will be performed by a professional in the field of psychology who is trained to exercise specific psychotherapy for insomnia. CBTI, in particular, has been shown to be effective in reducing insomnia as well as mood and anxiety symptoms in several comorbid populations.

CBTI is an intervention normally carried out in face-to-face sessions, once a week for 30–40 minutes, for 6 to 8 weeks. Treatment manuals describe CBTI as consisting of three main components (Sleep Restriction Therapy, Stimulus Control Therapy, and Sleep-Specific Cognitive Therapy), along with sleep psychoeducation and sleep hygiene.

In this study, participants will receive weekly sessions of 60 to 90 minutes, for 8 weeks. The CBTI program will consider the guidelines of experts in the field, with session format and application of the treatment using a focused structure (SADLER et al., 2018). Actions proposed in the CBTI protocol will include, in the first four sessions, control stimuli (for example, going to bed only when feeling sleepy), sleep restriction (e.g. initially limiting the time spent in bed to increase the efficiency of the sleep), sleep hygiene (e.g. removing stimulating sources from the bedroom, such as television/radio/clock), and relaxation (e.g. diaphragmatic breathing, guided imagination). Cognitive restructuring of unhelpful sleep beliefs (e.g.
thought diaries, behavioral experiments) and relapse prevention (e.g. summary of effective skills, maintaining progress) were included in the second half of the program (SADLER et al., 2018).

**Data analysis**

Data will be analyzed using statistical measures: mean and standard deviation values for numerical variables and percentage frequencies for categorical variables. Intergroup comparisons will be performed using Student's t test or Mann-Whitney test for numeric variables and Pearson's chi-square test for categorical variables. Intragroup comparisons of initial and final values will be performed using the paired Student's t test or the Wilcoxon test for paired data for numerical variables, and the McNemar test for categorical variables.

The unpaired and paired t tests will be used in situations where the data presents normal distribution, while the Mann-Whitney test and the Wilcoxon test for paired variables will be used in situations where it is normality rejected. The Shapiro-Wilk test will be used to determine data normality and Levene's F test will be used to determine the equality of variances.

The margin of error used in the decisions of the statistical tests will be 5%, and 95% confidence intervals will be calculated. Data will be entered into an EXCEL spreadsheet and the Statistical Package for the Social Sciences (SPSS version 23) will be used for all statistical calculations.

A statistician will perform the calculations and statistical analyses of the participants taking substances A and B. The masking will only be removed at the end of the statistical analyses.

**Sample Size Calculation**

The final sample will be calculated from a pilot study and conducted according to the guidelines proposed by Azevedo (2008). This will include the identification and classification of the variables of interest, the expected difference to be observed between the measures of these variables in the groups, the error probabilities called error type I (a) and error type II (b), whose values derive from the standardized Gaussian distribution scale (z table of the normal curve) (MASSAD, SILVEIA, ORTEGA, 2004), and finally the level of significance and the probability of correctly detecting a significant difference between groups. Thus, a formula for obtaining the sample related to the mean of the differences between the intervention groups will be adopted, namely:

**Reducing the risk of bias**

The dose of Amitriptyline for the treatment of chronic insomnia conditions meets the pre-established criteria, from previous trials, which showed positive results in reducing insomnia symptoms. It has also been established by the current Consenso Brasileiro de Insônia 2019.
Ethical considerations

The project received approval from the Ethics Committee for Research with Human Beings of the Federal University of Pernambuco (certificate number: 5.167.260 of 12/15/2021) and the Ethics Committee for Research with Human Beings of IMIP (certificate number: 5.307.597 of 03/23/2022). For the proper execution of the activities related to the research, it will be necessary to meet the following demands in sequence of occurrence:

1. Letter(s) of consent(s) from the institutions: to obtain participants and carry out the treatments.
2. Consent of the Research Ethics Committee (REC): in compliance with the recommendations expressed in resolution No. 466 of 2012, of the National Health Council.
3. Confidentiality Agreement of those responsible for the research: in order to ensure that the data shared in the activities is protected and reserved only for the purposes proposed in the project; those responsible for the research will sign confidentiality terms.
4. Completion of the terms of consent: all participants will be informed about the objectives of the research, the necessary steps and the risks and benefits that will arise with the acceptance of participation. The right to freely choose whether or not to participate in the research will be assured and withdrawal will be allowed at any time. There will be anonymity regarding all information contained in the dissemination of the study results. The acceptance of the participant will be finalized through due and complete clarification of these terms, and ensured by the voluntary signature of the Free and Informed Consent Form.
5. Criteria for Suspension and Termination of Research: The participant is assured the right to withdraw from participation at any time, as well as to have complete access to the information acquired and analyzed. Participants will have their participation suspended or terminated if any casuistry criterion is found that is not in compliance and has not been declared, such as, for example, the finding of a pregnancy. The decision on suspension and conclusion of the individual's participation in the research will be carried out considering the well-being and health of the patient and the integrity and reliability of the research and its results.
6. Benefits: The study presents the benefits of evaluating the psychotherapeutic intervention of CBTI in patients with depression, insomnia and suicidal behavior.
7. Risks: This research presents minimal risk, which concerns the discomfort of volunteers when approached by unknown people to answer the questionnaires, as well as the deviation or loss of any of the instruments, causing harm and/or embarrassment to the volunteer. In order to minimize any embarrassment, the place of the interview will be private for the interviewees and researchers. Only the researchers will have access to the evaluation instruments. It is at the discretion of the volunteer during the research to allow a trusted companion to be present in the environment chosen for the research. After the period of 8 sessions, if the volunteer still has symptoms, he will be referred to the psychiatry service for a new, more careful evaluation.

Primary outcomes
Prior to each of the treatments, participants will complete self-report questionnaires. The evaluator, blinded to group allocation, will ask participants to complete outcome measures in a separate location from the treatment room.

1- Therapeutic effects of CBTI on insomnia, evaluated by the Insomnia Severity Index - ISI;

2- CBTI therapeutic effects on depressive symptoms assessed by the Montgomery-Asberg Depression Scale.

**Secondary outcomes**

1- Therapeutic effects of CBTI in reducing the risk of suicide, as assessed by the Columbia-Suicide Severity Rating Scale.

2- Reduction in the frequency of suicidal thoughts and ideation evaluated by the Columbia-Suicide Severity Rating Scale.

**Analysis plan and outcome measurement**

1- Insomnia – The mean change in the Insomnia Severity Index score from the beginning to the end of the intervention, measured for all participants, starting from non-significant insomnia (scores from 0 to 7 points), or from the lower limit for insomnia (scores from 8 to 14 points) – ISI reference;

2- Depression – Reduction of the total score obtained using the Montgomery-Asberg Depression Scale represented by scores less than or equal to 10 points, which characterize the remission of the depressive episode. MONTGOMERY, A.S.; Åsberg, M. – New Depression Scale Designed to be Sensitive to Change. British Journal of Psychiatry 134, pp382-389, 1979.

3- Suicide risk – Reduction in the total score obtained in the Columbia-Suicide Severity Rating Scale evaluation, represented by the absence of a minimum score in any of the five sub-items of the scale. POSNER, K.; BROWN, G.K.; STANLEY, B. et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American journal of psychiatry*, v.168, n.12, p. 1266-77, 2011.

**Discussion**

This study will be a randomized, controlled and blind clinical trial with the objective of exploring the therapeutic effects of Cognitive-Behavioral Therapy for Insomnia related to depression and suicidal ideation, in patients with depression and insomnia. This will determine the feasibility of future large-scale clinical trials in patients with insomnia and depression who are also at risk for suicide.
Cognitive behavioral therapy for insomnia (CBTI), the most evidence-based non-drug treatment for insomnia, is a multicomponent intervention that targets cognitive and behavioral factors that contribute to chronic sleep disturbances. Multiple controlled trials indicate that CBT for insomnia benefits 70–80% of individuals with chronic insomnia [22–24], with nearly 50% achieving post-treatment insomnia remission [25, 26]. Moreover, the trials showed that early treatment gains are well maintained over time, with follow-up periods of 2 to 3 years [27–30].

Combining CBTI to reduce insomnia in depressive patients may lead to the optimization of therapy for depression with greater tolerability and without additional side effects. In addition, the therapeutic effects of CBTI may also have an impact on the remission of suicide risk, a common aspect among patients with insomnia and depression [27–30].

This study has some strengths. First, this is the first randomized trial in Brazil investigating CBTI as an adjunctive therapy to medication for patients with insomnia conducted for 2 months. Second, our study may provide evidence that reflects the configurations of Brazilian traditional medical clinical practice, because most patients who visit traditional medical clinics only have medication use in their treatment protocol. Finally, we will collect important data on sleep quality through self-reported questionnaires.

The result of this study may provide preliminary data for a new large-scale randomized controlled trial, to obtain consistent evidence on the effectiveness of CBTI for insomnia and depression. Another potential benefit of this clinical trial is the contribution to public policies that address the importance of psychological therapy as an adjuvant in cases of insomnia.

The results and conclusions of this clinical trial will be submitted to national and international symposiums, as well as to peer-reviewed journals.

**Ethics and intellectual property**

This clinical trial was approved by the Ethics Committee for Research with Human Beings of the Federal University of Pernambuco (certificate number: 5.167.260 of 12/15/2021) and the Ethics Committee for Research with Human Beings of IMIP (certificate number: 5.307.597 of 03/23/2022).

**Access, reuse and sharing of data**

The datasets used and analyzed during the study will be made available by the author upon any reasonable request.

**Long-term storage, curation and preservation**

The datasets used and analyzed during the study will be under the custody of the researcher responsible for the project.
Limitations

The study will be carried out in a philanthropic institution, which operates in the areas of medical and social assistance, teaching, research and community outreach.

Participants will need to go to the outpatient clinics every two weeks for evaluation with the three instruments, for eight weeks, which can lead to absenteeism. To work around this problem, a member of the research team can carry out the assessment virtually in cases of non-attendance to the service.

Antidepressant drugs can be determined by the attending psychiatrist. Thus, the researchers of the present clinical trial will not have control over the type or dosage of antidepressants prescribed for the unipolar depressive condition. This lack of standardization of antidepressant medications may be a source of research bias.

Test registration:

Trial registration: Check-copy: http://www.ensaiosclinicos.gov.br/org Number: RBR-10b889rz/ UTN number: U1111-1287-9616 (February 13, 2022). Recruitment (patient screening) started in the first half of 2022 and collection is scheduled to end in the first half of 2023. Thus, the study is currently in progress.

Abbreviations

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

PRISMA – Preferred reporting items for systematic reviews and meta-analyses

UFPE - Universidade Federal de Pernambuco

IMIP- Instituto de Medicina Integral de Pernambuco

CBTI- Cognitive Behavioral Therapy for Insomnia

SPSS – Statistical Package for the Social Sciences

Declarations

Ethical approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki and received approval from the Ethics Committee for Research with Human Beings of the Federal University of Pernambuco (certificate number: 5.167.260 of 12/15/2021) and the Ethics Committee for Research with Human Beings of IMIP (certificate number: 5.307.597 of 03/23/2022). The study protocol was also retrospectively registered in

Consent for publication

All participants agreed to publish the results.

Availability of data and materials

Not applicable.

Competitive Interests

There are no competing financial and non-financial interests.

Funding

There are no external funding sources. The protocol and the study are being financed by the researcher with personal resources.

Author Contributions

All authors made substantial contributions to the study design and participated in the preparation of the submission request. DLF1 designed the study, developed the criteria and wrote the present protocol. TPSS2 and EBS3 guided all phases of the article and carried out the revision of the manuscript. All authors read and approved the final version.

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Author Information

EBS3 is a permanent professor at the Neuropsychiatry and Behavioral Sciences Program at the Federal University of Pernambuco. TPSS2 is a postdoctoral researcher at the Neuropsychiatry and Behavioral Sciences Program at the Federal University of Pernambuco. DLF1 is a doctoral student in the Neuropsychiatry and Behavioral Sciences Program at the Federal University of Pernambuco.

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community mental health services. Sleep, (). – doi:10.1093/sleep/zsy104

Figures
Figure 1

Study flowchart
Diferença entre médias de dois grupos

\[ n = \frac{(\alpha + \beta)^2 \sigma^2}{d^2} \]

onde \( \sigma^2 \) corresponde à varância esperada e \( \sigma \) é a diferença esperada entre as médias da variável quantitativa estudada.

Diferença entre proporções de dois grupos

\[ n = \frac{(\alpha + \beta)^2 \left[ p_1/p_2 + 1 \right] - p_2 \left[ p_1/p_2 \right]^2 + 1}{p_2 \left(1 - p_1/p_2\right)^2} \]

onde \( p_1 \) e \( p_2 \) são as proporções do evento nos grupos 1 e 2, respectivamente.

Figure 2

Figure 1- Sample calculation of the difference between the means of two groups, proposed by Azevedo 2008. Available at: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-42302008000400007