Developing and Testing a Spanish-Language Intervention to Reduce Cancer-Related Sleep Disturbance

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BACKGROUND AND SIGNIFICANCE

Cancer-Related Sleep Disturbance

Cancer-related sleep disturbance is clinically significant difficulty falling asleep or staying asleep that is distressing to patients or causes daytime disfunction and is caused, worsened, or perpetuated by cancer or treatment for cancer.[1,2] It is similar to primary insomnia,[3-5] understood to stem from a precipitating event that temporarily causes acute sleep disturbance which is perpetuated by behavioral changes to patients' sleep habits and environment, as well as cognitive factors. An important difference between cancer-related sleep disturbance and primary insomnia is that cancer survivors experience unique precipitating and perpetuating factors that are not experienced among the general, healthy population. For example, healthy individuals have some underlying predisposing factors for insomnia, develop acute insomnia due to precipitating factors, and this continues to chronic insomnia due to behavioral and cognitive perpetuating factors. These behavioral factors are typically maladaptive strategies to account for acute insomnia (e.g., napping after work).

In contrast, cancer survivors face unique precipitating and perpetuating factors. These include the cancer itself as well as pain, nausea, and other side-effects not experienced by most others with no history of cancer. Thus, cancer-related sleep disturbance and primary insomnia differ in terms of their etiology. These differences underscore the rationale for adapting an intervention for cancer-related sleep disturbance that was specifically developed for cancer survivors. The study team has developed a collaboration with an investigator who led the development of just such an intervention. This intervention has demonstrated efficacy towards reducing sleep disturbance[6] and impacting immune function.[7]

Need for Spanish-Language Intervention for Cancer-Related Sleep Disturbance

Although cancer-related sleep disturbance is largely overlooked among Hispanic cancer survivors, large epidemiologic studies among cancer-free individuals have demonstrated that Hispanics have worse sleep disturbance than non-Hispanic Whites, especially older Hispanics.[8] Despite this documented disparity, there is an acute lack of behavioral interventions for Spanish-speaking cancer survivors. For example, although numerous specialized courses are available in English to train behavioral therapists to provide first-line therapy for insomnia,[9] many therapists are unable to pay the travel and registration fees. Numerous English-language manuals exist that enable behavioral therapists to provide first-line therapy for insomnia, we are unaware of a single manual that Spanish-speaking behavioral therapists in the USA can follow. Moreover, we are unaware of a single Spanish-language course that provides training to administer this treatment. The numerous negative biological, emotional, and psychological consequences of sleep disturbance underscore that Spanish-speaking cancer survivors are at a distinct disadvantage because they are largely unable to receive first-line therapy for cancer-related sleep disturbance.

The Current Study

The current project will leverage an existing intervention that has demonstrated efficacy among cancer survivors[6] to create and test a Spanish-language behavioral intervention in a pilot randomized clinical trial. We will first gather qualitative data from patients, caregivers, and providers to determine the best mode of delivery of this new intervention (e.g., in person, in print, via Internet). We will then adapt the existing intervention into a Spanish-language intervention. Lastly, we will test this new intervention in a sample of 30 Spanish-speaking breast cancer survivors using a randomized controlled design. Data will be used to address the following aims:

SPECIFIC AIMS

Aim 1: Gather qualitative data from cancer survivors, caregivers, and clinicians to determine the best modality to deliver the new intervention.

Aim 2: Develop a new behavioral intervention to reduce cancer-related sleep disturbance in Spanish-speaking cancer survivors. Hypothesis 1: We hypothesize that we will be able to adapt an existing, written, and manualized behavioral intervention and culturally target this intervention for Spanish-speaking cancer survivors.

Aim 3: Pilot test the new intervention for feasibility, acceptability, and preliminary efficacy in a sample of N=30 participants. Hypothesis 2: We hypothesize that participants randomized to receive the new intervention will

report greater pre- to post-treatment reductions in cancer-related sleep disturbance than participants randomized to a wait-list control condition.

Aim 4: Explore changes in sleep disturbance during the COVID-19 pandemic which may influence future trials of the new intervention.

RESEARCH DESIGN AND METHODS

Aim 1: Gather qualitative data from cancer survivors, caregivers, and clinicians to determine the best modality to deliver the new intervention.

Overview

The qualitative component will begin by inviting 10 cancer survivors, 10 survivors' caregivers, 5 clinicians, and 5 cancer support group leaders to participate in individual interviews about how best to deliver a cancer-related sleep disturbance intervention. We hypothesize that qualitative interviews with patients, providers, and caregivers will demonstrate that Spanish-speaking cancer survivors in Puerto Rico with cancer-related sleep disturbance will prefer to receive this intervention in group sessions and printed materials rather than via the Internet or via printed materials only.

Role of PIs: Dr. Gonzalez will oversee all aspects of Aim 1 in close collaboration with Dr. Morales-Cruz, who will supervise identification of potentially eligible participants, recruitment of participants, and collection of qualitative interview data. Drs. Gonzalez and Morales-Cruz will analyze qualitative data together. Participants will be recruited only within the Southern Puerto Rico area.

Eligibility Screening and Recruitment

Eligible cancer survivors (n=10) will: a) be ≥ 18 years old, b) be able to speak and read Spanish, c) have no documented or observable disabilities that would preclude participation in the qualitative interviews, d) be required to have completed primary treatment for breast cancer, and e) report clinically significant sleep disturbance (i.e., ≥ 8 on the Insomnia Severity Index). Eligible caregivers (n=10) will be required to be ≥ 18 years old and a caregiver for a friend or relative who meets eligibility criteria to participate as a survivor. Eligible clinicians (n=5) will be required to be ≥ 18 years old and be medical providers for cancer survivors. Eligible cancer support group leaders (n=5) will be required to be ≥ 18 years old and be leaders of cancer support groups in the Southern Puerto Rico area.

Potential cancer survivor participants will be recruited from medical clinics and cancer support groups in the Southern Puerto Rico area. Potential participants will be approached in a HIPAA-compliant manner by a trained research associate in person and/or via telephone. Those who are approached through medical clinics will be identified in consultation with the medical team. Those who are approached through cancer support groups will be identified in consultation with the cancer support group leader(s). A Spanish-speaking study team member will determine eligibility through chart review and discussion with the medical team or cancer support group leaders, approach patients via telephone or in person, and confirm eligibility with a brief questioning of the potential participant. Participants who meet all eligibility criteria will be provided with oral and written explanations of the study and the opportunity to ask questions. Eligible and interested patients will then be invited to nominate caregivers to be approached for participation. Lastly, eligible and interested patients will be invited to provide informed consent and complete the interview or schedule an appointment to provide informed consent and complete the interview.

Potential caregiver participants will be nominated by eligible cancer survivors. Potentially eligible caregivers will be contacted in person and/or via telephone by a study team member who will describe the study, confirm eligibility, and provide an opportunity to ask questions about the study. Eligible and interested caregivers will then be either invited to provide informed consent and complete the interview or schedule an appointment to provide informed consent and complete the interview.

Clinicians and cancer support group leaders will be identified through Southern Puerto Rico area medical clinics and cancer support groups, respectively. Potentially eligible clinicians and support group leaders will be approached in person and/or via telephone by a study team member who will describe the study, provide an

opportunity to ask questions about the study, and either provide informed consent and complete the interview or schedule an appointment provide informed consent and complete the interview.

Interviews

Survivors and caregivers will be interviewed separately by phone or in person at the location of the participant's choosing. Interviews will be aimed at identifying how best to deliver the cancer-related sleep disturbance intervention. In addition, interviews will assess patients' perceptions of: 1) medications that may impact sleep disturbance, 2) non-pharmacological interventions for insomnia (vs. pharmacotherapy), 3) need to address sleep disturbances in cancer patients, 4) when this treatment should be offered in the cancer care trajectory, and 5) what kind of professionals should offer this service. Interviewers will follow a semi-structured interview guide to be developed by Drs. Gonzalez and Morales-Cruz. Interviews are expected to last up to 30 minutes and will be audio-recorded and professionally transcribed verbatim. Clinicians and cancer support group leaders will be interviewed individually by phone or in person at a location of their choosing. Each participant will be provided a $50 gift card after completion of the interview.

Data Analysis

All transcripts will be entered into NVivo, a qualitative data analysis program. This software will facilitate review of transcripts by Drs. Gonzalez and Morales-Cruz to determine the consensus recommendation from patients, caregivers, clinicians, and cancer support group leaders regarding how to deliver the intervention.

Aim 2: Develop a new behavioral intervention to reduce cancer-related sleep disturbance in Spanish-speaking cancer survivors.

Overview

The new cancer-related sleep disturbance intervention will be adapted from an existing, manualized cognitive-behavioral intervention developed by Dr. Savard to meet the needs of Spanish-speaking cancer survivors. The modality of this intervention will be selected based on input from cancer survivors, caregivers, clinicians, and cancer support group leaders in Aim 1. We hypothesize that we will be able to adapt an existing, written, and manualized behavioral intervention and culturally target this intervention for Spanish-speaking cancer survivors.

Role of PIs: Dr. Gonzalez will oversee all aspects of Aim 2 in close collaboration with Dr. Morales-Cruz. Dr. Gonzalez will lead the development of the intervention with regular input and feedback from Dr. Morales-Cruz. No participants will be recruited as part of Aim 2.

Intervention Development

The protocol has been amended to include the results from Aim 1. Most participants in Aim 1 recommended in-person group therapy sessions as the preferred intervention modality. Development of this manual began by translating relevant French-language text, provided by Dr. Savard, into Spanish verbatim. With input from Dr. Savard, Drs. Gonzalez and Morales-Cruz, the text was edited to ensure 1) the language is culturally appropriate and not specific to any particular Spanish-speaking subgroup, 2) intervention materials are relevant to cancer survivors, 3) minimal burden for cancer survivors. Study investigators also re-ordered select modules from Dr. Savard's original intervention to give participants time to practice sleep hygiene skills earlier on in the intervention.

The revised text was then used to develop a printed therapy manual as well as a patient manual for administration of the intervention in Aim 3.

Aim 3: Pilot test the new intervention for feasibility, acceptability, and preliminary efficacy in a sample of N=30 participants.

Overview

A randomized, wait-list controlled trial will test the feasibility and acceptability of the new intervention in a sample of 30 breast cancer survivors. Acceptability will be assessed by examining the consent rate, obtaining verbal feedback from the group after each intervention session, and through a 10-item version of the Treatment Perception questionnaire administered to participants at the follow-up assessment. Feasibility will be determined using the number of participants who attend/receive most of the therapy sessions/content. We hypothesize that

≥ 50% of eligible participants approached to participate will sign consent and that ≥ 75% of participants will attend/receive most of the sessions/content. Intervention fidelity will be measured by a trained staff member who will listen to the recorded intervention sessions and note the completion of key intervention elements identified a priori for each session. Preliminary efficacy will be assessed with the Pittsburgh Sleep Quality Index[10] completed before and after completing the intervention.

Role of PIs: Dr. Gonzalez will oversee all aspects of Aim 3 in close collaboration with Dr. Morales-Cruz, who will supervise identification of potentially eligible participants, recruitment of participants, and collection of data. Drs. Gonzalez and Morales-Cruz will analyze data together. Participants will be recruited only from within Puerto Rico. The intervention sessions will take place via videoconference sessions. The day before each scheduled session a group text message will be sent reminding participants of the next session's date and time and providing a videoconference web link to join the session. It is important for participants to complete a sleep diary each morning noting various characteristics of their sleep the previous night. Because these data are an important topic of discussion during sessions, the group text message will also request participants send a reply text message with a photograph of their sleep diary.

Eligibility Screening and Recruitment

Eligible breast cancer survivors (n=30) will: a) be ≥ 18 years old, b) be able to speak and read Spanish, c) have no documented or observable disabilities that would interfere with study participation, d) have completed primary treatment for breast cancer (e.g., surgery, chemotherapy, radiation), e) report clinically significant sleep disturbance (i.e., ≥ 8 on the Insomnia Severity Index), f) be at low risk of other sleep disorders that are not amenable to treatment with cognitive-behavioral therapy using the Duke Structured Interview for Sleep Disorders, and g) have access to the Internet and a digital device (e.g., smartphone) capable of using videoconference software.

Potential cancer survivor participants will be recruited from clinics, cancer support groups in the Southern Puerto Rico area, using flyers, postings to online bulletin boards, and via referral from individuals who have heard of the study. All potentially eligible survivors will be approached in a HIPAA-compliant manner by a trained research team member in person and/or via telephone. Those who are approached through medical clinics will be identified in consultation with the medical team. Those who are approached through cancer support groups will be identified in consultation with the cancer support group leader(s). Those who learn of the study via flyers, online postings, or referrals will contact the study team via the telephone number provided to them.

Eligibility will be confirmed through a brief questioning of the potential participant. Participants who meet all eligibility criteria will be provided with an explanation of the study and the opportunity to ask questions. Eligible and interested patients will be asked for an e-mail address and sent an e-mail invitation to a web link to an electronic informed consent form. Participants may also op to be sent the invitation via a text message. Participants who follow the link and sign consent electronically will then be asked to complete a baseline assessment via the Internet. Participants will then be randomized to either the intervention or a wait-list control condition. After completing the 6-week waiting period, wait-list control group participants will be asked to complete the assessment via the Internet again before being invited to participate in an intervention group. Participants who have been sent the e-mail invitation but have not completed the informed consent form and/or baseline survey within 2 days will be contacted up to 3 times to provide any necessary clarifications and/or assistance with completing the consent form and/or survey.

Intervention Procedure

Participants will be randomized to one of two arms: 1) the Spanish-language cancer-related sleep disturbance intervention or 2) wait-list control condition. Participants in the intervention group will be asked to attend videoconference group therapy sessions to be scheduled by the study team. These groups will be comprised of up to 10 participants per group and will meet weekly for 6 weeks. The groups will provide patients instruction in the following components of cognitive-behavioral therapy for cancer-related sleep disturbance:

- Sleep Education: education regarding sleep
- Sleep Hygiene: recommendations to ensure the bed and bedroom are conducive to sleep
- Sleep Restriction: consolidate time spent in bed to the actual sleep time and retrain the sleep-wake cycle

- Stimulus control: limiting non-sleep activities in bed, such as watching television, using mobile devices and re-associate the bed/bedroom with sleep
- Relapse Prevention: strategies to continue improvements made during the intervention
- Cognitive Restructuring: helping patients avoid automatic negative thoughts regarding difficulty sleeping that may make it more difficult for patients to fall asleep or stay asleep

Participants randomized to the wait-list control condition will wait 6 weeks, complete a follow-up assessment via the Internet, and then be provided access to videoconference intervention group sessions identical to those provided to intervention group participants.

Measures

All participants will complete the Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, and Fatigue Symptom Inventory after consent (i.e., baseline) and after the 6-week intervention (i.e., post-intervention). The post-intervention assessment will also include the Insomnia Severity Index, which will have been administered as part of the screening process. Participants in the intervention group will thus complete two assessments. Participants in the wait-list control group will complete these two assessments (i.e., at baseline and after the 6-week waiting period; i.e., post-waiting) as well as a third assessment after participating in the sessions (i.e., post-intervention). Participants will be sent an e-mail and/or a text message with a link to the follow-up assessment. Participants who have been sent the survey e-mail but have not completed the follow-up survey within 2 days will be contacted up to 3 times to provide any necessary clarifications and/or assistance with completing the survey.

All participants will also complete a 10-item version of the Treatment Perception Questionnaire to assess intervention satisfaction after participating in the sessions (i.e., post-intervention). This validated measure, available in English and Spanish, assesses satisfaction with the intervention, the degree to which participants used the intervention, and the degree to which participants used specific strategies to improve their sleep. Verbal feedback will also be obtained from session participants at the end of each session to identify any terminology that was confusing, or other suggestions for improving the intervention for the future.

Each participant will be sent a $25 gift card after completing the baseline assessment and a $75 gift card after completing the post-intervention assessment. Participants randomized to the wait-list group will be provided a $50 gift card after completing a third assessment after completing an additional assessment after the therapy sessions.

Data Analysis

The primary outcomes for this intervention are acceptability and feasibility. The study will be deemed acceptable if ≥ 50% of eligible cancer survivors who are approached agree to participate and > 50% of intervention group participants report that, on average, they agree with positive statements about the intervention (i.e., report an average score of ≥ 3 on a scale of 0 to 4). The study will be deemed feasible if ≥ 75% of the intervention group participants attend at least half of the educational components of the intervention. This will be operationalized as having attended at least half of the sessions. The secondary outcome is sleep disturbance, and efficacy data will be examined at the conclusion of the intervention. Sleep disturbance will be operationalized by scores on the Pittsburgh Sleep Quality Index, sleep efficiency (the percentage of time spent in bed that is spent asleep), and the Insomnia Severity Index. The primary efficacy outcome will be the continuous measures of sleep disturbance. For secondary efficacy analyses, participants will be categorized as having sleep disturbance if 1) their Pittsburgh Sleep Quality Index score is ≥ 5 (for subjectively-measured sleep disturbance), 2) if their sleep efficiency is <85% (for objectively-measured sleep disturbance), and 3) if their Insomnia Severity Index score is ≥ 8. Although statistical significance will be evaluated, the primary purpose is to compute the effect size at follow-up (Cohen's *d*; difference between groups divided by the pooled standard deviation). Intent-to-treat analyses will be conducted, such that all participants who are randomized will be asked to provide follow-up data at the end of the intervention period regardless of the level of use of the intervention. Participants who do not provide complete follow-up data will not need to have data imputed due to the use of mixed model analyses.

Aim 4: Explore changes in sleep disturbance during the COVID-19 pandemic which may influence future trials of the new intervention.

Overview

Participants will join a semi-structured focus group to assess the degree to which patterns in sleep disturbance changed as a result of the pandemic so that the study team can prepare for a future efficacy trial that may need to take into account such pandemic-related changes in sleep disturbance.

Eligibility Screening and Recruitment

Eligible breast cancer survivors (n=40) will: a) be ≥ 18 years old, b) be able to speak and read Spanish, c) have no documented or observable disabilities that would interfere with study participation, d) have completed primary treatment for cancer (e.g., surgery, chemotherapy, radiation), e) have access to the Internet and a digital device (e.g., smartphone) capable of using videoconference software, and f) report clinically significant sleep disturbance (i.e., ≥ 8 on the Insomnia Severity Index).

The study team will post a study flyer with study team contact information to online bulletin boards, in community oncology clinics, and at meeting places for support groups. Potentially eligible survivors will contact the study team. Study team members will describe the study procedures, offer an opportunity for the individual to ask questions, determine eligibility, review consent information, and solicit verbal informed consent from eligible and interested individuals. Verbally consented participants will be sent a PDF copy of the consent information sheet for their records.

Verbally consented participants will be asked to respond to demographic questions regarding age, relationship status, employment, and education history and medical history questions regarding cancer diagnosis and treatment history. Participants will then be asked for an e-mail address and/or a cellular telephone number to which they can be sent a videoconference session link via unencrypted e-mail and/or text message. Participants will also be asked to provide an address to which they can be sent a gift card after completing the focus group. Participants will then be scheduled for a focus group session. Participants who miss a scheduled focus group or request to reschedule will be scheduled for an upcoming focus group, if available. Each participant will be sent a reminder text message and/or unencrypted e-mail up to 2 days before the scheduled focus group with the videoconference session link.

Semi-Structured Focus Groups

Participants will join a semi-structured focus group via videoconference with up to 10 participants. The goal of the focus groups will be to learn whether and how the study team should further adapt cognitive-behavioral therapy for insomnia in the context of the COVID-19 pandemic. Focus groups will be led by study team members who are fluent in Spanish and have experience and training in conducting qualitative focus groups. Each focus groups is expected to last approximately 1.5 to 2 hours. Participants will be sent a $50 gift card after completing the focus group.

Focus groups will continue until thematic saturation is reached, [11] which we expect to require approximately 4 focus groups with 7-8 participants each. Because some participants are expected to be unable to join a scheduled focus group, we will schedule up to 10 participants for each focus group (up to 40 participants total) to ensure focus groups have about 8 participants.

Data Analysis

Focus groups will be audio- and video-recorded and transcribed. Transcripts will be entered into qualitative analysis software to facilitate review of transcripts by study team members with expertise and experience in qualitative analyses. Qualitative analyses will be overseen by Dr. Jennifer Morales-Cruz and will identify themes relevant to Aim 4.

Confidentiality of Participant Data

All participant data will be maintained confidential and will not be made publicly available to the extent permissible by applicable laws and/or regulations. Publications based on study data will maintain participant confidentiality and will not publish identifiable data.

All investigators have received training in research ethics and all study staff will be required to receive this training as well. Confidentiality will be maintained by using participant numbers on data, rather than participants' names.

Participant data will be available only to the research team. All electronic study data will be password protected with access restricted to approved study personnel. Paper-based data will be kept in locked filing cabinets and identifying information will not be reported. In the extensive experience of the research team, these measures will likely be highly effective in minimizing potential risks to participants. We will also implement a Data Safety Plan as described below to ensure the privacy of subjects.

Participant data will be made available, upon request, to designated Protocol Review and Monitoring Committees, Institutional Review Boards, Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.

Data Safety Plan

All participant data will be maintained in locked file cabinets and on secure servers with access restricted to only research team members. These data will be retained until 10 years after the last publication of findings from this project. The PIs and research team will retain the data keys that link patient names with their unique identifiers for 10 years.

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