1 - Results for Self-Reported Sleep Measures

Results before Outliers' Exclusion

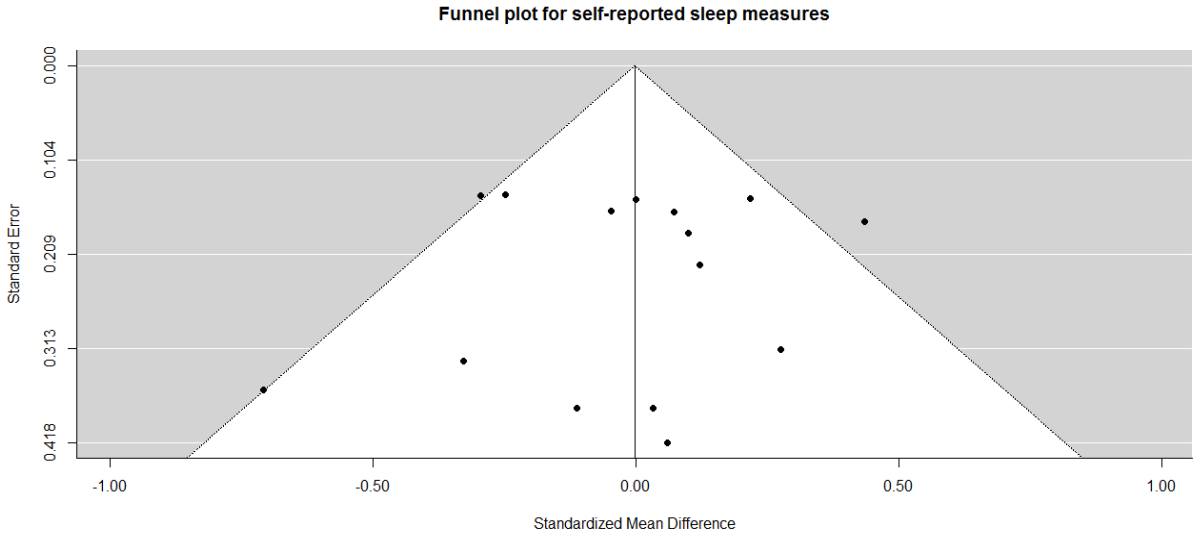
d = -0.13 (p = 0.20; 95% CI = -0.33 - 0.07)

I^2 = 75.29%; Q(df = 16) = 55.29, p < .0001

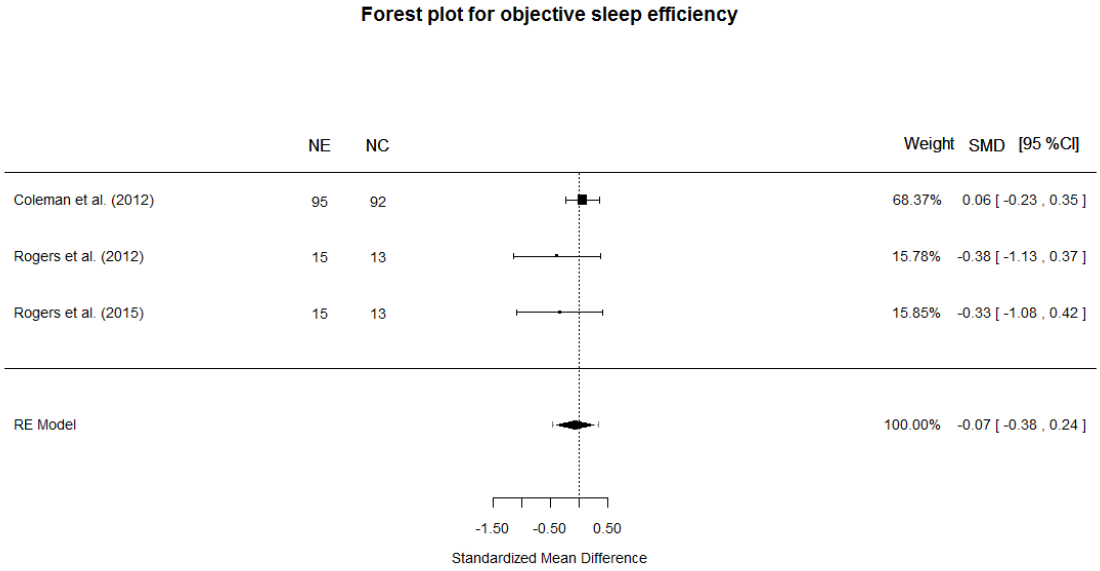
Studies Excluded from the Meta-Analysis

Dodd, M. J., Cho, M. H., Miaskowski, C., Painter, P. L., Paul, S. M., Cooper, B. A., … Bank, K. A. (2010). A Randomized Controlled Trial of Home-Based Exercise for Cancer-Related Fatigue in Women During and After Chemotherapy With or Without Radiation Therapy: *Cancer Nursing*, *33*(4), 245–257. http://doi.org/10.1097/NCC.0b013e3181ddc58c

Payne, J. K., Held, J., Thorpe, J., & Shaw, H. (2008). Effect of Exercise on Biomarkers, Fatigue, Sleep Disturbances, and Depressive Symptoms in Older Women With Breast Cancer Receiving Hormonal Therapy. *Oncology Nursing Forum*, *35*(4), 635–642. http://doi.org/10.1188/08.ONF.635-642



2 - Results for Objectively-Assessed Sleep Efficiency



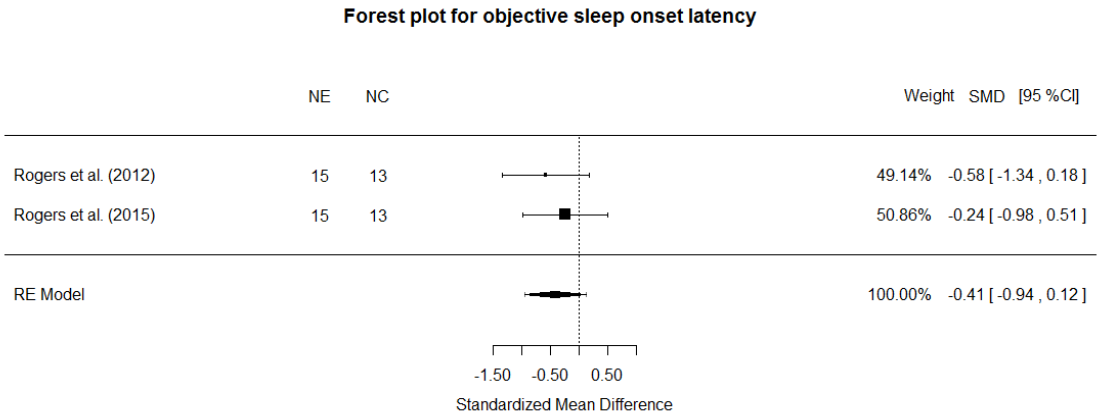
Note. CI: 95% Confidence Interval; NC: Number of Control participants; NE: Number of Experimental participants; RE Model: Random-effects model; SMD: Standard Mean Difference; 95%

I^2= 15.44%; Q(df = 2) = 1.8714, p = 0.3923

Study Excluded from the Meta-Analysis

Coleman, E. A., Coon, S., Hall-Barrow, J., Richards, K., Gaylor, D., & Stewart, B. (2003). Feasibility of Exercise During Treatment for Multiple Myeloma: *Cancer Nursing*, *26*(5), 410–419. http://doi.org/10.1097/00002820-200310000-00012

3 - Results for Objectively-Assessed Sleep Onset Latency



Note. CI: 95% Confidence Interval; NC: Number of Control participants; NE: Number of Experimental participants; RE Model: Random-effects model; SMD: Standard Mean Difference; 95%

I^2= 0%; Q(df = 1) = 0.3998, p = 0.5272

Study Excluded from the Meta-Analysis

Coleman, E. A., Coon, S., Hall-Barrow, J., Richards, K., Gaylor, D., & Stewart, B. (2003). Feasibility of Exercise During Treatment for Multiple Myeloma: *Cancer Nursing*, *26*(5), 410–419. http://doi.org/10.1097/00002820-200310000-00012

4. Criteria used to characterize studies' methodology

Exercise program description

1 = Exercise program fully described (frequency, duration and intensity)

?= Exercise program not fully described

0 = No description at all of the program

Sample size powered calculation

1= *A priori* calculation of sample size and power analysis reported in the article

? = Sample size and power analysis calculation reported, but sample size included in the trial was lower than expected

0 = No sample size calculation and power analysis reported or sample size not determined in function of power analysis (e.g., budget constraint)

Attrition justification

1 = description of attrition reported

? = incomplete description of attrition

0 = no justification of attrition

Attrition bias

1= % of retention rate ≥ 90%

? = Attrition not reported

0 = % of retention rate ≤ 90%

Intention-to-treat analysis

1= ITT reported

0 = not reported

Exercise program adherence

1= Attendance > 60% of exercise prescription

? = Exercise adherence not reported or not clear enough

0 = Attendance < 60% of exercise prescription

Randomization and allocation concealment

1= Method used to conceal allocation sequence is described in sufficient detail

? = Randomized allocation is reported but the method is not clearly detailed

0 = No randomization at all

Article 2
Un essai contrôlé et randomisé de non-infériorité comparant une intervention d'exercice physique réalisée à domicile à une thérapie cognitive-comportementale pour améliorer l'insomnie en contexte de cancer

Résumé

Introduction. Trente à 60% des patients atteints de cancer présentent des symptômes d'insomnie, une condition pouvant entraîner de nombreuses conséquences négatives et qui nécessite une prise en charge efficace. Cet essai contrôlé et randomisé avait pour objectif d'évaluer l'efficacité d'un programme d'exercices physiques aérobiques (EX) réalisé à domicile et de le comparer à une thérapie cognitive-comportementale de l'insomnie (TCC-I) en format auto-administré. **Méthode**. Quarante et un patients (78,1% de femmes, âge moyen de 57 ans) atteints de divers types de cancer et présentant des symptômes d'insomnie (score à l'Index de sévérité de l'insomnie ≥ 8) ont été assignés à l'intervention d'EX (n = 20) ou à la TCC-I (n = 21). Les mesures ont été administrées avant et après le traitement, ainsi que trois et six mois suivant la fin des interventions. **Résultats**. L'intervention d'EX s'est avérée statistiquement inférieure à la TCC-I pour réduire les scores à l'ISI en post-traitement, mais était toutefois non-inférieure aux suivis trois et six mois. Les deux interventions ont conduit à une réduction significative des difficultés de sommeil évaluées à l'aide de l'ISI et de l'Inventaire de qualité du sommeil de Pittsburgh (IQSP) et une amélioration significative de la plupart des paramètres d'auto-enregistrement du sommeil au post-traitement. Toutefois, aucune différence n'a été observée entre les groupes sur ces améliorations. Les tailles d'effet calculées en post-traitement correspondaient à des effets de magnitude modérée à grande (ds > 0,50 pour ISI, IQSP, latence d'endormissement, temps d'éveil après l'endormissement, temps total d'éveil et efficacité du sommeil) pour les deux groupes. Des améliorations significatives ont également été obtenues pour les deux groupes sur les variables secondaires, tels que les symptômes de dépression, de fatigue et la qualité de vie générale. **Conclusion**. Les deux interventions ont produit des gains significatifs sur le sommeil ainsi que sur d'autres symptômes étudiés. Cependant, l'intervention d'EX s'est avérée statistiquement inférieure à la TCC-I pour réduire les scores à l'ISI au post-traitement. Ces résultats suggèrent que la TCC-I demeure le traitement de choix pour le traitement de l'insomnie comorbide au cancer, bien qu'une intervention d'EX puisse représenter une alternative intéressante.

A non-inferiority randomized controlled trial comparing a home-based aerobic exercise program to a self-administered cognitive-behavioral therapy for insomnia in cancer patients

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Abstract

Introduction. Thirty to 60% of cancer patients have insomnia symptoms, a condition which may lead to numerous negative consequences and for which an efficacious management is required. This randomized controlled trial aimed to assess the efficacy of a 6-week home-based aerobic exercise program (EX) compared to that of a 6-week self-administered cognitive-behavioral therapy for insomnia (CBT-I) to improve sleep in cancer patients. **Method**. Forty-one patients (78.1% female, mean age 57 years) with various types of cancer and having insomnia symptoms (*Insomnia Severity Index* [ISI] score ≥ 8) were randomized to the EX (*n*=20) or the CBT-I (*n*=21). Measures were completed at pre- and post-treatment, as well as at 3- and 6-month follow-ups. **Results**. The EX intervention was statistically inferior to CBT-I in reducing ISI scores at post-treatment but was non-inferior at follow-up. However, no significant group-by-time interaction was found on any outcome and both interventions led to a significant reduction of subjectively-assessed sleep impairments on the ISI, the *Pittsburgh Sleep Quality Index* (PSQI) and most sleep parameters from a daily sleep diary at post-treatment corresponding to medium to large time effects (*d*s > 0.50 for ISI, PSQI, sleep onset latency, wake after sleep onset, total wake time and sleep efficiency). Significant time effects were also obtained in both groups on secondary variables (i.e., depression, fatigue, napping and quality of life). **Conclusion**. Both interventions produced significant improvements of sleep and other symptoms at post-treatment. However, EX was found to be significantly inferior to CBT-I in reducing ISI scores at post-treatment, which contradicts the initial non-inferiority hypothesis. These findings suggest that CBT-I remains the treatment of choice for cancer-related insomnia, although EX can lead to some beneficial effects.

Keywords : cancer; insomnia; exercise; cognitive-behavioral therapy; self-help treatment.

ClinicalTrials.gov Identifier: NCT02774369

Introduction

Insomnia is among the most prevalent symptoms associated with cancer with 30 to 60 % of patients reporting this condition, and approximately 20 % of them meeting the diagnostic criteria of an insomnia syndrome (Palesh et al., 2010; J. Savard, Ivers, et al., 2011). Sleep difficulties may occur before and during cancer treatment, and may persist long after their cessation (Ancoli-Israel et al., 2006; Berger et al., 2007; Palesh et al., 2010; Roscoe et al., 2007). The consequences of insomnia are numerous and can negatively affect both psychological and physical functioning (Berger et al., 2005; O'Donnell, 2004; Otte & Carpenter, 2009; Sateia & Lang, 2008). Patients with insomnia commonly report symptoms of fatigue, psychological distress, impaired daytime functioning and disrupted cognitive functioning (Caplette-Gingras et al., 2013; Davidson et al., 2002; J. Savard & Morin, 2001). Yet, the economic burden of insomnia has been found to be very high in the general population and much more costly than the insomnia treatment itself (Daley et al., 2009). In order to reduce the individual and societal burden associated with this condition, it is essential to provide effective treatments to cancer patients with sleep difficulties.

Cognitive-behavioral therapy for insomnia (CBT-I), a multifaceted treatment that generally includes stimulus control strategies, sleep restriction, cognitive restructuring and sleep hygiene education, is the treatment of choice for chronic insomnia and has been recommended as the first-line intervention for cancer-related insomnia (Howell et al., 2014; National Institute of Health, 2005). Indeed, an increasing body of research supports the efficacy of CBT-I specifically in cancer patients (Arico, Raggi, & Ferri, 2016; Davidson et al., 2001; Epstein & Dirksen, 2007; Espie et al., 2008; Fiorentino & Ancoli-Israel, 2006; Garland, Johnson, et al., 2014; J. Savard et al., 2005). Results of previous trials have revealed significant improvements of subjective measures of sleep, a decreased hypnotic medication consumption, a reduction of anxiety, depression and fatigue symptoms and an increased global quality of life. A recent review and meta-analysis of the available literature revealed between-groups differences, when compared to control conditions, that corresponded to medium to large effect sizes and improvements that were durable up to 6 months after the intervention (Johnson et al., 2016).

However, CBT-I is not widely accessible mainly due to the lack of trained professionals in cancer settings to administer this therapy. Other barriers include the costs of sessions and the constraints related to insurance reimbursement, (A. K. Morin, 2006). A possible solution is to provide a self-administered version of this therapy. A meta-analysis of studies conducted in the general population showed that self-administered CBT-I efficaciously improves subjective sleep, with group-by-time interaction effects of a low to medium size relative to controls (Ho et al., 2015; van Straten et al., 2009). In the context of cancer, Savard and colleagues (2014) compared a standard CBT-I administered by a professional with a video-based CBT-I. Both intervention groups showed significantly greater improvements of subjective sleep measures as compared to a no-treatment control group at post-treatment. In addition, a small randomized controlled trial (RCT) found that a web-based CBT-I was superior to a waiting-list control condition to decrease insomnia symptoms assessed subjectively at post-treatment, changes that were clinically significant (Ritterband et al., 2012).

Another even more accessible alternative could be exercise (EX). Recognizing its various benefits, the *Canadian Cancer Society* and the *National Cancer Institute* in the United States recommend that cancer patients remain as active as possible throughout treatment and survivorship phases (Canadian Cancer Society, 2015; National Cancer Institute of the National Institutes of Health, 2017). Surveys and cross-sectional studies have shown associations between higher levels of physical activity and better sleep in cancer patients (Humpel & Iverson, 2010; Mustian et al., 2006; Stevinson et al., 2009). Also, a number of quasi-experimental and small RCTs have evaluated the effect of exercise interventions on sleep in this population (Coleman et al., 2003a; Mock et al., 1997; Payne et al., 2008; Rabin et al., 2009; Young-McCaughan et al., 2003). Two reviews summarizing this literature have been published (Chiu et al., 2015; Tomlinson et al., 2014). However, no firm conclusions could be drawn from these reviews as reviewed studies generally assessed sleep with poor measures (e.g., 1-item scale) or had several significant methodological limitations. More recently, we published a systematic review and meta-analysis of the literature assessing the effect of EX interventions on sleep in cancer patients (Mercier, Savard, & Bernard, 2016). Twenty-one studies were included in the review, of which 17 were RCTs. The qualitative review of available evidence suggested a beneficial effect of

EX interventions on sleep in several studies (48%). However, the meta-analysis including all RCTs revealed no significant effect either on both subjective and objective sleep measures (Mercier et al., 2016). This lack of significant effect could be due, at least in part, to a floor effect given that participants of reviewed studies were not selected on the basis of significant sleep impairments at baseline. Retrieved studies were also characterized by many methodological limitations (e.g., lack of statistical power, no intention-to-treat analyses, attrition bias, lack of control for potential confounders such as usage of sleep medication). Hence, it remains to be established whether EX interventions produce a significant and durable effect on sleep in cancer patients. In particular, comparative studies with treatments whose efficacy is well established for treating cancer-related insomnia, such as CBT-I, are greatly needed.

The main goal of this pilot study conducted in cancer patients was to evaluate whether a home-based EX program leads to a reduction of insomnia severity that is significantly non-inferior to that of a more standard self-administered CBT-I (non-inferiority hypothesis). This study also aimed at comparing the effects of both interventions on various sleep parameters (subjective and objective) and other variables often associated with insomnia (i.e., anxiety, depression, fatigue, quality of life) at post-treatment and at 3- and 6-month follow-ups. It was postulated that the EX intervention would be statistically non-inferior to CBT-I in producing reduction of ISI scores at post-treatment but would be inferior at follow-up. It was also hypothesized that both interventions would lead to significant improvements of various sleep parameters and other symptoms measured at post-treatment but that CBT-I would be associated with a better sustainment of treatment effects over time. This last hypothesis was advanced because CBT-I targets more specifically factors associated with the maintenance of insomnia (maladaptive sleep behaviors and dysfunctional beliefs about sleep) (C. M. Morin, 1993; Spielman et al., 1987) and because continuing to be physically active in the absence of support is a challenge for many people (Bourke et al., 2014).