Article 1
L'exercice physique pour améliorer le sommeil chez les patients atteints de cancer : une revue systématique de la littérature et une méta-analyse

Résumé

La pratique d'exercice (EX) entraîne de nombreux bienfaits sur la santé en général. Cependant, la question à savoir s'il s'agit d'une option efficace pour traiter les symptômes d'insomnie chez les patients atteints de cancer demeure sans réponse. Les objectifs de cette étude étaient de réaliser une revue systématique et une méta-analyse des essais cliniques randomisés et non randomisés qui ont évalué l'effet d'une intervention d'EX sur le sommeil des patients évalué subjectivement et objectivement. Les études pertinentes, publiées avant mai 2016, ont été identifiées grâce à une recherche systématique dans les bases de données Pubmed, Embase, PsyInfo, SportDiscus et Cochrane Library. Au total, 21 études ont été incluses, dont 17 étaient des essais contrôlés et randomisés (ÉCR). Les mesures de sommeil étaient le plus souvent des variables secondaires dans les études examinées. Dans la majorité des cas, les interventions étaient des programmes de marche réalisés à domicile et les patientes atteintes de cancer du sein étaient le sous-groupe le plus représenté. Les études s'avéraient très hétérogènes au plan méthodologique. L'examen qualitatif des données disponibles suggère un effet bénéfique des interventions d'EX sur le sommeil dans 10 études (48%). Cependant, la méta-analyse réalisée à partir des ÉCR n'a révélé aucun effet significatif des interventions d'EX sur des mesures de sommeil subjectives et objectives. Cette absence d'effet pourrait s'expliquer, du moins en partie, par un effet plafond. Ainsi, des études plus rigoureuses, en particulier des ÉCR réalisés avec des patients présentant des symptômes d'insomnie au départ, sont nécessaires afin d'évaluer l'effet des interventions d'EX chez cette population.

Exercise interventions to improve sleep in cancer patients:
A systematic review and meta-analysis

Joanie Mercier [1-3] , Josée Savard [1-3] & Paquito Bernard [1-3]

[1] School of Psychology, Université Laval; [2] CHU de Québec-Université Laval Research Center; [3] Université Laval Cancer Research Center, Québec, Canada

This study was conducted at the CHU de Québec-Université Laval Research Center, Québec, Québec, Canada.

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Corresponding author : Josée Savard, Ph.D., Centre de recherche du CHU de Québec-L'Hôtel-Dieu de Québec, 11 Côte du Palais, Québec, Québec, G1R 2J6. Tel: (418) 691-5281; Fax: (418) 691-2971; e-mail: josee.savard@psy.ulaval.ca

Summary

Exercise leads to several positive outcomes in oncology. However, the question as to whether exercise is a valuable option for improving patients' sleep, which is frequently disturbed in cancer patients, remains unanswered. The aims of this study were to conduct a systematic review and meta-analysis of randomized and non-randomized clinical trials that have investigated the effect of exercise on sleep outcomes, assessed subjectively and objectively. Relevant studies, published before May 2016, were traced through a systematic search of Pubmed, Embase, PsyInfo, SportDiscus and Cochrane Library databases. The review looked at twenty one trials, including 17 randomized controlled trials. Most interventions were home-based aerobic walking programs and breast cancer patients were the subgroup most represented. Sleep variables were most commonly used as secondary outcomes in the reviewed studies. Studies were highly heterogeneous in terms of methodology. The qualitative review of available evidence suggested a beneficial effect of exercise interventions on sleep in several studies (48%). However, the meta-analysis conducted on RCTs revealed no significant effect either on subjective and objective sleep measures. This lack of significant effect could be due, at least in part, to a floor effect. More rigorous studies are needed to assess the effect of exercise interventions in cancer patients, in particular randomized controlled trials conducted in patients with clinically significant sleep disturbances at baseline.

Keywords. Cancer, sleep, insomnia, physical activity, exercise

Introduction

Rationale

Sleep difficulties, and more specifically insomnia, are among the most prevalent symptoms associated with cancer. Indeed, 30 to 60 % of cancer patients report insomnia symptoms, while approximately 20 % of them meet the diagnostic criteria of an insomnia syndrome, which is at least twice as frequent as in the general population (Berger, 2009; Davidson et al., 2002; J. Savard, Ivers, et al., 2011; J. Savard & Morin, 2001; J. Savard et al., 2001; J. Savard, Villa, et al., 2009). Prevalence rates of sleep disturbances have also been found to be up to three times higher in patients undergoing chemotherapy compared to the general population (Palesh et al., 2010). Sleep difficulties may occur before, during, and may persist long after the end of cancer treatment (Ancoli-Israel et al., 2006; Ancoli-Israel et al., 2001; Berger et al., 2007; Palesh et al., 2010; Roscoe et al., 2007; J. Savard et al., 2001). An 18-month longitudinal study revealed that such persistence was even more likely to occur in patients with an insomnia syndrome (J. Savard, Ivers, et al., 2011). Moreover, about 20% of patients who experienced an insomnia remission had a relapse later on during the study (J. Savard, Ivers, et al., 2011).

The consequences of insomnia are numerous and can negatively affect both psychological and physical functioning (Berger et al., 2005; Fiorentino & Ancoli-Israel, 2007; O'Donnell, 2004; Otte & Carpenter, 2009; Sateia & Lang, 2008; Theobald, 2004). Compared to the consequences of cancer itself, those related to insomnia are often overlooked both by the patients and the health care providers (Engstrom et al., 1999; O'Donnell, 2004; J. Savard & Morin, 2001; Theobald, 2004). The most common consequences reported by the patients are 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). Insomnia is also associated with an increased risk to subsequently develop a psychiatric disorder (e.g., anxiety and depressive disorder), exacerbation of pain, impaired immune functioning and increased risk of infections (Lee et al., 2004; Ruel et al., 2015; Sateia & Lang, 2008; J. Savard & Morin, 2001; Theobald, 2004). Moreover, the economic burden of insomnia has been found to be very high and, overall, untreated insomnia is much more costly than the insomnia treatment itself (Daley et al., 2009; Wickwire, Shaya, & Scharf, 2015). For example, in the province of Quebec alone, the average annual direct and indirect per-person costs of insomnia syndrome have been found to be 5,010$ for a total annual cost of insomnia amounting to $6.6 billion (Cdn$) (Daley et al., 2009). It is therefore essential to provide effective treatments to patients with sleep difficulties in order to reduce the individual and societal burden associated with this condition.

Pharmacotherapy is currently the most common treatment employed to counteract sleep difficulties in the general population, as well as in cancer patients (Berger et al., 2005; Donovan & Jacobsen, 2007; Fiorentino & Ancoli-Israel, 2007; Graci, 2005; J. Savard & Morin, 2001). Surveys that have documented the use of sedative and/or hypnotic medications among cancer patients reached utilization rates near 25% (Casault et al., 2011; Davidson et al., 2002; Derogatis et al., 1979; Guo et al., 2007; Moore et al., 2011; Paltiel et al., 2004). According to the National Institutes of Health's recommendations (2005), the use of hypnotics is appropriate in the management of acute insomnia, but daily use has been recommended to a maximum of 35 days or less to limit the risks associated with chronic use (32). Side effects and risks associated with the usage of hypnotics include drowsiness, dizziness, headache, cognitive impairments, loss of motor coordination and a risk of tolerance and dependence when the medication is used daily on a chronic basis (Berger et al., 2005; Fiorentino & Ancoli-Israel, 2006; Holbrook et al., 2000; National Institute of Health, 2005; J. Savard & Morin, 2001). This emphasizes the need to develop and to assess the efficacy of various non-pharmacological options for insomnia treatment and to make these interventions as available as prescription sleep aids.

In cancer, exercise during and after treatment has been associated with many benefits, such as improving physical functioning and fitness, reducing side effects of cancer treatments, preventing bone loss and weight gain, improving quality of life, decreasing symptoms of fatigue and depression, and even reducing the risk of cancer recurrence, although this last effect needs further investigation (Courneya, 2003; Courneya & Friedenreich, 2011; Ferrer et al., 2011; Pinto et al., 2008; Schmitz et al., 2010; Speck et al.; Sprod, Hsieh, et al., 2010). It has been extensively demonstrated that exercise is safe and well tolerated by patients undergoing cancer treatments or in the rehabilitation phase (Schmitz et al., 2010; Schwartz, 2008). Recognizing these benefits, the *Canadian Cancer*

Society and the *National Cancer Institute* recommend that cancer patients remain as active as possible throughout treatment and survivorship (Canadian Cancer Society, 2015; Health, 2015).

In the general population, studies have consistently found that exercise also improves sleep (Driver & Taylor, 2000; Kredlow et al., 2015; O'Connor & Youngstedt, 1995; Sherrill et al., 1998; Vuori et al., 1988; Youngstedt & Kline, 2006). Accordingly, a recent meta-analytic review of the effect of acute and regular exercise on sleep concluded that both types of exercise have a small to moderate beneficial impact on objective and subjective sleep measures (Kredlow et al., 2015). Previous meta-analyses have described some of the available evidence in cancer patients. However, these reviews included a pool of studies assessing the efficacy of interventions to improve quality of life in general (Mishra et al., 2012a) or fatigue (Tomlinson, Diorio, Beyene, & Sung, 2014), or included only walking interventions (Chiu et al., 2015), thus limiting the conclusions that could be drawn. A systematic review and meta-analysis of the literature specifically assessing the effect of exercise on sleep is therefore needed at this point to summarize the available empirical evidence and to determine to what extent exercise has been established as a sleep enhancing intervention in cancer patients.

Objectives

The purposes of this systematic review were to: (1) summarize the available literature on the effects of exercise interventions on sleep in cancer patients; (2) in RCTs, conduct a meta-analysis of post-treatment effects of exercise on sleep outcomes in cancer patients (undergoing treatment or in the post-treatment phase); (3) identify subgroups of patients benefiting the most from this type of intervention, if sufficient data are available to investigate this question; and (4) formulate recommendations for clinical practice and to guide future research on this topic.

Methods

PRISMA guidelines for the conduct of systematic reviews and meta-analyses were followed (Moher, Liberati, Tetzlaff, & Altman, 2009).

Eligibility Criteria

To be eligible, studies had to be published as a full paper in English or in French. RCTs, as well as non-randomized trials, were included. This decision was made *a priori* in order to appraise all available evidence. Studies were included if they involved adult patients only (18 years and older) with a non-metastatic cancer diagnosis. The presence of an advanced disease may restrain patients' adherence to an exercise program due to functioning impairments, thus affecting its possible effects. Participants, men and women, could have any type of cancer and could be at any stage of the cancer care trajectory (during or after treatment). Various forms of exercise interventions were considered eligible including aerobic, resistance or a combination of both. Exercise interventions could be combined with flexibility exercises or with another type of intervention (e.g., counseling). However, yoga interventions were excluded given the large heterogeneity of yoga types, being more or less demanding physically. No restriction was made regarding frequency, intensity or duration of the program. Interventions could be home-based or supervised. Control arms could be usual care (no exercise intervention) or an alternative intervention (e.g., relaxation). Finally, to be included, trials had to contain at least one sleep measure. However, studies that used only single-item measures were excluded (e.g., one item of a general QOL questionnaire), given their low specificity.

Information Sources

The following electronic databases were searched from the earliest date available through May 2016 : Pubmed/Medline, the Cochrane Library, Embase, PsycINFO and SportDiscus. Reference lists of relevant studies were also searched to identify additional potential trials.

Search and Study Selection

The search strategy was adapted for each database using its specific vocabulary map, employing Mesh terms that referred to "cancer", "sleep" and "exercise". For example, the Pubmed/Medline search strategy first included Mesh terms related to cancer ("Neoplasm") AND sleep ("Sleep", "Sleep Disorders", "Sleep Initiation and Maintenance Disorders") AND exercise ("Exercise", "Physical Therapy Modalities", "Motor Activity", "Exercise Therapy", "Sports"). This algorithm was then adapted to other electronic databases. After duplicates were removed, titles and abstracts of all studies identified were examined independently by two research assistants to determine those meeting the selection criteria. The inter-rater agreement reliability was very high; Kappa = 0.84 (IC 95% = 71.6 to 96.5) (Landis & Koch, 1977).

Data Collection Process

All relevant studies were scrutinized attentively to extract data on participants' characteristics, study design, exercise interventions and results following the PICO (Population, Intervention, Comparison, Outcomes) framework (Moher et al., 2009). Risks of bias were assessed using criteria listed in the Supplementary file.

Statistical Analyses (Meta-Analysis)

The standardized mean difference (SMD) effect size was calculated for both self-reported and objective sleep outcomes using the pooled standard deviation of the treatment and control conditions at post-treatment of RCTs only (Lipsey & Wilson, 2001). Between-groups effect sizes were weighted according to the sample size, thus yielding Hedges' g (Lipsey & Wilson, 2001). A positive effect size always indicated a result in favor of the exercise group in comparison with the control condition. When means and standard deviations were not reported in the publication, authors were contacted to request missing information. When the information was not provided, the effect size could not be calculated and these studies were therefore excluded from the meta-analysis.

To assess the effect of exercise intervention on sleep outcomes, summary effect sizes were estimated by weighting SMDs by the inverse of their variance based on random effects models. Heterogeneity was tested with Cochran's chi-square test (Q), a significant **Q** indicating the absence of homogeneity (i.e., more variation in effect sizes than sampling error alone would predict) (Higgins, Thompson, Deeks, & Altman, 2003). Then, residual between-variance study was quantified with the I^2 statistic ranging from 0% to 100% (small: < 25%; moderate: 25 to 50%; large: ≥ 50%). A possible publication bias was evaluated by using funnel plot representations and the Egger's test with $p < .10$ indicating a publication bias (Higgins et al., 2003).

Random-effects models were performed due to the expected heterogeneity of effect sizes. The standardized **g** value can be interpreted as 0.20, 0.50, and 0.80, representing small, medium, and large sleep improvements, respectively (Cohen, 1988). Regression residuals were screened to identify potential multivariate outliers using residual Cook distances. All analyses were carried out in R 3.2 using the *metafor* package (Viechtbauer, 2010).

Results

Study Selection

The initial electronic searches identified 339 references, of which 136 were duplicates. Seven additional studies were identified through hand search of relevant articles, for a total of 243 articles. After a review of titles and abstracts, 212 were excluded because they did not meet all inclusion criteria. Hence, 31 full-text articles were assessed for eligibility and 23 of them (representing 21 different trials) were included in the review (see Figure 1).

Studies' Characteristics

Table 1 summarizes the studies' characteristics. Seventeen of the 21 included studies (81%) were RCTs. Seven of these trials were pilot or feasibility studies. Most of the time, participants in the control group were encouraged to remain active (to maintain their current lifestyle) but did not receive a specific program of exercise. Four trials (Courneya et al., 2014a; Dodd et al., 2010; Kampshoff et al., 2015; van Waart et al., 2015) used a 3-arm RCT that included 2 groups receiving different forms of exercise, in addition to the control group or three experimental conditions (Courneya et al., 2014a). Three studies (Rabin et al., 2009; Rajotte et al., 2012; Young-McCaughan et al., 2003) used a single-group design and one used a quasi-experimental design (Kröz et al., 2013). The particularity of Kröz et al.'s study (Kröz et al., 2013) was that the aerobic training group was considered the "standard group", as the purpose of the study was to compare a multimodal intervention to aerobic training only for chronic cancer-related fatigue. Sample sizes of included studies varied from 20 to 301 patients. Ten studies had a total sample of 50 participants or less, 3 studies had a total sample of between 51 and 100 and 8 studies had a total sample of more than 100 participants. Most of the studies had pre- and post-treatment assessments without any follow-up measure and 7 trials included a follow-up measure that varied from 2 weeks to 6 months after the end of the intervention.

Participants

The mean age across studies varied from 47 to 64 years old, with a standard deviation of approximately 9 years. Eleven studies (52%) included women only and none was exclusively conducted with men. Ten studies (48%) included only breast cancer patients, seven (33%) included mixed cancer sites, in which breast cancer was always the most frequent type of neoplasm, except for Wenzel et al.'s trial (2013) in which 55.6% of the participants had prostate cancer. Two studies (9.5%) were conducted with multiple myeloma patients, one (5%) with gynecological cancer patients and one (5%) with patients with a lymphoma. Eleven of the retrieved studies (52%) included patients undergoing cancer treatments at the time of the study, while 2 trials (11%) were conducted during and after treatment. Eight other studies (38%) investigated only patients having completed their treatment. Cancer stage was not always reported but, most of the time, studies included stages I to III (trials conducted exclusively with patients with metastatic disease were excluded from this review). Some trials also included stage IV patients in their sample (Courneya et al., 2012; Kampshoff et al., 2015; Kröz et al., 2013; Young-McCaughan et al., 2003).

Two studies had a fatigue complaint as an inclusion criterion (Donnelly et al., 2011; Kröz et al., 2013), one included patients reporting either fatigue or sleep disturbance symptoms (Rogers et al., 2015) and only one specifically included patients who had sleep difficulties at baseline (Tang, Liou, & Lin, 2010). In that study, participants were considered eligible if they obtained a total score of greater than 5 on the *Pittsburgh Sleep Quality Index* (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). In spite of the absence of such a specific inclusion criterion, studies generally had an important proportion of poor sleepers at baseline based using the same PSQI cutoff score (Donnelly et al., 2011; Kampshoff et al., 2015; Kröz et al., 2013; Payne et al., 2008; Rabin et al., 2009; Rogers et al., 2015; Rogers et al., 2013; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Sprod, Palesh, Janelsins, Peppone, Heckler, Jacob Adams, et al., 2010; Tang et al., 2009; van Waart et al., 2015; Wang et al., 2011; Wenzel et al., 2013). Overall, 15 trials (71%)

reported a mean PSQI global score > 5 at baseline. For example, in Courneya et al.'s studies (Courneya et al., 2014a; Courneya et al., 2012), 47% and 52% of participants, respectively, were considered poor sleepers at pre-treatment. Nevertheless, the standard deviation of baseline PSQI mean scores was often large, indicating that participants were highly heterogeneous in terms of the severity of their sleep difficulties.

Exercise Interventions

Table 2 provides a summary of exercise program interventions tested and the main results obtained for each study. Exercise interventions varied widely across studies. Twelve trials (57%) offered home-based unsupervised interventions. Rogers et al. (Rogers et al., 2013; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009) offered a 12-week supervised exercise program that gradually shifted into home-based exercise over the first 6 weeks. Rogers et al. and Kampshoff et al. (Kampshoff et al., 2015; Rogers et al., 2015) tested a combination of supervised and home-based sessions. A particularity of Van Waart et al.'s trial (van Waart et al., 2015) was to compare a low-intensity home-based exercise intervention to a moderate- to high-intensity supervised program in addition to a usual care condition. The four (22%) remaining studies used a supervised exercise intervention (Courneya et al., 2014a; Courneya et al., 2012; Rajotte et al., 2012; Young-McCaughan et al., 2003). In Young-McCaughan et al.'s and Rajotte et al.'s trials (Rajotte et al., 2012; Young-McCaughan et al., 2003), 2 sessions per week of supervised exercise were offered and participants were encouraged to also exercise at home, whereas in Courneya et al.'s trials, additional unsupervised exercise sessions were not prescribed. Ten studies (48%) tested aerobic exercise training alone and 11 (52%) assessed a combination of aerobic and resistance training. Rajotte et al. (Rajotte et al., 2012) published the only trial that used mainly resistance exercises preceded by an aerobic warm-up. Walking was the aerobic exercise most often suggested (n = 13; 62%), while other studies (n= 8; 38%) had recourse to a cycle ergometer or a combination of different aerobic exercises (e.g., walking, jogging, bicycling or swimming). Studies incorporating resistance training used machines, resistance bands or a combination of different modalities.

The intensity of exercise performed varied from low to moderate, except for two trials which involved vigorous aerobic exercise (Courneya et al., 2014a; van Waart et al., 2015). However, the method used to calculate the intensity of exercise varied from one trial to another. More than a third (*n* = 8; 38%) of retrieved studies employed the index of percentage of the maximum heart rate (from 40 to 80%) or the percentage of heart rate reserve corresponding to a range from low to vigorous intensity, while 5 studies (24%) used the Borg scale (6-20) or the modified Borg scale (0-10) with a rating of perceived exertion corresponding to low to moderate or the corresponding metabolic equivalent. Other studies omitted to specify how exercise intensity was monitored. Exercise frequency ranged from 2 to 5 sessions per week, except for Sprod et al.'s trial (Sprod, Palesh, Janelsins, Peppone, Heckler, Jacob Adams, et al., 2010), in which participants were instructed to increase their number of daily walking steps by 5-20% and to perform a low to moderate resistance training 7 days/week in order to maintain strength. In Naraphong et al.'s trial (Naraphong, Lane, Schafer, Whitmer, & Wilson, 2015), the instruction of increasing daily steps by 5% was given in addition to the 3 to 5 sessions per week of low to moderate walking. The session length was not always specified but most studies involved exercise sessions of approximately 30 minutes. Regarding the duration of the exercise program, it varied from 4 weeks to up to 12 months. However, a majority of trials (*n*=15; 71%) had interventions that lasted from 6 to 15 weeks.

Four studies (19%) added another treatment component to the exercise program. In order to improve adherence, participants of Rogers et al.'s study (Rogers et al., 2015) were invited to take part in 6 group sessions providing behavioral support. Rajotte et al. (Rajotte et al., 2012) added a 30-minute discussion after each of the 24 training sessions during which participants were invited to share their personal experiences and received experiential training in breathing, stress management, nutrition and other complementary treatments. Rabin et al. (Rabin et al., 2009) included, in addition to exercise, a progressive muscle relaxation component. Participants received a CD with specific directives and were instructed to practice this strategy at least 4 days per week. Finally, Young-McCaughan et al. (Young-McCaughan et al., 2003) added an education component offering information about cancer therapies, sleep, spiritual health, quality of life and health evaluation.

Adherence and Compliance

The most frequently used measure to record exercise was a daily exercise log. The proportion of participants who were compliant with the exercise prescription based on their self-report varied widely. For instance, only half of the trials (52%) reported an attendance > 60% for prescribed exercise sessions. In addition, studies with a supervised exercise protocol recorded the attendance at each session. Seven studies (33%) used an accelerometer to objectively measure exercise and another one used a heart rate ring monitor to capture the intensity of exercises performed. Adherence rates (% of people who completed study measures), when reported, varied from 58% to 96%. Study dropouts were fairly equal between intervention and control groups, except for one study in which 14 participants withdrew in the exercise group compared to 0 in the usual care group (Tang et al., 2010).

Sleep Outcomes

The primary objective of most studies was to evaluate the effect of exercise on physical functioning, and as a second objective, to evaluate its effect on several cancer-related symptoms, including sleep disturbances. Sleep measures were predominantly self-report scales (when a single-item was used, an actigraphy measure was also included). The PSQI was the most commonly used measure of sleep (n = 15; 71%). Seven studies (33%) used actigraphy as an objective measure of sleep, of which 4 also used the PSQI (Kröz et al., 2013; Payne et al., 2008; Rogers et al., 2015; Rogers et al., 2013). Participants wore an actigraphic device from 2 to 7 days depending on studies. Sleep-onset latency (SOL), total wake time (TWT), sleep efficiency (SE), the number of nocturnal awakenings and duration of daytime sleep were the main parameters used. No studies utilized PSG as a sleep measure.

Of note, none of the retrieved trials reported the use of a sleep diary, which is a standard measure in sleep trials (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006) and none used the *Insomnia Severity Index* (C. M. Morin, 1993), which has been validated in cancer patients (M. H. Savard, Savard, Simard, & Ivers, 2005) and is commonly used in RCTs investigating CBT for insomnia.

Description of Study Results

Summary of Outcomes (see Table 2). Sleep outcomes improved in 10 studies (47.6%). At post-treatment, a significant between-groups effect between exercise and a control group, favoring the exercise intervention, was found in 7 RCTs (33% of all studies included) (Courneya et al., 2014a; Donnelly et al., 2011; Payne et al., 2008; Rogers et al., 2015; Rogers et al., 2012; Tang et al., 2010; Wang et al., 2011) and a significant time effect (pre- vs. post-treatment) was obtained in the exercise group in each of the three single-arm studies (Rabin et al., 2009; Rajotte et al., 2012; Young-McCaughan et al., 2003). However, all of these three quasi-experimental trials included another component in addition to exercise making it impossible to delineate the effect of exercise on sleep outcomes. The trial by Payne et al. (Payne et al., 2008) was the only one which showed objective sleep improvements as assessed with actigraphy out of the 7 studies that used this sleep measure. It is noteworthy that Kröz et al.(Kröz et al., 2013) did not report any results derived from the accelerometer measures they took. Three studies that included both objective and subjective sleep measures revealed significant improvements of subjectively-assessed sleep on a questionnaire (a single item in Young-McCaughan et al. (Young-McCaughan et al., 2003)) but null findings on actigraphy parameters (Rogers et al., 2015; Rogers et al., 2013; Young-McCaughan et al., 2003). Studies conducted by Coleman et al. (Coleman et al., 2003b; Coleman et al., 2012) did not use any subjective sleep measure; it is therefore impossible to know whether participants perceived a sleep improvement despite the absence of such an effect on objective measures.

Protocol and methodology. Among the 10 studies that obtained positive effects on sleep, five offered a home-based program (representing 42% of all home-based programs retrieved for this review), three used supervised exercise (representing 75% of all supervised protocols retrieved) and two combined supervised and home-based exercise. Forty percent (n = 4) of studies that obtained positive effects on sleep included an aerobic training modality only and 60% (n = 6) employed a combination of aerobic and resistance training. Interestingly, walking was the aerobic exercise prescribed in 8 of them. However, none of the retrieved studies tried to distinguish the effects of different aerobic modalities on sleep outcomes. A majority of the reviewed studies had no follow-up assessment (n = 14; 67%). Among the seven trials that included a follow-up, Rabin et al. (Rabin et al.,

2009) found sleep improvements to be sustained at a 6-month follow-up (single-arm trial) and Rogers et al. (Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009) reported a significant between-groups effect favoring exercise on SOL 6 months after post-treatment (but no significant effect on sleep was found at the end of the 12-week exercise intervention). Conversely, the significant between-groups difference found on global sleep at post-treatment in Donnelly et al.'s (Donnelly et al., 2011) trial was no longer significant 6 months later. Van Waart et al. (van Waart et al., 2015) did not observe any sleep improvement at post-treatment, nor at a 6-month follow-up. The three remaining trials that included a follow-up did not report effects on sleep for this specific time point (Courneya et al., 2012; Payne et al., 2008; Sprod, Palesh, Janelsins, Peppone, Heckler, Jacob Adams, et al., 2010).

Also, more studies (*n* = 7; 70%) in which positive effects on sleep were observed included a majority of participants who had completed their cancer treatment, in comparison to studies with non-significant effects (*n* = 3; 27%). On the other hand, only one trial in which a significant between-groups effect was observed and in which participants were receiving chemotherapy at the time of the study showed that exercise could prevent the worsening of sleep as compared to the control group (Courneya et al., 2014a). More precisely, participants in the usual care condition had significantly more sleep disturbances at post-treatment, while sleep of the exercise group remained stable. In Dodds et al.'s study (Dodd et al., 2010), the only trial that compared different times of administration of exercise, one group of patients who received the exercise program throughout the study (i.e., both during and after cancer treatment) was compared to a second group who received the program after completing cancer treatments, and to a third group who received usual care. Results revealed no significant difference across groups on all cancer-related symptoms measured, including sleep. The authors raised the possibility of a floor effect to explain these results as patients had mild levels of symptoms on average at baseline.

Sleep difficulties at baseline. Interestingly, among the 10 trials that observed positive effects on sleep, 8 of them (80%) included participants with a mean PSQI score > 5 at baseline. Hence, presenting clinical levels of sleep disturbance at baseline appears to be an important inclusion criterion for these studies to avoid a floor effect. Consistent with this interpretation, Courneya et al. (Courneya et al., 2012) observed a significant positive effect of their exercise intervention on sleep outcomes but only for the subgroup of patients who were poor sleepers at baseline as defined by a global sleep quality score ≥ 4.3 using 6 of the 7 PSQI components (the cut-off score was prorated) .

Meta-Analysis of RCTs

Risk of Bias. Risk of bias assessment of studies included in the meta-analysis is presented in Figure 2. Overall, the exercise programs were well described in RCTs. A little more than half reported power analyses, attrition justification, attrition bias, randomization and allocation concealment and carried-out intention-to-treat analyses. However, less than half of the studies reported exercise program adherence.

Effects on self-reported sleep. The total number of participants across study arms with available data was 1595 (experimental = 811 and control = 784). Self-reported sleep was assessed with the PSQI global score in 14 interventions and the General Sleep Disturbance Scale in one intervention. Two studies, in which no significant intervention effect was found, were excluded from the analyses due to incomplete statistical information (Dodd et al., 2010; Payne et al., 2008). The Cook distances analysis identified two multivariate outliers that were also excluded from the final analyses (Tang et al., 2010; Wang et al., 2011).

The overall average effect size of the 15 interventions tested in the 12 RCTs was -0.002 (p = .98; 95% CI = -0.14 – 0.13), indicating no significant superiority of exercise interventions on subjective sleep measures, as compared to control groups. The effect sizes obtained for each of the 15 interventions are presented in Figure 3. No significant heterogeneity was noted (Q = 22.3, p = 0.07; I^2 = 39%).

The funnel plot displaying the exercise interventions (relative to controls) appeared to be relatively symmetrical (see the Supplementary file). In addition, the Egger's test was not significant (p = 0.59). Together these results provide no evidence of a publication bias.

Effects on objective sleep measures (actigraphy). Based on available data, analyses could be carried out for SE (i.e., 3 interventions) and SOL parameters (i.e., 2 interventions) only. The total number of participants across interventions with available data was 233 (experimental = 125 and control = 118) for SE and 56 (experimental = 30 and control = 26) for SOL. The analyses revealed that exercise interventions were not significantly superior to control interventions: SE: $g = -0.07$ ($p = 0.65$; 95% CI = -0.38 – 0.24); SOL: $g = 0.40$ ($p = .13$; 95% CI = -0.93 – 0.12). Detailed results are shown in the Supplementary file.

Discussion

Summary of Evidence

This systematic review summarizes the available empirical evidence on the effect of exercise interventions on sleep outcomes in cancer patients. To the best of our knowledge, this is the first systematic review to address this specific question. A total of 21 studies were included in the systematic review. Given that the effect of exercise interventions on sleep in cancer patients has received attention relatively recently, both RCTs and non-RCTs were included.

Although studies were difficult to compare because of various methodological particularities and limitations (e.g., no statistical power analyses performed), some interesting observations can be made. First, breast cancer patients were the most represented subgroup of patients among trials in which positive effects of exercise on sleep were found. However, it cannot yet be concluded that breast cancer patients benefit the most from this intervention, as this may only reflect that the majority of studies conducted on the topic included this specific type of cancer. Positive outcomes were also obtained more frequently after the cancer treatment phase than in patients still receiving treatment. Because patients are particularly at risk of developing sleep difficulties while undergoing treatment (Graci, 2005; Palesh et al., 2010; J. Savard, Ivers, Savard, & Morin, 2015), exercise may be less effective during this period. On the other hand, exercise could contribute to preventing the occurrence of sleep difficulties while patients are receiving treatment. Consistent with this hypothesis, one study found that exercise prevented the aggravation of insomnia symptoms during treatment that was observed in the usual care condition (Courneya et al., 2014a). However, these findings need to be replicated. More positive effects of exercise were found when using subjective sleep measures. However, only a few studies have objectively-measured sleep. The lack of concordance between subjective and objective sleep measures is a consistent result in insomnia research (Kay, Buysse, Germain, Hall, & Monk, 2015; J. Savard & Ganz, 2016). Although objective measures, in particular polysomnography, are often considered the gold standard measure of sleep, insomnia is increasingly recognized as a subjective phenomenon characterized by dissatisfaction with sleep and psychological distress (American Psychiatric Association, 2013; C. M. Morin, 2000).

Walking was the aerobic modality the most often used in studies showing a positive effect. This observation is consistent with conclusions of the meta-analysis of Langford et al. (Langford, Lee, & Miaskowski, 2012), in which walking appeared to be associated with a more positive impact on sleep than any other aerobic exercise. More specifically, among the 8 studies (38%) that offered another modality than walking or included a combination of different aerobic exercises (e.g., walking and/or running and/or cycling), 6 failed to find a significant effect on sleep. However, it is still unclear whether walking is the most effective type of training or if this finding is due to higher patients' adherence to this type of program. The dosage of exercise required to improve sleep also remains unknown as only one retrieved study compared a higher dose of aerobic exercise to a standard dose (Courneya et al., 2014). Results indicated that a weekly higher dose of vigorous aerobic activity (150 min) versus a standard dose (75 min) leed to statistically superior global sleep quality in breast cancer patients receiving chemotherapy.

However, only 7 RCTs (41% of all RCTs included) found a significant between-groups effect between exercise and a control group, favoring the exercise intervention. Moreover, the meta-analysis conducted with RCTs only (15 experimental arms) did not show any significant effect of exercise interventions on self-reported sleep measures at post-treatment. This lack of effect is in contrast with conclusions of earlier meta-analyses with cancer patients (Chiu et al., 2015; Mishra et al., 2012a; Tomlinson et al., 2014). Although we nonetheless performed a meta-analysis on actigraphic data, no conclusion could be drawn about the effects of exercise interventions on objective sleep measures. Indeed, our results were based on only four published RCTs. Overall, the absence of significant effects of exercise interventions on sleep could, at least partly, be explained by a floor effect. In fact, a large proportion of participants in included RCTs were good sleepers, thus leaving little room for improvement. The absence of significant effects could also be due to a contamination effect; contamination rates from 22 to 52% have been reported in other studies on the issue (Courneya et al., 2004; Mock et al., 2005; Shang, Wenzel, Krumm, Griffith, & Stewart, 2012). Such an effect was more likely to occur in studies in which participants of the usual care group were instructed to remain physically active even though they did not receive a specific exercise program. Finally, the results of the meta-analysis could simply indicate that exercise is not an efficacious intervention for cancer-related sleep difficulties. This could be due to the fact that exercise does not target the behavioral and cognitive factors that are believed, according to a cognitive-behavioral conceptualization of insomnia, to maintain sleep disturbances over time(C. M. Morin, 1993; J. Savard & Savard, 2013). However, there are other possible mechanisms through which exercise could improve sleep and that could be explored. These include changes in homeostatic and immune processes, a thermogenic hypothesis, energy conservation and body restoration, improved mood and increased light exposure (for more extensive information on possible mechanisms, see Driver & Taylor and Buman & King) (Buman & King, 2010; Driver & Taylor, 2000). For instance, the study by Sprod et al. observed an association between increase levels of IL-6 and reduced sleep efficiency and duration, which suggested that exercise could improve sleep through regulating pro-inflammatory cytokines. Another potential mechanism relevant for the cancer population may be increased light exposure. In fact, when performed outside, exercise could have a beneficial effect on sleep through an increased exposure to natural daylight, which is a powerful *zeitgeber* that helps resynchronize circadian rhythms and may consequently improve nocturnal sleep (Leger, 2005; Monteleone & Maj, 2009).

Future Directions

Large RCTs evaluating the effects of exercise interventions on sleep as a main outcome and using a clinical level of insomnia symptoms as an inclusion criterion are clearly needed before any firm conclusion can be drawn about the effects of exercise interventions on sleep. Ideally, objective and subjective measures of both sleep and exercise should be included. It appears particularly important to compare the effects of exercise with those of treatments whose efficacy is well established for clinical insomnia, such as CBT.

In fact, CBT is considered the treatment of choice for insomnia and its efficacy has been demonstrated in the specific context of cancer (Espie et al., 2008; Garland, Johnson, et al., 2014; Roscoe et al., 2015; J. Savard et al., 2005). It would be important to decrease the risk of contaminating the control groups, minimally by avoiding giving any instructions about exercising and by monitoring actual exercise performed in control patients in order to take that variable into account in the analyses. There is also a need to systematically include follow-up assessments to determine whether or not the beneficial effect of exercise on insomnia symptoms is sustainable in the long-term. Mechanisms linking exercise with sleep and optimal dosage of exercise needed to have a beneficial effect on sleep also warrant investigation.

Strengths and Study Limitations

This study is the first to systematically and specifically review the literature on exercise interventions to improve sleep in cancer patients and to quantitatively assess their efficacy in a meta-analysis. Although we did our best to perform a comprehensive search of the literature, it is still possible that relevant studies were missed. In particular, because sleep has often been a secondary variable, it is possible that other studies not reviewed here have examined this outcome, without reporting the results. This is especially likely if the effect on sleep was not significant.

Conclusions

A large body of evidence supports the numerous benefits of exercise in the cancer context (e.g., improved physical functioning, decreased fatigue). The available empirical evidence on the possible effect of exercise on sleep outcomes is scarcer and, overall, suggests that it can have a limited effect. However, the studies were characterized by many methodological limitations. Future studies need to be conducted using clinical insomnia as an inclusion criterion. In addition, comparative studies with treatments for which efficacy is well established for treating cancer-related insomnia (e.g., CBT) are warranted.

Practice points

- The empirical evidence on the efficacy of exercise interventions on subjective and objective sleep measures in adults with cancer is limited

- Breast cancer patients were the subgroup of patients the most represented among trials in which positive effects of exercise on sleep were found.
- Positive outcomes were obtained more frequently after the cancer treatment phase than in patients still in treatment.
- Walking appeared to be associated with a more positive impact on sleep than any other type of aerobic exercise.

Research agenda

- Large RCTs evaluating the effects of exercise on sleep as a main outcome and using a clinical level of insomnia symptoms as an inclusion criterion are very much needed.
- Objective and subjective measures of both sleep and exercise should be used.
- Efforts should be devoted to compare the effects of exercise with those of treatments whose efficacy is well established for clinical insomnia, such as CBT.
- It would be important to decrease the risk of contaminating the control groups.
- Future studies should better control for confounding variables such as sleep medication use and baseline fitness level.
- There is a need to systematically include follow-up assessments to assess the sustainability of therapeutic gains over time.