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Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice

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Sleep disturbance is prevalent in cancer with detrimental effects on health outcomes. Sleep problems are seldom identified or addressed in cancer practice. The purpose of this review was to identify the evidence base for the assessment and management of cancer-related sleep disturbance (insomnia and insomnia syndrome) for oncology practice. The search of the health literature included grey literature data sources and empirical databases from June 2004 to June 2012. The evidence was reviewed by a Canadian Sleep Expert Panel, comprised of nurses, psychologists, primary care physicians, oncologists, physicians specialized in sleep disturbances, researchers and guideline methodologists to develop clinical practice recommendations for pan-Canadian use reported in a separate paper. Three clinical practice guidelines and 12 randomized, controlled trials were identified as the main source of evidence. Additional guidelines and systematic reviews were also reviewed for evidence-based recommendations on the assessment and management of insomnia not necessarily in cancer. A need to routinely screen for sleep disturbances was identified and the randomized, controlled trial (RCT) evidence suggests benefits for cognitive behavioural therapy for improving sleep quality in cancer. Sleep disturbance is a prevalent problem in cancer that needs greater recognition in clinical practice and in future research.

Key words: cancer, insomnia, interventions, review, sleep disturbance

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introduction

Sleep disturbance rates in cancer ranges from 25 to 59% [1–4]. Sleep disturbance or insomnia symptoms usually present as a transient inability to initiate or maintain sleep lasting for >2 weeks in response to anxiety or stress provoking events [5–8]. Acute insomnia is characterized as lasting up to a month and sleep is described as non-refreshing or poor quality with impairment in daytime functioning. Whereas insomnia syndrome is defined as insomnia occurring more than three nights per week, difficulty falling asleep or night time awakenings (>30 min), ratio of sleep time to time spent in bed <85% (sleep efficiency), impaired daytime functioning and marked distress [5, 6, 9]. Insomnia syndrome is also called chronic insomnia, as it usually persists nightly for >4 weeks [4, 9]. Insomnia syndrome is clinically significant as it affects daily functioning, daytime fatigue, cognition (i.e. poor concentration and memory) with negative consequences on employment, relationships, quality of life and other health problems [10–12].

In cancer populations, the causes of insomnia are multifactorial and include predisposing, precipitating and perpetuating factors [9–13]. Predisposing factors include female gender, older age, hyperarousability as a trait, personal or family history, mood or anxiety disorders; precipitating factors include cancer treatments that alter levels of inflammatory cytokines or disrupt circadian rhythms or sleep–wake cycles, side-effects of cancer treatment, menopausal symptoms, hospitalization, distress in response to cancer, co-occurring symptoms, i.e. pain or fatigue, and medications used to treat or manage treatment side-effects, such as corticosteroids; and perpetuating behavioural factors such as excessive daytime sleeping, long-term use of medications or use of inappropriate medications, and maladaptive cognitions, i.e. inaccurate appraisal of sleep difficulty and quality and daytime impairments [9–13]. Unfortunately, in spite of its prevalence and clinical significance, insomnia is a frequently overlooked problem in cancer practice and patients may fail to report it, assuming it to be a normal and temporary reaction to a cancer diagnosis or treatment [1, 5]. Insomnia is rarely included as part of routine screening in cancer programs and psychological [5] interventions are not offered to patients with cancer [14].

The purpose of this systematic review was to review the evidence base to inform the development of best practice recommendations for screening, assessment and management of sleep disturbances in a pan-Canadian guideline for the Canadian Partnership Against Cancer (www.partnershipagainstcancer.ca/).

methods and materials

this systematic review was conducted in two steps as follows

step 1. In this step, we conducted a search for clinical practice guidelines for the assessment and management of insomnia or sleep disturbances in cancer following the ADAPTE Methodology. ADAPTE methodology [15, 16] is a rigorous 24-step method for searching and adapting knowledge from existing guidelines following a quality appraisal in accordance with the AGREE II convention [17]. This methodology allows for adaptation of evidence in high-quality guidelines for use in a specific healthcare context [15, 16]. Clinical practice guidelines (CPGs) are defined as systematically developed statements to assist practitioner and

patient decisions about appropriate healthcare for specific clinical circumstances [18]. In this step of the review, grey literature data sources were used to identify guidelines as follows: the Canadian Partnership Against Cancer's Inventory of Cancer Guidelines, Guidelines International Network, American Academy of Sleep Medicine (AASM), National Guidelines Clearinghouse (AHRQ), National Health Service (NHS), UK, National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Network (SIGN), National Comprehensive Cancer Network (NCCN), provincial guideline organizations, including Cancer Care Ontario (CCO), Fraser Health in British Columbia, Cancer Care Nova Scotia (CCNS), the Canadian Medical Association (CMA) and the American Medical Association (AMA). *Search Strategy:* The search of guidelines combined sleep terms (insomnia or sleep or sleep disturbance or sleep problems) and terms for cancer (cancer or oncology or neoplasms) and terms for clinical guidelines (practice guidelines or clinical guidelines or consensus). Inclusion/exclusion: CPGs were excluded if recommendations were not linked to the evidence and/or a formalized method was not used to reach expert panel member consensus. We also searched for guidelines to identify recommendations for treatment of insomnia in the general adult population as a secondary source of evidence.

step II. A systematic literature search using empirical databases was also conducted to identify randomized, controlled trials (RCTs), systematic reviews with/without meta-analyses or published guidelines of interventions for insomnia in cancer based on the PRISMA guidelines [19]. The trials identified were appraised for quality based on the Cochrane Risk of Bias Tool (www.cochrane.org) [20]. Databases searched included: Embase (1996 to June 2012), Ovid Healthstar (1966 to May 2012), Ovid MEDLINE(R) (1996 to June 2012), PsycINFO (2002 to June 2012), CINHAUL (2002–2012).

search strategy

The search terms and strategy are available online as supplementary material, available at *Annals of Oncology* online. Two reviewers (separately) examined all titles and abstracts followed by a review of full papers to determine eligibility for the review based on the following inclusion and exclusion criteria:

inclusion criteria

- Data on adult cancer patients or survivors with sleep disturbance and/or insomnia,
- Intervention targeted treatment of sleep disturbance and/or insomnia,
- Sleep identified as a primary outcome and a valid measure for assessing one or more dimensions of sleep: onset latency, total sleep time, quality, efficiency, time spent awake after sleep onset, or insomnia severity,
- RCTs, controlled clinical trials, clinical practice guidelines and
- Systematic review with/without meta-analyses.

exclusion criteria

- Data for cancer in general population studies are not analysed/reported separately or analyses conducted *post hoc* (not planned *a priori*),

- Language other than English and
- Intervention studies in non-cancer populations.

results

As shown in Table 1, three clinical practice guidelines [20–22] and an additional published source for a guideline were reviewed [23]. In addition, 12 RCTs were identified and appraised for quality (see CONSORT, Figure 1 in supplementary material, available at *Annals of Oncology* online) [24–35]. Secondary sources of data included eight practice guidance or expert consensus documents on the assessment and/or management of insomnia in general populations [36–43] or co-morbid with fatigue in cancer [38]. Systematic reviews for insomnia in the general population [44–50] and specific to cancer [51] as well as four papers focused on the measurement of sleep disturbance were also identified [52–55]. An interdisciplinary panel comprised sleep experts, researchers and guideline methodologists, and clinicians reviewed all the evidence and were asked to identify other trials not identified in the review. A pharmacist also reviewed pharmacological recommendations in non-cancer-specific guidelines for application in the treatment of cancer-related insomnia.

practice guidelines

Three practice guidelines were assessed for reporting quality using the AGREE II Instrument (see Table 2) [17]. The guidelines scored relatively highly on rigour ($\geq 55\%$), the evidence was clearly presented, the recommendations were systematically developed, and the authoring bodies were from credible institutions.

randomized trials

Characteristics and quality of the twelve RCTs are described in Tables 3 and 4. Five trials included breast cancer patients only [26–28, 31, 33], six trials had a mixed cancer sample [24, 25, 29, 30, 34, 35] and one trial included only patients with lymphoma [32]. Eight trials were in post-treatment survivors [24, 26, 28, 32, 35], while the remaining four trials included patients undergoing cancer treatments: chemotherapy [25, 27], hormone therapy [33] and radiotherapy [34].

The sample sizes in RCTs ranged from 14 to 312 patients. Five of the 12 trials used cognitive behavioural therapy (CBT) as the intervention [24, 26, 28, 29, 31]. Other trials included a behavioural intervention with all the components of CBT but not described as CBT [27], activity enhancement [25] and a self-hypnosis intervention [30]. The remaining four trials [32–35] tested the effect of exercise. Three trials [33–35] used a home-based walking or exercise intervention and one used Tibetan yoga [32]. Control group conditions included usual care [29, 31], a waitlist control [24, 30, 32, 35], single CBT component [28] or healthy eating [25, 27]. One trial used a crossover design [26]. No pharmacological intervention trials or guidelines were identified for insomnia in cancer populations.

All but one trial [35] reported the source of funding (government or charitable organization). All of the trials included a statistical methods section reporting statistical analyses and most included trial size calculations. Patient follow-up was $>75\%$ in 10 trials [24, 25, 27, 28, 30–35]. In the remaining two trials,

follow-up results were reported on 71% and 73% of patients enrolled [26, 29]. Seven trials [24, 25, 27, 29, 30, 34, 35] used an intention-to-treat analysis. Adequate sequence generation was reported in half of the trials, but information regarding blinding and allocation concealment was not adequately documented in most trials. The key findings from the evidence reviewed are summarized below:

screening and assessment

screening

Most guidelines recommended a two-step process for identification of sleep disturbance starting with an initial screen followed by a comprehensive assessment for those who screen positive. The National Institutes of Health (NIH) in a review of patient-reported outcome measures [52] recommended two questions be used to screen for sleep problems: (i) Do you have problems with your sleep or sleep disturbance on average for three or more nights a week? If yes (ii) Does the problem with your sleep negatively affect your daytime functioning? If the answer is yes to both questions, a more focused assessment of sleep disturbance is indicated. The Alberta Medical Association (AMA) recommended assessment of sleep experience using a daily diary and a screening questionnaire (i.e. Epworth Sleepiness Scale) to rule out co-morbid problems as part of routine practice for adults in the general population [36, 37]. Use of the Insomnia Severity Index, a tool to identify insomnia for case identification, was also recommended to screen for cases of insomnia in cancer patients and for assessing the effects of treatment [55].

focused assessment

The AASM [21] recommended a patient history, completion of a general medical/psychiatric questionnaire, the Epworth Sleepiness Scale [54] and completion of a 2-week self-report sleep log. Sleep logs including reports of sleep quality, sleep parameters, napping, daytime impairment, medications, activities, time of evening meal, caffeine and/or alcohol consumption and stress level before bedtime were recommended. The NHS [22] recommended assessment include six areas: (i) explore the person's beliefs about sleep; (ii) ask about the impact that insomnia has on the person's quality of life, daytime functioning, ability to drive, employment, relationships and mood; (iii) determine whether there is an underlying cause of insomnia or an associated co-morbid condition; (iv) take a sleep history; (v) determine the duration of symptoms and (vi) ask the patient to complete a sleep diary. Underlying causes and/or co-morbidities include asking about recent stressors and a detailed history and physical examination if necessary, and taking a drug history. If a daily sleep diary is kept, the NHS [22] recommended completing the information for a minimum of 2 weeks similar to recommendations made by the AASM [21]. In cancer, other symptoms that can precipitate insomnia, i.e. pain or fatigue, should also be assessed [11].

interventions for insomnia

sleep hygiene

The AASM [21] and the NHS [22] recommended that sleep hygiene education should be a standard part of best practice for management of insomnia. However, there is insufficient

Table 1. Literature Search Results

Report type	Ref
Practice Guidelines	
ONS, sleep-wake disturbances	[20]
AASM, Clinical guideline for the evaluation and management of chronic insomnia in adults	[21]
NHS, Clinical Knowledge Summaries (CKS), Insomnia	[22]
ONS, Evidence-based interventions for sleep disturbances	[23]
Randomized, controlled trials (RCTs)	
Cognitive Behavioural Therapy Interventions	
Ritterband et al. (2011)—Internet intervention	[24]
Barsevick et al. (2010)—information and behavioural skills	[25]
Fiorentino et al. (2009)—individualized program with crossover	[26]
Berger et al. (2009)—individualized sleep promotion plan	[27]
Dirksen et al. (2008)—stimulus control, sleep restriction therapy, relaxation therapy, sleep hygiene	[28]
Espie et al. (2008)—stimulus control, sleep restriction therapy, cognitive therapy, sleep education and hygiene	[29]
Farrell-Carnahan et al. 2010—self-hypnosis	[30]
Savard et al. (2005)—stimulus control, sleep restriction, cognitive therapy, sleep hygiene, fatigue management	[31]
Exercise therapy interventions	
Cohen et al. (2004)—Tibetan yoga	[32]
Payne et al. (2008)—walking	[33]
Sprod et al. (2010)—home-based exercise	[34]
Tang et al. (2010)—walking	[35]

ONS, Oncology Nursing Society; AASM, American Academy of Sleep Medicine, NHS National Health Service (NHS); Ref=Reference number.

evidence for the efficacy of sleep hygiene as a single intervention [21, 40]. Sleep hygiene education includes: wake up at the same time every day, maintain a consistent bedtime, exercise regularly but not within 2–4 h of bedtime, carry out relaxing activities before bed, keep the bedroom quiet and temperature regulated, do not watch the clock at night, avoid caffeine and nicotine for at least 6 h before bedtime, drink alcohol only in moderation and avoid use for at least 4 h before bedtime, avoid napping and avoid excess fluid intake before bedtime [21,40].

behavioural therapies

CBT aims to improve sleep performance through the use of a multimodal intervention approach, including sleep hygiene, sleep restriction, stimulus control, cognitive restructuring and relaxation therapies [11,40,50]. The AASM [21] recommended a CBT combination of stimulus control, sleep hygiene education, relaxation therapy and sleep restriction therapy for insomnia in the general population.

Five randomized trials evaluated CBT in cancer-related insomnia [24,26,28,29,31]. One of the largest trials that used an energy conservation and activity enhancement intervention for sleep disturbance reported no significant differences between the intervention and control groups [25]. Sleep quality improvements were noted for CBT delivered in an online format [24]

Table 2. Critical appraisal of clinical practice guidelines

Domains	ONS (2006) [20, 23] Sleep/wake disturbance	AASM(2008) [21] Chronic insomnia	NHS(2009) [22] Insomnia
1. Scope and purpose	77.8%	69%	83%
2. Stakeholder involvement	51.9%	47%	53%
3. Rigour of development	64.6%	56%	78%
4. Clarity of presentation	75.9%	94%	83%
5. Applicability	22.2%	54%	46%
6. Editorial independence	30.6%	67%	67%
No of reviewers*	3	2	2

Note that the recommended number of reviewers ranges from two to four; however, if two independent reviewers are consistent in their scoring, no further review is necessary. A quality score is calculated for each of the six domains by summing up all the scores of items in the domain and by scaling the total as a percentage of the maximum possible score for that specific domain. See more at: <http://www.nccmt.ca/registry/view/eng/100.html#sthash.FjRcwhAL.dpuf>

and for a multicomponent, and behavioural intervention not described as CBT that was not sustained at 1 year [27]. In a crossover study, Fiorentino *et al.* [26] reported significant differences in sleep quality, insomnia severity and objective sleep outcomes measured by actigraphy; however, patients were only followed for 6 weeks post-intervention. Dirksen *et al.* reported reduction in insomnia severity and improvement in quality of life and fatigue in the CBT group over their baseline status. However, both arms reported an improvement according to the Insomnia Severity Index with a 9.5% increase in the behavioural intervention group and a 6.4% increase in the control group [28]. Espie *et al.* [29] found CBT to be significantly better than usual care for reducing sleep-onset latency and increasing sleep efficiency. In the trial by Farrell-Carnahan et al., 71% of the intervention group had some reduction in insomnia severity using a web-based self-hypnosis therapy, while 36% of patients experienced improvements in sleep in the control group [30]. The overall adjusted effect sizes showed small effects on sleep and quality of life; however, differences were not statistically significant. Savard *et al.* reported significant improvements for a CBT group intervention on sleep efficiency, total wake time, sleep latency and insomnia severity that was maintained at the 12-month follow-up assessment period [31]. In this trial, the intervention group increased sleep efficiency by 15% from baseline to 12-month follow-up. It is important to note that insomnia syndrome was not measured or targeted in these RCTs making extrapolation of results to that patient population difficult and increasing the risk of floor effects. A variation in intervention dose, outcome measures for sleep, small effect sizes and the low quality of trials makes it difficult to draw any definitive conclusions about efficacy in cancer populations. However,

Table 3. Randomized trials of sleep interventions: Methods and Outcomes

Author Reference	Cancer type	Met criteria for Insomnia syndrome?	Sample size follow-up (FU) period in months	Intervention, dose and comparison	Sleep measure (s)	Sleep outcomes/results
Ritterband et al. [24]	Mixed stage 1-3	No	14 FU-6	Internet delivered CBT included six core modules (weekly completion about 45 minutes over 9 weeks) to improve insomnia symptoms in cancer survivors. Included sleep restriction, sleep stimulus control, cognitive re-framing, sleep hygiene education and relapse prevention.	Sleep diary, ISI	Significant improvements in the intervention group in overall insomnia severity ($P < 0.001$), sleep efficiency ($P = 0.002$), sleep onset latency ($P = 0.03$), soundness of sleep ($P = 0.005$), restorative sleep ($P = 0.002$) and general fatigue ($P = 0.001$).
Barsevick et al. [25]	Mixed stage 1-4	No	14 FU-2	Waitlist. Information and behavioural skills taught by an oncology nurse in three telephone sessions for energy conservation and activity enhancement to patients on chemotherapy.	Actigraph PSQI	Patients reported sleep disturbance (PSQI) at baseline and follow-up was much greater than the cutoff score of 5 in both groups indicating moderate levels of sleep disturbance. However, the actigraphy revealed that the total sleep time was almost eight hours, and sleep percent was greater than 85% for both groups at both time points (normal range).
Fiorentino et al. [26]	Breast stage 1-4	No	159 FU-17	Control—healthy eating and nutrition group Six weekly individualized sessions of CBT for insomnia and crossover to no treatment. Patients on different types of cancer treatment.	Actigraph Sleep diary, PSQI, ISI	Self-reported insomnia was significantly improved with treatment compared with controls. Pooled analyses showed improvements in self-rated insomnia severity, sleep quality, and objective measures of sleep.
Berger et al. [27]	Breast stage 1-3	No	8 FU-3,12	Control—no treatment and crossover to six weekly individualized sessions Behavioural-individualized sleep plan of stimulus control, modified sleep restriction, relaxation therapy and sleep hygiene set before adjuvant chemotherapy.	Actigraph Sleep diary, PSQI	CBT group had significant improvement on sleep quality compared with controls. Pair-wise comparisons revealed significant differences between the groups at 3 months ($P = 0.002$) but not at 1 year ($P = 0.052$). PSQI scores > 8 were found in 22% of the CBT group and 36% of the control group at 3 months ($P = 0.004$) and at 1 year in (19% versus 28%, $P = NS$).
Dirksen et al. [28]	Breast stage 1-3	Yes	106 FU-3	Control - healthy eating in-person sessions of equal time, Behavioural/CBT intervention—10-week intervention of stimulus control instructions, sleep restriction therapy, and sleep education and hygiene in post-treatment survivors (3 months post-treatment)	ISI	CBT significantly improved insomnia severity, quality of life and fatigue versus baseline. The ISI was improved from baseline to post-treatment by both CBT (14.38% versus 23.91%) and control treatment (16.3% versus 22.7%).
Espie et al. [29]	Mixed post-Rx	Yes	41 FU-6	Control - sleep education and hygiene only. Cognitive behavioural therapy - 5 weekly 50 minute sessions to discuss stimulus control, sleep restriction and cognitive therapy strategies	Actigraph Sleep diary	CBT was significantly better than normal clinical practice (control) for cancer related sleep and fatigue, Sleep diary measures of sleep onset latency and wake time after sleep onset were significantly reduced ($P < 0.001$), and sleep efficiency significantly increased ($P < 0.001$).
			50	Control—usual care		

Continued

Table 3. Continued

Author Year Reference	Cancer type	Met criteria for Insomnia syndrome?	Sample size follow-up (FU) period In months	Intervention, dose and comparison	Sleep measure (s)	Sleep outcomes/results
Farrell-Carnahan et al. [30]	Mixed stage 1–3 Post-Rx	Unclear	14 FU-2	Self-hypnosis - sleep healthy using the internet - patients were to visit a website for four weeks and view the self-hypnosis recordings.	ISI, sleep diary	Overall adjusted effect sizes show small self-hypnosis treatment effects in sleep and quality of life. 71% of the intervention group and 36% of the control group had reduced insomnia severity but not significant.
Savard et al. [31]	Breast stage 1–3	Yes	14 27 FU-3,6,12	Control—waitlist control Cognitive behavioural—8 weekly sessions of stimulus control, sleep restriction, cognitive therapy, sleep hygiene and fatigue management	ISI PSQI	Sleep efficiency ($P < 0.0001$), total wake time ($P = 0.001$), sleep onset latency ($P < 0.05$), wake after sleep onset ($P = 0.0001$) and ISI ($P = 0.05$) improved significantly with CBT; total sleep time did not increase significantly after CBT therapy. CBT patients increased their sleep efficiency from 69% to 84% at 12-month follow-up.
Cohen et al. [32]	Lymphoma stage-NI	No	30 19 FU-3	Control—waitlist control Tibetan yoga intervention - 7 weekly yoga sessions during or 12 months post-treatment.	PSQI	Patients in the TY group reported significantly lower sleep disturbance scores during follow-up compared with patients in the waitlist control group (5.8 versus 8.1; $P < 0.004$). This included better subjective sleep quality ($P < 0.02$), faster sleep latency ($P < 0.01$), longer sleep duration ($P < 0.03$), and less use of sleep medications ($P < 0.02$).
Payne et al. [33]	Breast Hormonal Rx	No	19 10 FU-3	Control—waitlist Home-based walking intervention—20 minutes a day, four times a week. Logs were provided to record frequency and length of walking.	PSQI, Actigraph	The effect of the exercise intervention on PSQI scores was significant ($P = 0.007$) for improved sleep quality. Sleep actigraphy also showed significantly shorter actual wake time and less movement in the exercise group ($P = 0.02$ and 0.05 , respectively).
Sprod et al. [34]	Breast and prostate stage 1–3	No	10 19 FU-3	Control—usual care Home-based exercise intervention (4 weeks)- exercise kit and intensity training. Post-treatment survivors.	PSQI	Better subjective sleep quality, less sleep latency and more sleep efficiency post-intervention with HBWE group versus control. There was also greater improvement in sleep quality in the exercise group from pre- to post-intervention ($P = NS$).
Tang et al. [35]	Mixed stage 1–4	No	19 36 FU-2	Control—usual care Home-based walking exercise intervention for 8 weeks - walk briskly for 3 days a week, 30 minutes per day.	PSQI	Exercise group reported significant improvements in sleep quality ($P < 0.01$) and the mental health dimension of QoL ($P < 0.01$). Sleep quality scores in the control group were stable.
			35	Control - waitlist		

CBT, cognitive behavioural therapy; WLC, Wait-list control, C, control group; HBWE, home-based walking exercise; IIS, Insomnia Interview Schedule; ISI, Insomnia Severity Index; NS, not significant; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; SH, self-hypnosis; TY, Tibetan Yoga; no of Pts, number of patients; NR, not reported; Rx, treatment; NI, not identified; P , P value.

Table 4. Quality Assessment of Randomized Controlled Trials

Author Year Reference	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Declaration of funding	Statistical analysis methods section	Patient follow-up status	Intent-to-treat
Ritterband [24]	+	+	–	+	+	+	+	+	+	+
Barsevick [25]	+	+	?	+	+	?	+	+	+	+
Fiorentino [26]	+	+	–	?	+	–	+	+	+	–
Berger [27]	+	?	?	?	?	+	+	+	+	+
Dirksen [28]	–	–	?	?	?	?	+	+	?	?
Espie [29]	+	–	–	?	+	+	+	+	+	+
Farrell-Carnahan [30]	?	?	?	?	?	–	+	+	+	+
Savard [31]	+	?	+	+	?	?	+	+	+	+
Cohen [32]	+	+	+	?	?	?	+	+	+	?
Payne [33]	?	?	?	?	?	–	+	+	+	?
Sprod [34]	–	?	–	–	?	–	+	+	+	+
Tang [35]	?	?	?	+	?	?	–	+	+	+

a Cochrane review of six RCTs ($n=282$ participants) of CBT for primary insomnia in adults aged ≥ 60 reported a small effect for CBT for sleep problems that was best demonstrated for sleep maintenance [50].

exercise interventions

Four small RCTs evaluated the effectiveness of exercise therapy specifically for improving sleep quality of cancer patients [32–35]. Three trials used a home-based walking/exercise intervention, all of which reported improvements in sleep quality for patients in the intervention arm in comparison to controls; however, only two trials reported statistically significant results [33, 35]. The remaining trial tested Tibetan yoga as an exercise therapy intervention [32] with significantly lower sleep disturbances reported in the experimental arm compared with the control group. While exercise may have beneficial effects on sleep quality in individuals with cancer, the evidence is inconclusive due to quality biases and the lack of identification of clinically significant levels of insomnia at baseline [46].

other interventions

The ONS [20, 23] and other reviews [42–47] reported low quality evidence for expressive therapy, expressive writing, healing touch, autogenic training, massage, muscle relaxation, mindfulness-based stress reduction, yoga, acupuncture, aromatherapy, music therapy, hypnotherapy, guided imagery, education/information or exercise.

pharmacological interventions

No RCT data involving pharmacological interventions for insomnia in cancer were identified. However, a number of guidelines reported on the use of pharmacological treatments for primary insomnia in the general population that may have relevance for application in cancer practice. The AASM reported that psychological and pharmacological interventions might be used alone or in combination [21]. The NCI [39] recommended a combined pharmacological and non-pharmacological approach, while the Alberta Medical Association recommended that pharmacotherapy should be considered an adjunctive

therapy to cognitive and behavioural therapies [36]. Buscemi *et al.* [41] reported the effectiveness of non-pharmacological and pharmacological interventions separately, citing insufficient evidence to recommend a combined approach. In cases where insomnia is due to cancer or cancer treatment, the main focus is to alleviate/treat or remove the causative condition (e.g. pain) or agent (e.g. medication) although this is not always possible [38].

Although the pharmacological impact of sleep medications on insomnia in the general population is reported to be effective in the short-term, the possibility of long-term dependence cannot be ignored. As a general rule, dosage should be kept to the minimum and long-term sleep medication use is not typically recommended [21, 22, 36, 39, 40, 45]. Given the documented adverse effects in certain populations, clinicians and patients should weigh the beneficial and harmful effects of medication according to individual circumstances, comorbidities, cancer type, stage of disease and/ or treatment characteristics. When pharmacotherapy is used, the choice of the specific agent within a class should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, cost, availability of other treatments, co-morbid conditions, contraindications, concurrent medication interactions and side-effects [21].

The NHS [22] recommended the consideration of a short course of a hypnotic drug if daytime impairment is severe for short-term insomnia (<4 weeks). They also recommended that if a hypnotic is prescribed, the lowest effective dose should be considered for the shortest period possible. However, the British Association for Psychopharmacology did not recommend antipsychotics as first-line for insomnia, due to side-effects [40]. The atypical antipsychotics are often used to treat insomnia; however, their metabolic side-effects can be very problematic. For short-term treatment of insomnia, the use of certain benzodiazepines or newer non-benzodiazepine medications (e.g. zaleplon, zolpidem) (short-term) are considered better treatment options.

The NCI [39] reported on the cautious use of antihistamines, due to daytime sedation and delirium (especially in older patients and patients with advanced cancer). In addition, they reported that long-acting benzodiazepines are characterized by half-lives longer than 24 hours, pharmacologically active

metabolites, accumulation with multiple dosages, and impaired clearance in older patients and those with liver disease. In addition, barbiturates should not be used for managing sleep disturbance in cancer patients.

Due to the relative lack of efficacy and safety, data and potential for rebound insomnia over-the-counter antihistamines or herbal substances (e.g. valerian and melatonin) were not recommended in the treatment of chronic insomnia [20–22, 48, 49]. Variable evidence is reported for the use of L-tryptophan, melatonin and valerian (natural, nutritional sleep aids) and the AMA concluded that the efficacy of melatonin is inconclusive [36, 37]. They also acknowledged that while over-the-counter products are available, they did not recommend their use as sleep aids (e.g. ‘Sleep Eze’, Benadryl®). *Post hoc* to this review, we did identify a phase III, double-blinded trial of Valerian (450 mg) compared with placebo in cancer patients during active treatment [56], which did not show an effect for Valerian on sleep quality measured by the Pittsburgh Sleep Quality Index [57].

The AMA also, due to a relative lack of evidence or side effects, did not recommend prescribing mirtazapine, fluvoxamine, tricyclics, amitriptyline, chlorpheniramine, anti-psychotics, intermediate and long-acting benzodiazepines (e.g. diazepam, clonazepam, lorazepam), triazolam (short-acting benzodiazepine), chlorals (chloral hydrate, ethchloroviny) or muscle relaxants. In cancer, a small RCT ($n=23$) was identified *post hoc* to this review, showed an effect for eszopiclone on improving sleep time, sleep quality and depth, and reducing nighttime awakenings in haematological patients experiencing mucositis-induced pain [58].

Pharmacological interventions in cancer populations must take into consideration other medications and the concomitant use of these agents with other agents for cancer treatment as well as the type of cancer (e.g. involvement of the central nervous system as primary or secondary to cancer may preclude their use and aggravate symptoms). A short-term pharmacological solution may be necessary until CBT takes effect or for those refractory to CBT [44], whereas experts in cancer recommend CBT to be used as first-line treatment of insomnia [59].

discussion

Screening for sleep disturbance by using key questions as recommended by the NIH [52] or measures sensitive and specific to case identification such as the Insomnia Severity Index is indicated as a best practice for routine oncology practice. This is particularly important, given the prevalence of sleep disturbance problems in cancer and its detrimental effects on quality of life and possible implications for disease progression [1–13]. There is consensus that a positive screen should always be followed by a focused assessment using valid and reliable measures for sleep disturbance that are conceptually valid for different dimensions of sleep problems [52–55] and sleep diaries [60] combined with medical evaluation [21]. Objective measures including actigraphy may also be useful [27]. Sleep assessment should capture a number of assessment parameters and its measurement should incorporate two conceptual categories: (i) overall sleep disturbances, quality, satisfaction with sleep and (ii) daytime impairments related to sleep or sleep problems [52]. Other reviews suggest the need

to specifically measure non-restorative sleep as a dimension of patient-reported outcome measures for sleep [61].

Sleep disturbances may be related to other symptoms such as pain or comorbid depression that must be managed concurrently [13]. However, it must be recognized that sleep problems in cancer are also distinct problems [62]. The treatment plan should address the multifactorial and treatable causes of insomnia. However, further research is needed to link interventions to causal mechanisms for insomnia, which are not yet fully elaborated. Most interventions identified in the review were behavioural. While it appears that CBT is effective on some dimensions of sleep disturbance, further research is needed, given the paucity of high-quality evidence. While exercise therapies such as walking and yoga may be beneficial for improving sleep quality, their efficacy for insomnia syndrome is not established and further research is recommended.

Following completion of this review, a literature review that included other study designs such as quasi-experimental designs and other types of interventions such as complimentary therapies and education for sleep disturbance as a primary or secondary outcome in cancer populations was identified [63]. In a meta-analysis of four of the 14 studies of CBT interventions included in the review, moderate effects for improving sleep disturbance were noted, but large confidence intervals were reported in half of the studies. Similar to our review, these authors suggest that the evidence supports the efficacy of CBT; however, its superiority to other types of interventions is not conclusive due to poor quality of other interventions such as education or complimentary therapies. Similar to the Langford *et al.* review [63], heterogeneity in intervention dose, duration, intervention components, mode of delivery, potential risk of bias and as noted in our review the lack of a clear target of insomnia syndrome versus sleep disturbance or insomnia symptoms in CBT interventions was problematic. Other reviews of RCTs in primary insomnia have also noted small effects for CBT [47]. Further high-quality research is recommended with clear identification of insomnia and that builds on existing dose and intervention components.

Evidence is emerging that self-help treatment for insomnia in cancer including shortened courses of group cognitive behavioural therapy [64], and self-help interventions delivered online for insomnia in cancer populations [65] or in the general public [66, 67] may improve the quality of sleep but further research regarding the efficacy of these approaches is needed in cancer populations.

A variety of pharmacologic agents have been recommended to manage sleep disturbances for insomnia in the general population, but their efficacy and safety in adults with cancer are not established. A recent review compared CBT for insomnia with pharmacological treatments in the general population and reported superiority of CBT compared with benzodiazepam and non-benzodiazepam drugs [68]. In this review, it was recommended that CBT be considered as a first-line treatment option for insomnia. The authors suggested contacting a registry of providers certified in the delivery of CBT and other behavioural sleep medicine specialists to deliver the interventions (<http://www.asbm.org/BSMSpecialists.aspx>). Other sources to identify sleep medicine specialists or sleep centres include The American Academy of Sleep Medicine or the Canadian Sleep Society.

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