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REVIEW ARTICLE

Psychostimulants for cancer-related cognitive impairment in adult cancer survivors: a systematic review and meta-analysis

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Abstract

Background Cognitive impairment is recognized as a common symptom experienced by cancer survivors which impacts on quality of life (QoL) and day-to-day activities. One of the treatment options is the use of psychostimulants but the evidence supporting its use remains unclear.

Objectives To identify the level of evidence of psychostimulants' effect on the management of cognitive impairment in adult cancer survivors.

Methods Electronic databases (MEDLINE, EMBASE, CENTRAL, CINAHL) and reference lists of relevant reviews were searched from inception to December 2017, with no language restrictions applied. Randomized controlled trials (RCTs), evaluating the effect of psychostimulants on cognitive impairment among cancer patients with no primary or secondary brain tumor or brain radiation, were included. The primary outcome was cognitive function changes, whereas secondary outcomes were adverse events (AEs) and QoL.

Results Six RCTs were included: three studies investigating methylphenidate and three modafinil, with a total of 244 and 146 patients, respectively. Due to important differences in methodologies between studies, a meta-analysis was assumed inappropriate for the primary outcome. A narrative synthesis was performed. One study using methylphenidate and two using modafinil demonstrated improvements in some cognitive functions as measured by objective cognitive assessment tests. Psychostimulants did not improve QoL and were not associated with more AEs.

Conclusion To date, limited evidence is available to estimate the usefulness (or lack) of psychostimulants on cognitive function in this population.

Keywords Cancer · Cognitive impairment · Psychostimulants · Survivorship

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Introduction

About 2 in 5 Canadians will develop cancer in their lifetime (202,400 Canadians in 2016) and the 5-year net survival rate for people diagnosed with cancer is about 60% [1]. With a rising number of cancer survivors due to an aging population and an increase in survival time, the burden of cancer and cancer treatment-related survivorship issues continues to grow [2]. Cognitive impairment, defined as a decline in one or more areas of cognitive function, including attention and concentration, executive functioning, information-processing speed, language, visuospatial skill, psychomotor ability, and memory [3], is recognized as a common symptom experienced by cancer survivors [4]. It is estimated that up to 40% of patients experience cancer-related cognitive impairment (CRCI) prior to any treatment; up to 75% during their treatment; and up to

60% upon completion of therapies [5]. These deficits have been reported after anti-inflammatory therapy such as chemotherapy, radiotherapy, and hormone therapy [6]. However, systemic oncological treatments do not appear to be the only factor for the decreased performance of cognition. It was observed that patients experienced cognitive difficulties before receiving systemic treatment for their cancer, suggesting other factors involved in cognitive alterations such as biological, genetic, socio-demographic, and physio-psychological factors [6–8]. To date, the mechanisms of cognitive impairment are not well known. Recent searches in neuroimaging have shown a reduction in gray matter density in the frontal, temporal, and cerebellar regions [9], as well as a decrease in the volume of white matter [10]. The damages in these anatomical structures could potentially explain the occurrence of these disorders. Moreover, in functional magnetic resonance imaging, abnormal activation of frontal and subcortical regions during working memory tasks in patients with breast cancer treated with chemotherapy or hormone therapy were observed [11].

Certainly, the presence of these cognitive symptoms may add a significant psychological distress in cancer survivors, negatively affecting their quality of life (QoL) and ability to function in day-to-day life [12–14]. However, effective management of this problem is not yet available [15]. Management options include the use of pharmacological and non-pharmacological interventions, but there is no clear gold standard treatment for CRCI. One of the treatment options of cognitive deficits in cancer patients that have been studied is the use of psychostimulants. A number of trials have explored their effect in the treatment of cognitive impairment, but these studies provided inconsistent results [15].

A brief review of literature was conducted by our team to identify types of psychostimulants that have been studied for the management of CRCI. Two psychostimulants were identified and constitute the focus of this review: methylphenidate and modafinil. Methylphenidate is a central nervous system stimulant mainly use in the treatment of attention-deficit hyperactivity disorder (ADHD). It promotes neural signal processing in the frontostriatal network [16] by increasing dopamine and noradrenaline concentrations [17]. Modafinil, also a centrally acting drug, is classically prescribed to treat narcolepsy and other sleep disorders. The mechanism of action of modafinil remains unknown, but it is suggested that it acts within sleep-wake centers in the anterior hypothalamus to improve wakefulness [18].

Although the overall level of evidence on the use of psychostimulants to treat CRCI is unclear, understanding the role of these drugs in the management of this condition remains essential. To date, most of the studies on CRCI among cancer survivors have focused on the cognitive impact of chemotherapy and many studies have been performed with the breast cancer population. Interestingly, studies examining CRCI in women with breast cancer indicate that a subset of these women had cognitive deficits before receiving chemotherapy [19]. Similar pretreatment deficits have been reported in colorectal cancer patients [20, 21], in head and neck cancer patients [22], and in hematological patients before hematopoietic stem cell transplants [23]. As improvements in treatment have increased survival rates, delayed treatment-related cognitive dysfunction has also been recognized as a significant problem in many cancer populations, such as primary central nervous system lymphoma treated with radiotherapy and chemotherapy, either combined or isolated [24], patients treated with hematopoietic stem cell allogeneic transplant [25], nasopharyngeal patients treated with radiotherapy [26], and colon cancer post-chemotherapy [27]. Cancer survivors can experience persisting cognitive deficits post-treatment, but the rate of cognitive symptoms varies substantially with the population evaluated, the definitions of impairment, and the cognitive function measurement tools used [28–34].

Of note, cognitive disorders resulting from cancer and its treatment are related to a significant decline in QoL and function of patients with cancer, thus increasing the need for health care services. The objective of this meta-analysis was to review the overall level of evidence of the psychostimulants' effect on cognitive impairment in adult cancer survivors with the overall goal of providing guidance for future research initiatives and clinical practice.

Methods

This systematic review of randomized controlled trials (RCTs) and meta-analysis when applicable were prepared according to the preferred reporting items for systematic review and meta-analyses (PRISMA) statement [35].

Criteria for considering studies for this review

Types of studies

All RCTs assessing the effect of psychostimulants on cognitive impairment in adult cancer survivors were considered. Crossover trials were eligible. No restrictions were applied regarding the language or the publication type (articles, short reports, and abstracts).

Types of participants

Studies that involved adult cancer patients (aged 18 years and over) who were experiencing cognitive impairment were included. Patients with cancer-onset during childhood and those aged less than 18 years old were excluded since there are differences between measures of cognitive function in childhood and adult cancer survivors [36]. Patients with primary or metastatic cancer of the brain or central nervous system (CNS) were also excluded because the tumor may have had a direct

impact in the brain and cognitive process [37, 38]. Finally, patients who received cranial radiation were excluded from this review (cognitive deficits in adults treated with cranial irradiation were previously addressed in a Cochrane Review [39]).

Types of interventions

Studies that investigated the effect of psychostimulants (e.g., methylphenidate, modafinil) in order to treat cognitive impairment in adult cancer survivors were considered, regardless of the route, duration, or therapeutic dose of the psychostimulant. Regarding control groups, trials that compared the intervention with a placebo, no treatment, standard care, or another active drug were included.

Types of outcome measures

The primary outcome of interest was cognitive functioning identified through a subscale or composite cognitive score, individual cognitive test scores of validated standardized self-reported cognitive function questionnaires, or objective cognitive function tests. Secondary outcomes included any adverse effects (AEs), as a result of psychostimulants use, and QoL. The effect of the intervention on the primary and secondary outcomes was estimated using the measurements obtained after completion of the intervention.

Search methods for identification of studies

An electronic search was conducted in MEDLINE (via OvidSP), EMBASE, CINAHL, and CENTRAL (Cochrane central register of controlled trials) from inception to December 2017 (see Appendix 1). No language or publication date restrictions were applied. The search strategy included a combination of free-text terms and index terms related to the population and intervention of interest, after which appropriate filters for randomized trials on MEDLINE and EMBASE were applied [40]. The reference lists of relevant reviews and included studies were scanned as well.

Data collection and analysis

Selection of studies

Records identified by the search were examined by two independent reviewers (NM, RD) in a two-step process. Titles and abstracts were screened to exclude the obviously non-eligible studies, followed by a full-text revision of the retained studies to establish eligibility. Any disagreements between reviewers were resolved by discussion to arrive at a consensus. Further information was sought from the authors by email when necessary.

Data extraction

Data extraction was performed using a data extraction form designed for this review, which was pilot tested on a reference study and corrected accordingly by a review author (NM). Whenever required, a second review author (RD) was consulted. Information about the study (eligibility criteria, sample size, and methodology), participant characteristics (age, sex, cancer site/stage, treatment history), description of the intervention (drug dose, frequency, duration), primary outcomes (cognitive functioning: method and timing of assessment, results of cognitive functioning measures), other outcome measures (including AEs and QoL: method and timing of assessment), comparators, and different quality evaluation criteria (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias) was extracted.

Assessment of risk of bias in included studies

The risk assessment of bias was performed independently by two review authors (NM, FJ) according to the Cochrane risk of bias assessment tool [40]. Sensitivity analyses were performed to explore the impact of the quality differences of the studies (high or low risk of bias) on the overall intervention effect.

Assessment of heterogeneity

Evaluation of heterogeneity across studies was done using the I^2 statistic, according to the Cochrane Handbook for Systematic Reviews of Interventions [40] and visual inspection of forest plots. When sufficient data was available, subgroup analyses were also performed to account for the expected differences between included studies on various categories (classes of agents, drug doses, duration of intervention, cancer site or stage, treatment history).

Measures of intervention effect and data synthesis

A quantitative synthesis of data was conducted with RevMan software Version 5.3 [41]. Data, including the final mean values, standard deviations, and the number of patients assessed at different endpoints for each treatment arm was extracted to estimate the overall mean differences between treatment arms. When the outcome was assessed at different time points during the same study, only the assessments performed at the end of the intervention were used, regardless of repeated evaluations along the trial. The intervention effect on cognitive impairment and QoL was treated as a continuous variable. The use of the standardized mean differences was planned to combine trials that measured the same outcome

but used different methods [40]. When included articles presented insufficient data to calculate the effect size (mean difference), their authors were contacted to obtain the required information. Risk ratios (RR) were used to compare treatment groups for dichotomous outcomes such as AEs. The inverse-variance and the Mantel-Haenzel methods were respectively used to combine continuous and dichotomous data from different studies, using a random effects model. For the evaluation of heterogeneity between studies, the I^2 test was used, with $I^2 > 50\%$ or greater indicating the presence of substantial heterogeneity [42].

Results

Results of the search

The search generated a total of 914 articles, of which 104 were duplicates, leaving 810 articles (see Fig. 1). Of those, we excluded 800 articles after screening of title and abstracts. Of the ten full-text articles assessed for eligibility, four studies were not suitable for quantitative analysis. Therefore, six studies were included in this review. Three authors were contacted to provide data in a different format than the one reported in their published article. Two authors did not follow-up on our request whereas one author responded that the study database was no longer available. Thus, the findings included in this review are only the ones reported in the original papers.

Description of studies

Characteristics of the included studies are summarized in Table 1. Three studies investigated the effect of methylphenidate, recruiting a total of 244 patients, and three studies investigated the effect of modafinil on the treatment of cognitive deficits, recruiting a total of 146 patients. Of these six studies, three were crossover randomized trials. All studies compared the interventions with a matched placebo. The population was breast cancer for the majority of the studies [43–46]. Intervention duration varied between studies and ranged from 8 days to 6 months.

Cognitive function was evaluated by objective tests across the six studies and a range of different outcome measures was used. Some tools were used to measure more than one domains of cognitive function. Two studies measured an overall cognitive function score using the high sensitivity cognitive

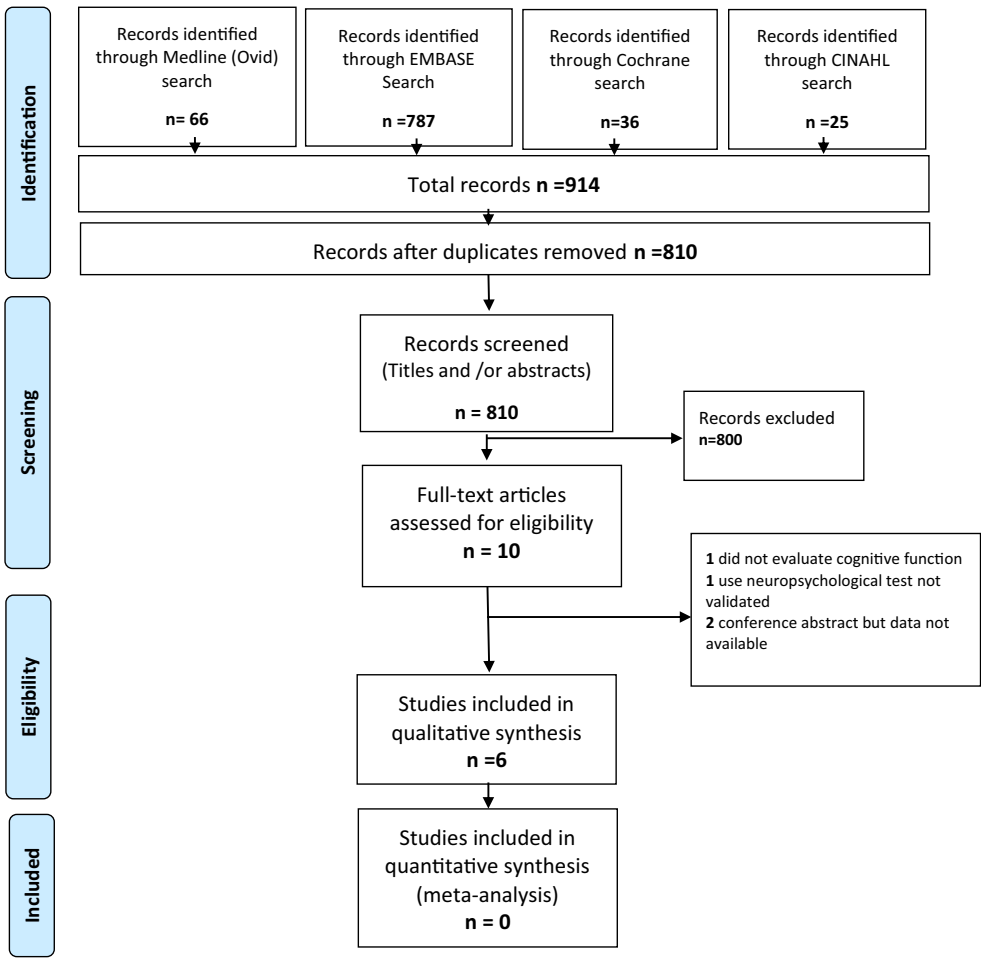

Fig. 1 Study flow diagram

Table 1 Summary characteristics of eligible studies (n=6)

Authors, Year, Country	Study design	Participants	Intervention	Outcomes measures	Findings
Methylphenidate					
Lower et al, 2009 USA	• Randomized double -blind, placebo--controlled study	• 154 women and men, any tumor type, off CT • Two randomized groups: - Methylphenidate (n=76; Mean $_{age}$ = 52.5 y) - Placebo control (n= 78; Mean $_{age}$ = 53.2 y)	Methylphenidate PO 10 mg/day (5 mg bid) or Placebo for height weeks; dose modifications were allowed: max 50 mg/day	• Primary outcome is fatigue. • Secondary outcome is cognitive function, measured by HSCS.	There was no significant change on the HSCS in either treatment group for the overall or subscale scores.
Mar Fan et al, 2008 Canada	• Randomized double -blind, placebo--controlled study.	• 57 women with breast cancer, undergoing CT • Two randomized groups: - Methylphenidate (n=29, Median $_{age}$ =50 y) - Placebo control (n= 28, Median $_{age}$ = 51 y)	• Beginning after one cycle of CT (if four cycles were planned) or beginning after up to two cycles of CT (if six cycles were planned) and ending with the final CT cycle. • Methylphenidate (d-MPH) PO: 5 mg bid (10mg/day) for one CT cycle (3-4 weeks), then 10 mg bid (20 mg/day) for remaining cycles (unless not well tolerated, then reduced to 5 mg bid) OR Placebo	• Primary outcome is cognitive function measured by HSCS and HVLT-R.	There was no significant group difference on the HSCS or HLTV-R scores at any time points.
Escalante et al, 2014 USA	Randomized, double blind, two period, placebo--controlled crossover trial	• 33 women with breast cancer, undergoing CT, Mean $_{age}$ = 57 y	The study duration was four weeks. Patients were randomized into one of two arms: sustained release methylphenidate PO (18 mg/day once) for two weeks followed by placebo for two weeks (Arm A) or placebo for two weeks followed by methylphenidate (18 mg/day) for two weeks (Arm B)	• Primary outcomes are fatigue, depression, sleep and mood. • Secondary outcome is cognitive function measured by HVLT-R, WAIS:Digit symbol	Participants performed significantly better on tests of verbal learning, memory, visual perception and scanning speed in the methylphenidate condition.
Modafinil					
Kohli et al, 2009 USA	Randomized clinical trial	• 68 women with breast cancer, had been received CT and/or RT, • Two randomized groups: - Modafinil (n=34, Mean $_{age}$= 52 y) - Placebo (n=34, Mean $_{age}$= 56 y)	• All 68 women participated in an open label four-week trial of modafinil and demonstrated good response on fatigue. Then women were randomized to one of two trial arms and received either four weeks of Modafinil PO, 200 mg/day once or placebo	• Primary outcome is cognitive function measured by tests of memory and attention selected from the CDR computerized assessment system.	• The modafinil group showed significant improvement in speed of memory, quality of episodic memory and attention compared with the placebo group.
Berenson et al, 2015 USA	Randomized, double-blind, placebo--controlled, crossover study	• 50 women and men with multiple myeloma. • Two randomized groups: - Armodafinil (n=25, Mean $_{age}$= 63 y) - Placebo (n=25, Mean $_{age}$= 67 y) followed by armodafinil	Patients were randomized to one of two arms: treatment-only, with armodafinil PO, 150 mg/day once, for 56 days OR placebo-first, for 28 days, followed by armodafinil 150 mg/day for 28 days.	• Primary outcome is fatigue • Secondary outcome is cognitive function measured by the SDMT, TMT-B, Digit Span Test.	No significant differences were observed between the placebo-first and the treatment only groups after 28 days in any measures of cognitive function.

Table 1 (continued)

Authors, Year, Country	Study design	Participants	Intervention	Outcomes measures	Findings
Lundorff et al, 2009 Denmark	Randomised, double-blind, cross-over trial	• 28 women and men, any tumor type, in advanced cancer treated in palliative care, Median $_{age}$= 62 y	On day 1 the patients were randomly assigned to receive modafinil 200mg, once PO, OR placebo and on day 4 they crossed-over to the alternative treatment.	• Primary outcome is cognitive function measured by FTT, TMT-A and B	FTT for the dominant hand and TMT were statistically significantly improved on modafinil compared to placebo.

CDR Cognitive Drug Research, *CT* chemotherapy, *FTT* Finger Tapping Test, *HSCS* High Sensitivity Cognitive Screen, *HVLT-R* Hopkins Verbal Learning Test-Revised, *PO per os*, *RT* radiotherapy, *SDMT* Symbol Digit Modalities Test, *TMT* Trail Making Test, *WAIS* Wechsler Adult Intelligence Scale.

screen (HSCS) [43, 44]. This test assesses several neurocognitive domains such as attention and concentration, executive function, language, motor function, visuospatial skill, and memory. Other studies were interested in evaluating composite measures of overall cognitive functioning. Learning and memory was assessed by using the Hopkins Verbal Learning Test-Revised (HVLT-R) in two studies [44, 45]. A composite score from the Cognitive Drug Research-subtest (CDR) (episodic memory, speed of memory, working memory) was used in one study [46]. Processing speed was measured in two studies by using the Trail Making Test (TMT) Version A [48] and the Wechsler Adult Intelligence Scale (WAIS-digit symbol) [45]. Executive function was assessed in two studies by using TMT Version B [47, 48]. Attention and concentration were also assessed by three studies using the Symbol Digits Modality Test (SDMT) [47], CDR-subtest [46], and WAIS-digit span [47]. A number of selected time points for assessment of cognitive functioning varied between studies, both in interventions using methylphenidate or modafinil.

Risk of bias in included studies

Studies were assessed using the Cochrane "risk of bias" tool [40]. A summary of the risk of bias is presented in Fig. 2. Overall, all of the included studies had an unclear risk of bias for one or more domains. Two studies had a high risk for selective reporting bias, as the data on all measured outcomes was not reported by the authors [45, 48].

Effects of intervention

The eligible studies used different patient populations, treatment courses, dosing schedules, and methods of assessing cognitive functioning, through general or composite scoring. Additionally, the unavailability of some mean values leads to inappropriate pooling of the data points. Thus, a meta-analysis was not undertaken and the results of the studies are reviewed separately.

Primary outcomes

The six studies meeting inclusion criteria only reported outcomes based on objective cognitive assessment tests. None included self-reported cognitive function questionnaires as primary outcome measures. Three studies examined the effect of methylphenidate on cognitive impairment. In a crossover study ($n = 33$) [45], Escalante et al. assessed the efficacy of sustained-release methylphenidate (18 mg/day) for cancer-related fatigue as a primary outcome in participants with breast cancer. Other secondary measures included improvements in cognitive function as evaluated at the end of the 2-week-treatment period. Results from the HVLT-R, when

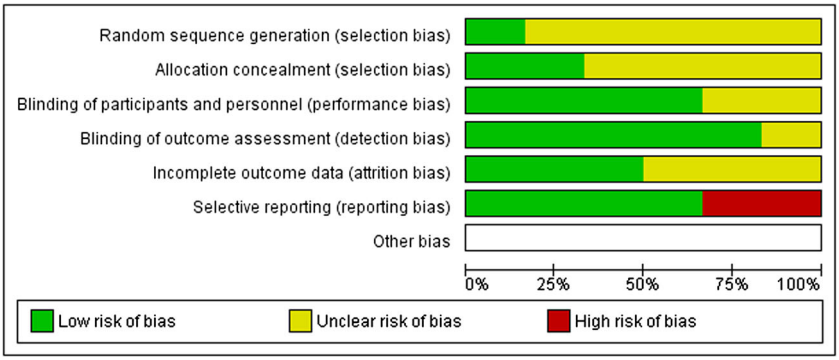

Fig. 2 Summary of the risk of bias

correlated with the interference and activity level of the Brief Fatigue Inventory (BFI), showed significant improvement in verbal learning and memory in the methylphenidate group. The WAIS-digit span also demonstrated improved cognitive-processing speed when correlated with the BFI. In the other two studies, no statistically significant difference in cognitive measures was observed [43, 44]. One study was multicenter ($n = 154$), conducted in patients with cancer (of which 78% had breast cancer) at least 2 months after chemotherapy, and had fatigue as a primary endpoint [43]. According to the preliminary results of the other study, conducted among breast cancer patients during adjuvant chemotherapy ($n = 57$), the differences in cognitive improvement between methylphenidate and placebo were constant at all time point. However, these results are insufficient because this study was interrupted due to slow recruitment and failure to meet its planned sample size, according to authors [44].

Modafinil, another psychostimulant, was used in three studies. The improvement in cognitive function was observed with modafinil being administered at 200 mg daily in two of the studies. In one study, authors looked at the effect of modafinil on cognitive dysfunction among breast cancer survivors ($n = 68$) as a secondary analysis of a previous trial, which looked at its efficacy in the treatment of cancer-related fatigue [46]. Modafinil demonstrated a cumulative improvement from baseline to week 8 in the speed of memory scores ($p = 0.029$) compared with placebo ($p = 0.116$) [46]. Regarding episodic memory, the scores in the drug group showed the significant change ($p = 0.015$) when compared with the placebo group ($p = 0.155$) [46]. Also, in a randomized crossover trial in patients with advanced cancer in palliative care, authors observed statistical improvements in cognitive tests [48]. Finger Tapping Test (FTT), Trail Making Test (TMT), and Edmonton Symptom Assessment System (ESAS) were conducted before tablet intake and again 4.5 h after. FTT for the dominant hand and TMT scores were significantly improved on modafinil (p values = 0.006 and 0.042, respectively) [48]. Lastly, in another randomized crossover trial, armodafinil was administered at 150 mg daily in patients with multiple myeloma [47]. No significant differences were observed between the two arms after 28 days [47].

Secondary outcomes

Adverse events Safety issues and AEs related to psychostimulants use were reported in all studies. Generally, no serious AEs related methylphenidate or modafinil were reported. In two studies, the rate of AEs was higher in the methylphenidate group than placebo: 63% vs 28% [43] and 10% vs 3.5% [44] with a higher incidence of insomnia, dizziness, headache, anxiety, and dry mouth among the methylphenidate treatment group. In the case of modafinil, overall, side effects that occurred during the trial were similar between the two arms [47, 48]. One study reported that AEs, considered as mild or moderate, occurred during open-label therapy (modafinil only) and were self-limited [46].

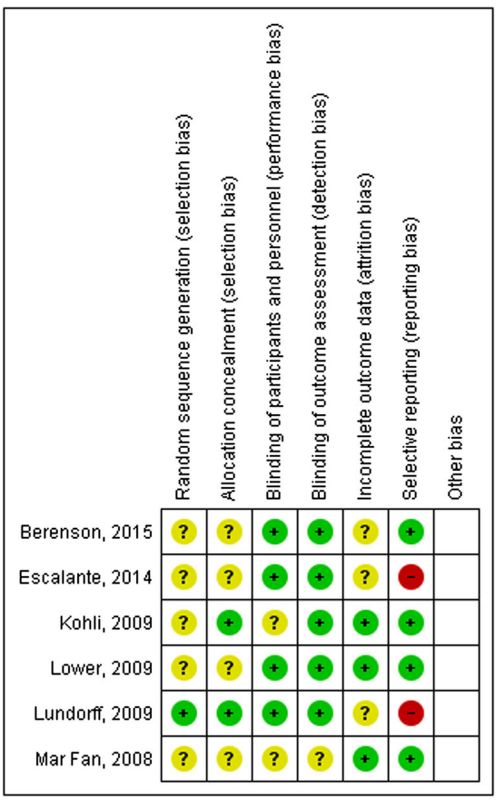

Fig. 3 Pooled mean differences of two randomized controlled trials

Quality of life QoL was assessed as a secondary outcome in only two studies using the Functional Assessment of Cancer Therapy-General (FACT-G) [44, 47]. In these two RCTs, the pooled mean differences demonstrated no impact of a psychostimulant on QoL associated with cognitive impairment (overall Z-score = 1.44; $p = 0.15$; MD = − 4.32; 95% confidence interval (CI) = − 10.19–1.56)) (Fig. 3).

Discussion

The objective of this review was to evaluate the effect of a psychostimulant on cognitive deficits in adult cancer survivors. Six RCTs were included, of which three evaluated methylphenidate and three others evaluated modafinil. Overall, the beneficial effect on cognitive deficits was observed in one study evaluating methylphenidate ($n = 33$) [45] and two studies evaluating modafinil ($n = 68$ and $n = 28$, respectively) [49, 50]. However, the level of evidence for the effect of psychostimulants could not be determined for either methylphenidate or modafinil due to the high heterogeneity between included studies. First, this heterogeneity has been identified among research objectives. Three of the six studies had as the main objective the evaluation of the effect of methylphenidate or modafinil on fatigue [43, 45, 51], whereas the effect on cognitive dysfunction was considered as a secondary objective. Thus, the cognitive assessments and doses used were not optimally selected to meet this objective and trials lacked power to detect differences in the secondary outcome. Second, documentation of a real presence of cognitive impairment prior to the intervention was almost absent for most studies. Only one study used cognitive tests such as MMSE (Mini-Mental State Examination) and HSCS to assess participants' eligibility [43].

Third, although all studies used objective neurocognitive tests, various outcome measures were provided. Attention, memory and learning, processing speed, and executive function are the most frequently affected cognitive domains by CRCI [31, 52, 53]. Therefore, they should be the primary targets of the cognitive tests used in the studies. Two studies calculated an overall cognitive score using HSCS [43, 44], whereas in the other studies, the majority evaluated only two specific areas of cognition. Moreover, the language was not evaluated in any of these studies. The International Cognition and Cancer Task Force (ICCTF) recommends that the following tests should, at minimum, be included in cognitive function assessment: HVLT-R to assess learning and memory, TMT to assess processing speed and executive function, and the COWA (Controlled Oral Word Association test of the Multilingual Aphasia Examination) to assess verbal fluency [54]. The ICCTF also suggests including additional measures such as tests evaluating working memory [54]. Fourth, it is noted that the robustness of the findings of these studies is compromised by the small sample size and crossover design of three studies among the six included. Fifth, the lack of mean differences and standard deviations in three of the studies [44, 45, 50] and the failure to obtain these through the corresponding authors further limit to conclude that the evidence currently available is insufficient to recommend the use of psychostimulants in the management of cognitive disorders in cancer survivors. Moreover, QoL was a secondary outcome in two of the six studies and pooled data suggested that there was no impact of a psychostimulant on QoL associated with cognitive impairment. However, these two studies differ in their methodology, nature, and duration of the psychostimulant use [44, 51]. Given that improving the QoL of the participant was an integral part of these interventions, this hypothesis is worthy of further investigation. Finally, there was a risk of bias in all studies, of which two had a high risk of selective reporting bias [45, 50].

Overall, this systematic review suffers from the limitations imposed by the methodological flaws of the included studies, such as small sample sizes, crossover designs, and their inherent bias, missing data for the primary (cognitive function) and secondary (AEs) outcomes. Heterogeneity of these studies was too high for a reliable meta-analysis. Thus, the methodological flaws of the included studies diminish the strength of the recommendations that can be drawn from their results.

Our results are similar to those of other reviews already published. Two systematic reviews summarized pharmacological interventions to treat cancer patients with cognitive dysfunction [55, 56]. Another review reported interventions for preventing or improving cognitive deficits in adults treated with cranial irradiation [39] whereas another review investigated interventions for cognitive deficits in breast cancer survivors treated with chemotherapy [57]. The studies included in these reviews did not provide additional evidence. Similar conclusions were made, highlighting the fact that evidence is limited by significant methodological limitations. Nevertheless, our review offers a comprehensive, systematic, and highly sensitive search of the currently available literature on the administration of psychostimulants (methylphenidate, modafinil) in cancer survivors with cognitive impairment. We conducted a rigorous and detailed methodological analysis of the included studies and, in order to minimize errors and selection bias, two reviewers selected studies independently, with the high inter-evaluator agreement. Beyond the methodological flaws of the included studies, a major challenge in our systematic review along with others [39, 55–57] was the selection, identification, and definition of the primary outcome (cognitive impairment). Until now, no clear definition nor a diagnostic tool for cognitive deficits in cancer survivors is available [54]. We are aware that studies on cancer patients pose many practical problems, such as limited recruitment times, incomplete or interrupted monitoring of individuals, and inconsistencies in measurements. But, in order to obtain

sufficient evidence to estimate a true effect, if one exists, and the magnitude of the effect, future studies should include larger samples and an adequate control group. We also contend that cognitive function should be adequately measured at baseline and at different times along the intervention, since different patterns of cognitive dysfunction have been demonstrated between patient groups. In conclusion, the management of cognitive impairment in cancer survivors is a major challenge in oncology. To date, studies that have investigated the effects of psychostimulants on cognitive disorders in this population presented important methodological flaws rendering conclusive statements regarding their role as therapeutic agents. Therefore, well-designed clinical trials are still needed to further elucidate the precise role of this drug in the care of cancer survivors with cognitive impairment. Some evidence is also emerging from animal models [58, 59] and clinical trials [60, 61] that Donepezil, a neurotransmitter regulator used in the management of Alzheimer's disease, may contribute to improve cognitive function. For now, non-pharmacological strategies have been deemed as likely to be beneficial in management in CRCI. Several interventions were described in literature such as cognitive training [62–64], cognitive-behavioral training (CBT) [65–67], compensatory strategies [68], cognitive rehabilitation [69–72], mindfulness-based stress reduction (MBSR) [73, 74], and physical activity (qigong, tai chi, yoga) [15, 75–79]. Among these, CBT suggests the most benefits for CRCI treatment [15, 75]. Pending the approval and validation of pharmacological prescriptions, non-pharmacological interventions may be beneficial and worth considering for CRCI management.

Compliance with ethical standards

Conflict of interest The corresponding author (NM) received a scholarship from Université Laval. This study was not done on primary data. Original data can be obtained from the primary authors of articles part of this review.

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