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Guideline for the Management of Fatigue in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem Cell Transplantation Recipients

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KEY MESSAGES:

- Strong recommendations were made for the use of physical activity, relaxation and mindfulness to reduce fatigue.
- In settings where these recommended approaches are not feasible or were not successful, cognitive or cognitive behavioral therapies may be offered.
- Systemic pharmacological approaches should not be routinely used for the management of fatigue in children.
- Future research should identify optimal approaches to the successful and safe implementation of these interventions into clinical practice.

ABSTRACT

Fatigue is a prevalent and bothersome symptom experienced by children and adolescents with cancer and pediatric hematopoietic stem cell transplantation recipients. A multi-disciplinary and multi-national group of experts in pediatric oncology and fatigue, together with patient advocates, developed a clinical practice guideline (CPG) for fatigue management. The systematic reviews which provided the evidence base for this CPG included 6 pediatric and 456 adult randomized studies. Using the Grades of Recommendation Assessment, Development and Evaluation approach, strong recommendations were made for the use of physical activity, relaxation and mindfulness to reduce fatigue. Where these approaches are not feasible or were not successful, cognitive or cognitive behavioral therapies may be offered. Maturity and cognitive ability will influence intervention feasibility. Systemic pharmacological approaches should not be routinely used for the management of fatigue in children. Future research should identify optimal approaches to the successful and safe implementation of these interventions into clinical practice.

INTRODUCTION

Cancer-related fatigue (CRF) is a common and distressing condition in adults and children with cancer which reduces quality of life.[1] It occurs throughout the cancer trajectory,[2-5] and is related to cancer itself, treatments and comorbid conditions.[1, 6] Hematopoietic stem cell transplantation (HSCT) recipients also experience severe fatigue, likely related to similar underlying mechanisms.[7, 8] Specifically in pediatric cancer, approximately 50 to 76% will experience fatigue,[9-11] and a recent cross-sectional study identified that 33% of inpatient children receiving cancer treatments voiced severely bothersome fatigue.[12] Among pediatric patients receiving cancer treatments, fatigue may be particularly important among adolescents.[13, 14]

Many approaches have been studied for the management of fatigue in cancer patients, resulting in guidelines developed for adults.[1, 15] However, similar guidelines are not available for children in spite of its high prevalence in this group.[9-11] Our objective was to create a clinical practice guideline (CPG) for the management of fatigue in children and adolescents with cancer and pediatric HSCT recipients.

METHODS

A multi-disciplinary and multi-national panel was convened for the purpose of creating this guideline with representation from pediatric oncology, general pediatrics, exercise psychology, physical therapy, nursing, pharmacy, psychology, two pediatric cancer survivors and a guideline methodologist (see Appendix 1).

We followed well-accepted procedures for creating evidence-based CPGs.[16] Each member completed conflict of interest forms and no member had conflicts which precluded participation in this panel (Appendix 2). The guideline was editorially independent from the funding body, the Pediatric Oncology Group of Ontario. The key clinical question addressed by the CPG was as follows: what are effective interventions for the management of fatigue in children and adolescents with cancer or pediatric HSCT recipients? The CPG recommendations are intended for children and adolescents up to 18 years of age with cancer and undergoing HSCT. They apply to those on therapy, in survivorship and receiving palliative care. The target users are pediatric oncology and HSCT physicians, nurse practitioners, nurses, pharmacists, social workers, psychiatrists, psychologists, child life specialists, physical therapists and other healthcare professionals who manage fatigue in pediatric cancer and HSCT patients.

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to generate recommendations.[17] With this approach, recommendations may be strong or weak. Strong recommendations are made when benefits clearly outweigh the risks or vice versa. In the case of a strong recommendation for an intervention, almost all patients should receive the recommended intervention as a matter of policy. In contrast, weak recommendations are made when the benefits and risks of the intervention are uncertain or are closely matched. Costs and resources were considered in formulating recommendations.

The evidence base for this CPG consisted of randomized trials in both adults and children as the panel was aware of the paucity of randomized trials of fatigue management conducted in children alone. The panel felt that the construct of fatigue and the efficacy of interventions should be similar between adolescents and younger adults although acknowledged this assumption is weaker for younger children and older adults. The panel believed that using indirect adult randomized evidence with consideration of how findings may or may not be generalizable to children and adolescents was preferable to using pediatric observational data related to the potential for bias with non-randomized studies. Data in children were identified and discussed in the context of the overall evidence base. If recommendations relied upon adult trials, evidence quality was downgraded due to indirectness. Three systematic reviews that underpin this CPG have been published separately;[18-20] methodological approach details are presented within those publications. In brief, all steps in the systematic reviews were performed by two investigators including screening of titles and abstracts, review of full articles for eligibility and data abstraction. For all three reviews, one reviewer was a methodologist and physician (PDR) while the second was a pediatric oncology fellow (SO), pediatric nurse (DT), university student (ND or HD) or pediatric oncologist (LS). With the assistance of a library scientist, we searched for randomized trials indexed from 1980 to May 11, 2017 in the following electronic databases: MEDLINE, MEDLINE in-process, Embase, Cochrane Central Register of Controlled Trials, CINAHL and PsychINFO. The

search strategy included Medical Subject Heading terms and text words that identified patients with cancer or HSCT recipients who received an intervention to reduce fatigue. Appendix 3 shows the full search strategies. We included studies if: (1) participants had cancer or were HSCT recipients; (2) it was a fully published primary randomized trial with a parallel group design; and (3) it evaluated an intervention for the prevention or treatment of fatigue. Exclusion criteria were: (1) less than 75% of participants had cancer or were HSCT recipients; (2) fatigue was not an end-point or was reported as an adverse event; (3) intervention evaluated was direct cancer treatment; and (4) less than five participants were randomized to any study arm. Studies published in any language were evaluated.

Interventions were classified into major categories as follows: (1) physical activity (aerobic, resistance, flexibility or neuromotor); (2) systemic pharmacological agents; (3) non-physical activity mind and body practices (acupuncture or acupressure, mindfulness, relaxation, massage, energy therapies or energizing yogic breathing); (4) cognitive and behavioral therapies; and (5) others. Appendix 4 illustrates the specific approach to categorization and sub-categorization within each major category and how each intervention category and sub-category was defined. The primary outcome was self-reported fatigue severity at the end of the intervention period across the fatigue scales used in the primary studies. If required, instruments were rescaled such that higher scores reflected worse or more fatigue. Authors were contacted in the event of missing primary outcome fatigue data.

Effects were presented as the standardized mean difference (SMD) and the corresponding 95% confidence intervals (CI) where a SMD of 0·20 is a small effect, 0·50 is a medium effect, and 0·80 is a large effect.[21] We decided *a priori* to identify the most commonly used fatigue scales across all studies and to synthesize results by these instrument. For this analysis, effects were presented as the weighted mean difference (WMD) and the corresponding 95% CI. Synthesis was performed when there were at least three studies within a stratum. A SMD or WMD less than 0 indicated that the mean fatigue scores were lower (better) in the intervention group as compared to the control group. Effects were weighted by the inverse variance and a random effects model was used for all analyses as we anticipated heterogeneity in effects. Meta-analyses were conducted using Review Manager 5·2 (Cochrane Collaboration, Nordic Cochrane Centre). All tests of significance were two-sided, and statistical significance was defined as $P<0·05$.

Risk of bias was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[22] We evaluated sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors and attrition bias. We focused on adequate sequence generation and adequate allocation concealment for stratified analyses because of their potential impact on bias.[23] Publication bias was explored by visual inspection of funnel plots when at least 10 studies were available for synthesis.[22]

Evidence tables were created using synthesized results. These tables were reviewed and recommendations were debated in a series of conference calls. Iterations of the final CPG were circulated until all authors agreed with its content. A final revised version was not sent to external experts prior to submission for publication as the guideline panel contained much pediatric fatigue expertise. Instead, we used the peer-review process during manuscript submission as a rigorous and efficient approach to external review. A guideline update is planned in five years or sooner in the event of the publication of important new information.

EVIDENCE BASE, RECOMMENDATIONS AND EXPLANATIONS

Overall, 462 randomized studies met the eligibility criteria and provided the evidence base for this CPG. The flow diagram of study identification and selection is presented in Figure 1. Agreement in study inclusion between reviewers was almost perfect (kappa = 0·97, 95% CI 0·95 to 0·99). The Functional Assessment of Cancer Therapy (FACT) 13-item fatigue subscale was the most frequently used scale (Appendix 5). Table 4 presents the recommendations and provides key remarks. Knowledge gaps are presented as Table 5.

Recommendation 1: U*se physical activity to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients*
(Strong recommendation, Moderate quality of evidence)

Literature Review and Analysis: Full details may be found in Oberoi et al.[19] Table 1 illustrates that of the 170 randomized studies of physical activity, only one was conducted in children and adolescents; it evaluated aerobic activity.[24] Specific interventions studied were aerobic (n=76, 44·7%), neuromotor (includes yoga and tai chi, n=28, 16·5%), resistance (includes free weights and dumbbells, n=15, 8·8%) and combination (n=46, 27·1%). Control groups were usual care or wait list (n=131, 77·1%) and others (n=39, 22·9%). Table 2 shows that as a group, physical activity reduced the severity of fatigue when compared to all controls (SMD -0·49, 95% CI -0·60 to -0·37). When assessed using the FACT 13-item fatigue subscale, the magnitude of benefit was WMD -3·40 (95% CI -5·25 to -1·55).

We found that the effect of physical activity on fatigue severity reduction differed by the type of physical activity performed (P for interaction=0·01). The effect of resistance exercises (SMD -0·21, 95% CI -0·35 to -0·07) was significant but smaller as compared to aerobic (SMD -0·36, 95% CI -0·52 to -0·21), neuromotor (SMD -0·56, 95% CI -0·97 to -0·14), and combination (SMD -0·61, 95% CI -0·80 to -0·42). Table 3 shows that the effect of physical activity did not differ depending on type of cancer, whether the intervention was applied during treatment or following treatment completion, presence of fatigue at study enrollment (meaning fatigue was required for study eligibility, specific threshold level varied by study) or duration of intervention in weeks (dichotomized at median duration).

The panel made a strong recommendation that physical activity should be offered to children and adolescents for the management of fatigue based on the consistent benefit across patient and intervention characteristics in adults, universal availability, very low risk of harm, low costs and likelihood of other associated health benefits. The quality of evidence supporting this recommendation was down-graded to moderate based on indirectness. However, the panel noted that children and adolescents are a heterogeneous group and that the evidence is more direct for adolescents. It is challenging to encourage physical activity in infants. However, even young children can be encouraged to play and children receiving intensive chemotherapy and undergoing HSCT as young as 8 years of age can participate in yoga.[25] While a quantitative interaction by physical activity type was noted, since all modalities were effective, any of them could be offered to patients although aerobic, neuromotor or combination exercises may be more effective for fatigue reduction. In all cases, physical activity should be tailored to the specific needs of individual children and adolescents. Identifying approaches to the safe implementation of physical activity which considers age-specific preferences and abilities is an important knowledge gap (Table 5).

Recommendation 2: D*o not routinely use pharmacological approaches to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients*
(Strong recommendation, Moderate quality of evidence)

Literature Review and Analysis: Full details may be found in Tomlinson et al.[18] Table 1 summarizes the 117 included studies of systemic pharmacological agents. No children were included in any of the studies. Specific interventions studied were erythropoietins (n=31, 26·5%), stimulants (n=19, 16·2%), L-carnitine (n=6, 5·1%), corticosteroids (n=5, 4·3%), anti-depressants (n=5, 4·3%), appetite stimulants (n=3, 2·6%), and others (n=48, 41·0%). The comparison groups were placebo (n=75, 64·1%), usual care (n=26, 22·2%) and other pharmacological interventions (n=16, 13·7%). Only 35/117 (29·9%) studies could be included in any synthesis because of the requirement to present an estimate of central tendency (mean or median) and a measure of variability by randomized group, and to have at least three studies with such data within a stratum. The pharmacological agents with synthesizable end of intervention data were methylphenidate and modafinil or amodafinil; these agents were not effective in reducing fatigue severity in this analysis (Table 2).

Many of the studies included in the systemic pharmacological agent systematic review[18] evaluated change scores rather than end of intervention scores. This approach was distinct from the physical activity,[19] mind and body practices[18] and cognitive and behavioral therapies reviews where most included studies evaluated end of intervention scores. When evaluating change scores, erythropoietin significantly improved fatigue when compared to all controls (SMD -0·52, 95% CI -0·89 to -0·14). When restricted to studies that used the FACT 13-item fatigue subscale, the effect of erythropoietin was WMD -2·98 (95% CI -4·41 to -1·55). In contrast to the end of intervention scores, when evaluating change scores, methylphenidate significantly improved fatigue (SMD -0·36, 95% CI -0·56 to -0·15 and WMD -2·87, 95% CI -4·68 to -1·07 using FACT) while modafinil or armodafinil was not effective in any comparison (data not shown). Stratified analyses were not performed because of the insufficient number of synthesizable studies.

The panel made a strong recommendation against erythropoietin use for fatigue management in children and adolescents with cancer or pediatric HSCT recipients because of described adverse effects outside pediatric oncology including tumor protection and veno-thrombotic events,[26, 27] effect size which was smaller than the minimal clinically important difference by the FACT 13-item fatigue subscale of 3 to 3·5,[28] and lack of any randomized data in children. Similarly, the panel made a strong recommendation against use of methylphenidate for fatigue reduction because of adverse effects including sleep problems and decreased appetite,[29] effect size which was smaller than the minimal clinically important difference by FACT, and the lack of any randomized data in children for this indication. Given these observations and since other pharmacological approaches were not effective at reducing fatigue in adults, the panel made a strong recommendation that pharmacological agents should not be routinely used for the management of fatigue in children and adolescents. However, future randomized clinical trials should include children and adolescents when possible (Table 5).

Recommendation 3: *Use relaxation or mindfulness, or both, for children and adolescents with cancer or paediatric HSCT recipients who can participate in these approaches to manage fatigue (Strong recommendation, Moderate quality of evidence)*

Literature Review and Analysis: Full details may be found in Duong et al.[18] There were 55 studies included in the non-physical activity mind and body practices systematic review. While mind and body interventions include yoga and tai chi,[30] these neuromotor interventions were excluded in this systematic review as they were included in the physical activity review.[19] Thus, interventions were acupuncture or acupressure (n=12, 21·8%), mindfulness (n=11, 20·0%), relaxation techniques (n=10, 18·2%), massage therapy (n=6, 10·9%), energy therapies (n=5, 9·1%), energizing yogic breathing (n=3, 5·5%), and other interventions evaluated in one or two studies (n=8, 14·5%). Control groups were usual care or wait list (n=37, 67·3%), sham (n=11, 20·0%), and attention controls (n=2, 3·6%). Three exclusively pediatric studies (Table 1) evaluated acupressure, massage and acupressure plus massage.[31-33]

Table 2 shows that mindfulness (SMD -0·50, 95% CI -0·85 to -0·15) and relaxation techniques (SMD -0·94, 95% CI -1·61 to -0·27) significantly reduced the severity of fatigue. There were not enough studies that reported fatigue using the FACT 13-item fatigue subscale to determine WMDs for any intervention. Effects did not vary based upon patient or intervention characteristics (Table 3).

The panel made a strong recommendation for the use of relaxation, mindfulness or both based upon the consistent benefit across patient and intervention characteristics in adults, very low risk of harm and low costs. Further, the panel noted that these interventions can be used without assistance once learned. The quality of evidence was down-graded to moderate because of the limited data in children. The panel recognized that younger children may not be able to meaningfully participate in relaxation and mindfulness due to immaturity and cognitive ability. It is challenging to delineate a lower age limit at which these approaches should be considered as the abilities of individual children will vary. However, strategies to engage with younger children should be developed. Survivors of cranial irradiation may have additional difficulties with these strategies because of therapy-related cognitive adverse effects. Approaches to implement these interventions successfully in children and adolescents require further study (Table 5).

Recommendation 4: *In settings where other recommended approaches are not feasible or were not successful, cognitive or cognitive behavioural therapies may be offered to children and adolescents with cancer or paediatric HSCT recipients who can participate in these approaches*
(Weak recommendation, Moderate quality of evidence)

Literature Review and Analysis: There were 17 studies that evaluated cognitive or behavioral therapies for the management of fatigue (Table 1). Details of the studies are shown in Appendix 6; none included children. The studies consisted of cognitive behavioral therapy (n=14, 82·3%), cognitive behavioral therapy with hypnosis (n=2, 11·8%) and cognitive therapy alone (n=1, 5·9%). The intervention was delivered by psychologists (n=8, 47·1%), nurses trained to deliver the intervention (n=5, 29·4%), psychotherapists (n=2, 11·8%) and others (n=2, 11·8%). Control groups were usual care or wait list (n=11, 64·7%), attention control (n=4, 23·5%) and others (n=2, 11·8%).

Table 2 and Appendix 7 show that cognitive and cognitive behavioral therapies were effective in reducing the severity of fatigue (SMD -0·45, 95% CI -0·81 to -0·10). There were not enough studies reporting fatigue using the FACT 13-item fatigue subscale to report WMD. Table 3 illustrates that the effect did not vary based upon patient or intervention characteristics. No evidence of publication bias was observed in the funnel plot (data not shown).

While cognitive or cognitive behavioral therapies were effective in adult studies and have a low risk of harm, the panel made a weak recommendation for their use in children and adolescents. The recommendation was based upon the costs associated with the specialized training required for their implementation and ongoing utilization and lack of any randomized data in children. However, children and adolescents may benefit from this approach if physical activity, mindfulness and relaxation are not feasible or were not successful. Earlier implementation of cognitive or cognitive behavioral therapies may be warranted if trained professionals are accessible at an institution. Further, research has begun to investigate strategies that may reduce required resources, such as computer-based delivery of cognitive behavioral therapy, and may influence the future feasibility of these interventions if successful.

Other Interventions:
There were 107 studies classified in the “other” category; two studies were pediatric (Table 1). Characteristics of these studies are summarized in Table 1 and details are provided in Appendix 8. Most studies evaluated miscellaneous single interventions (n=28) or included 3 or more distinct components, which were termed multicomponent interventions (n=52). In terms of single intervention studies, the most common interventions were: symptom screening (n=7), nutrition-focused (n=4), music therapy (n=3) and cognitive rehabilitation training (n=3). Synthesis was not possible for any of these interventions either because there were fewer than three studies reporting outcome data or the interventions were too heterogeneous to synthesize. Appendix 9 illustrates the 52 multi-component studies and identifies which components were included in each study. Most studies included general education about fatigue or cancer and many included some form of physical activity. However, there were less than three studies that applied the same combination of interventions with outcome data available and thus synthesis was not performed. Determining the efficacy of combination approaches for the management of fatigue was identified as a knowledge gap (Table 5).

DISCUSSION
In this CPG focused on children and adolescents with cancer and pediatric HSCT patients, we made strong recommendations to use physical activity, mindfulness and relaxation for fatigue management. In implementing these recommendations, providers do not need to choose one intervention but can apply multiple approaches depending on the preferences of patients and families as well as the needs and abilities in individual circumstances. Developing tools to facilitate implementation of these recommendations into routine practice is an important knowledge gap.

For all interventions recommended in this CPG, it is of primary interest to know if a minimum age threshold should be applied when considering each intervention type. Unfortunately, given the paucity of the pediatric evidence base, it is neither possible to determine these minimum ages, nor to determine if program adaptations to accommodate younger patients affect intervention efficacy. Consequently, these are important knowledge gaps.

Implicit in these recommendations is that healthcare providers have a way to measure fatigue in children. While several instruments to measure fatigue in children have been developed and validated,[34, 35] repeated use in clinical practice will require a quick tool with a short recall period. A tool which has been validated for self-report in children as young as eight years of age is the Symptom Screening in Pediatrics Tool (SSPedi) and may be appropriate for clinical utilization.[12, 36, 37] Other multi-system assessment scales include the Memorial Symptom Assessment Scale,[10, 38] Advanced Symptom Management System[39] and the Symptom Distress Scale.[40]

The most important limitation of this CPG is the small number of identified randomized trials for fatigue management in pediatric patients. While recommendation will be more direct for older children and adolescents, recommendations are indirect for younger children and thus, more research is required. First, adapting interventions for younger children and evaluating feasibility is important. Second, measuring the efficacy of these adapted interventions is also needed. Another limitation of this CPG is that few of the randomized trials were conducted among HSCT recipients or explicitly among palliative care patients. While there is no reason to believe that these recommendations would not be applicable to these populations, more sub-group specific studies would be useful. Consequently, in general, high quality randomized trials for fatigue management in pediatric patients with cancer and HSCT recipients are required.

In conclusion, we present a CPG for fatigue management in children and adolescents with cancer and pediatric HSCT recipients. Future research should identify optimal approaches for the successful and safe implementation of these interventions into clinical practice.

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Table 1: Characteristics of Included Studies by Intervention Group

Characteristic	Physical Activity N=170	Pharm N = 117	Mind and Body N=55	Cognitive Behavioral N=17	Other N=107
Study Population					
Adults	169 (99·4%)	117 (100%)	52 (94·5%)	17 (100%)	105 (98·1%)
Children	1 (0·6%)	0 (0%)	3 (5·5%)	0 (0%)	2 (1·9%)
Type of Cancer*					
Breast	80 (47·1%)	18 (15·4%)	24 (43·6%)	11 (64·7%)	30 (28·0%)
Other single cancer type	45 (26·5%)	36 (30·8%)	7 (12·7%)	0 (0%)	17 (15·9%)
More than one cancer	45 (26·5%)	63 (53·8%)	24 (43·6%)	6 (35·3%)	56 (52·3%)
Stage of Cancer*					
Non-metastatic	93 (54·7%)	8 (6·8%)	27 (49·0%)	10 (58·8%)	29 (27·1%)
Metastatic	7 (4·1%)	5 (4·3%)	0 (0%)	1 (5·9%)	4 (3·7%)
Both	29 (17·1%)	61 (52·1%)	12 (21·8%)	1(5·9%)	30 (28·0%)
Included HSCT Recipients	13 (7·6%)	2 (1·7%)	4 (7·3%)	0 (0%)	5 (4·7%)
Timing of Intervention*					
During cancer treatment	93 (54·7%)	80 (68·4%)	32 (58·2%)	9 (52·9%)	52 (48·6%)
Following end of treatment	39 (22·9%)	15 (12·8%)	8 (14·5%)	6 (35·3%)	21 (19·6%)
Both during and following	36 (21·2%)	18 (15·4%)	11 (20·0%)	2 (11·8%)	22 (20·7%)
Not reported	2 (1·2%)	4 (3·4%)	4 (7·3%)	0 (0%)	12(11·2%)
Palliative Care Setting Only	2 (1·2%)	20 (17·1%)	2 (3·6%)	0 (0%)	6 (5·6%)
Fatigue at Enrollment	15 (8·8%)	28 (23·9%)	22 (40·0%)	3 (17·6%)	16 (15·0%)
Control Group Type					
Usual care or wait list	106 (62·3%)	26 (22·2%)	37 (67·3%)	11 (64·7%)	83 (77·6%)
Placebo or sham	0 (0%)	75 (64·1%)	11 (20·0%)	0 (0%)	7 (6·5%)
Attention control	25 (14·7%)	0 (0%)	2 (3·6%)	4 (23·5%)	3 (2·8%)
Other	39 (22·9%)	16 (13·7%)	5 (9·1%)	2 (11·8%)	14 (13·1%)
Risk of Bias Adequacy					
Sequence generation	109 (64·1%)	68 (58·1%)	28 (50·9%)	13 (76·5%)	67 (62·6%)
Allocation concealment	69 (40·6%)	41 (35·0%)	20 (36·4%)	10 (58·8%)	27 (25·2%)
Participants, personnel blinded	0 (0%)	44 (37·6%)	0 (0%)	0 (0%)	4 (3·7%)
Outcome assessors blinded	0 (0%)	55 (47·0%)	14 (25·5%)	0 (0%)	7 (6·5%)
Lack of attrition bias	103 (60·6%)	95 (81·2%)	42 (76·4%)	9 (52·9%)	30 (28·0%)
Free of selective reporting	119 (70%)	106 (90·6%)	52 (94·5%)	17 (100%)	84 (78·5%)

*May not add to total number of studies as some studies did not report all data elements.
Abbreviations: Pharm – pharmacological; HSCT – hematopoietic stem cell transplantation

Table 2: Effect of Interventions on Fatigue by Specific Intervention*

Outcome	No. of Studies	No. of Patients	SMD	95% CI	I^2 (%)	P Value
All Physical Activity Interventions	134	8927	-0·49	-0·60, -0·37	85	<0·00001
Aerobic	59	3624	-0·36	-0·52, -0·21	80	<0·00001
Neuromotor	24	1601	-0·56	-0·97, -0·14	93	0·008
Resistance	13	761	-0·21	-0·35, -0·07	0	0·004
Combination exercises	35	2803	-0·61	-0·80, -0·42	83	<0·00001
All Pharmacological Interventions	ND					
Methylphenidate	6	305	-0·32	-0·80, 0·17	73	0·20
Modafinil/amodafinil	5	905	-0·04	-0·17, 0·09	0	0·51
All Mind and Body Practices**	37	2808	-0·51	-0·73, -0·29	86%	<0·00001
Acupuncture and acupressure	7	462	-0·40	-0·86, 0·05	79%	0·08
Acupuncture	3	119	-0·13	-0·65, 0·39	40%	0·63
Acupressure	4	343	-0·60	-1·28, 0·09	87%	0·09
Mindfulness	7	807	-0·50	-0·85, -0·15	77%	0·005
Relaxation techniques	8	682	-0·94	-1·61, -0·27	93%	0·006
Energy therapy	5	189	0·08	-0·64, 0·80	82%	0·83
Energizing yogic breathing	3	201	-0·48	-1·06, 0·10	54%	0·10
Cognitive and Behavioral Interventions	13	1377	-0·45	-0·81, -0·10	90%	0·01

Abbreviations: ND – not done; SMD – standardized mean difference; CI – confidence interval
* Total number of studies is less than in Table 1 as not all studies presented data which could be synthesized
****Excludes neuromotor mind and body practices (included in physical activity)**

Table 3: P Values for Interaction Effects by Population and Methodological Factors*

Characteristic	Physical Activity	Mind and Body	Cognitive Behavioral
Type of Cancer**	0·09	ND	0·91
Timing During or Following Treatment	0·51	0·82	0·05
Fatigue at Enrollment	0·74	0·42	0·40
Intervention Duration in Weeks (Longer than Median)	0·22	0·78	0·47
Adequate sequence generation	0·52	0·91	0·54
Adequate allocation concealment	0·20	0·47	0·52

* Table shows P values for interaction which indicate whether the effect of the intervention differs by the characteristic evaluated. A P value > 0.05 suggests that the intervention is similarly effective among subgroups evaluated. Too few studies to evaluate pharmacological interventions
** Distribution of cancer types differed among systematic reviews

Table 4: Summary of Recommendations for the Management of Fatigue in Children and Adolescents with Cancer or Pediatric Hematopoietic Stem Cell Transplant Recipients and Remarks

Recommendations	Remarks
Use physical activity interventions to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients Strong recommendation Moderate quality of evidence	Strong recommendation based on consistent benefit across patient and intervention characteristics in adults, universal availability, very low risk of harm, low costs, and probable other associated health benefits We downgraded the quality of evidence to moderate because of the scarce data in children
Do not routinely use pharmacological approaches to manage fatigue in children and adolescents with cancer or paediatric HSCT recipients Strong recommendation Moderate quality of evidence	Erythropoietin and methylphenidate reduced fatigue in adults, but we made a strong recommendation against their use in children and adolescents on the basis of evidence of adverse effects outside paediatric oncology, small effect sizes (which might not be clinically important), and the absence of data from randomised trials in children Other pharmacological approaches did not effectively reduce fatigue in adults
Use relaxation or mindfulness, or both, for children and adolescents with cancer or paediatic HSCT recipients who can participate in these approaches to manage fatigue Strong recommendation Moderate quality of evidence	Strong recommendation based on consistent benefit across patient and intervention characteristics in adults, very low risk of harm, low costs, and potential for self-administration after training Ability to use mindfulness or relaxation, or both, depends on the patient's maturity and cognitive ability. We downgraded the quality of evidence to moderate because of the scarce data in children
In settings where other recommended approaches are not feasible or were not successful, cognitive or cognitive behavioural therapies may be offered to children and adolescents with cancer or paediatric HSCT recipients who can participate in these approaches Weak recommendation Moderate quality of evidence	Cognitive or cognitive behavioural therapies were efficacious in adult studies. However, we made a weak recommendation on the basis of the additional resources needed for implementation and use, and the absence of data from randomised trials in children Some children and adolescents might benefit from this approach when physical activity, mindfulness, and relaxation are not feasible or were not successful

Table 5: Identified Knowledge Gaps

Age-specific approaches to safe implementation of physical activity in children and adolescents with cancer or pediatric HSCT recipients
Determine characteristics of physical activity approaches which result in greater reduction in fatigue for children and adolescents with cancer or pediatric HSCT recipients
Inclusion of children and adolescents in pharmacological trials designed to reduce fatigue
Optimal approaches to implement relaxation, mindfulness or both in children and adolescents with cancer or pediatric HSCT recipients
Determine the feasibility of relaxation and mindfulness in young children and identify strategies to improve successful implementation in this population
Determine if symptom screening and feedback can improve fatigue
Determine the efficacy of integrated and multidisciplinary approaches for the management of fatigue
Determine the effectiveness of approaches to reduce fatigue in pediatric populations
Describe the cost effectiveness of different approaches for fatigue management in children and adolescents with cancer or pediatric HSCT recipients
Identify approaches to monitor self-reported fatigue in children and adolescents with cancer or pediatric HSCT
Determine minimum age thresholds at which interventions for fatigue management may be considered
Determine whether adaptations to accommodate younger children affect intervention efficacy to reduce fatigue

Abbreviation: HSCT – hematopoietic stem cell transplantation