This is the accepted Word version of the published article in Lancet Child and Adolescent Health currently available as an early view article at: [http://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(18)30059-2/abstract](http://www.thelancet.com/journals/lanchi/article/PIIS2352-4642%2818%2930059-2/abstract)

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

1Paula D. Robinson MD, MSc, 1Sapna Oberoi MD, 2Deborah Tomlinson MN, RN, 2Nathan Duong, 2Hailey Davis, 3Danielle Cataudella PsyD, CPsych, 4Nicole Culos-Reed PhD, 5Faith Gibson RN, RSCN, PhD, 6Miriam Götte PhD, 7Pamela Hinds RN, PhD, FAAN, 8Sanne L Nijhof MD, PhD, 8Patrick van der Torre MSc, 1Sandra Cabral, 2,9L. Lee Dupuis RPh, PhD and 2,10Lillian Sung MD, PhD

**AFFILIATIONS:**

1Pediatric Oncology Group of Ontario, 480 University Ave, Suite 1014, Toronto, ON, Canada, M5G 1V2

2Child Health Evaluative Sciences, The Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada, M5G 1X8

3Department of Pediatric Psychology, Children's Hospital, London Health Sciences Centre, 800 Commissioners Rd E, London, ON, Canada, N6A 5W9

4Faculty of Kinesiology, University of Calgary, 2500 University Dr NW, Calgary, AB, Canada, T2N 1N4

5Centre for Outcomes and Experiences Research in Children's Health, Illness, and Disability, Great Ormond Street Hospital for Children NHS Foundation Trust, London, and School of Health Sciences, University of Surrey, 388 Stag Hill, Guildford, UK, GU2 7XH

6University Hospital Essen, Center for Child and Adolescent Medicine, Department of Pediatric Hematology/Oncology, Hufelandstraße 55, 45147 Essen, Germany

7Department of Nursing Science, Professional Practice, and Quality, Children's National Health System, Washington, District of Columbia, USA; Department of Pediatrics, George Washington University, 111 Michigan Ave NW, Washington, DC, USA, 20010

8Division of Pediatrics, Wilhelmina Children's Hospital (part of UMC Utrecht), Utrecht University, Lundlaan 6, 3584 EA, Utrecht, Netherlands

9Department of Pharmacy, The Hospital for Sick Children, and Leslie Dan Faculty of Pharmacy, University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada, M5G 1X8

10Division of Haematology/Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada, M5G 1X8

**Corresponding Author:**

Lillian Sung MD, PhD

Division of Haematology/Oncology

The Hospital for Sick Children

555 University Avenue, Toronto, Ontario, M5G1X8

Telephone: 416-813-5287 Fax: 416-813-5979

Email: lillian.sung@sickkids.ca

**Key words:** practice guideline; fatigue; pediatric oncology; physical activity; mindfulness; relaxation; cognitive behavioral therapy

**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 pediatricpatients 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 review18 evaluated change scores rather than end of intervention scores. This approach was distinct from the physical activity,19 mind and body practices18 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*

*paediatic 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 System39 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.

**Acknowledgements**

Funding was provided by the Pediatric Oncology Group of Ontario. The funder did not have any influence over the content of this manuscript or the decision to submit for publication.

**Conflict of interest statement**

No authors declare a conflict of interest.

**Author contributions:**

Study concepts and design: PR, SO, DT, ND, HD, LS

Data acquisition: PR, SO, DT, ND, HD, SC, LS

Data analysis: PR, SO, DT, ND, HD

Data interpretation: All

Drafting the manuscript or revising it critically for important intellectual content: All

Final approval of version to be published: All

Agreement to be accountable for all aspects of the work: All

**References**

1. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-Related Fatigue, Version 2.2015. *J Natl Compr Canc Netw*. 2015 Aug;13(8):1012-39.

2. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer*. 2008 Jul;16(7):791-801.

3. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007;12 Suppl 1:4-10.

4. Wang XS, Zhao F, Fisch MJ, O'Mara AM, Cella D, Mendoza TR, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer*. 2014 Feb 01;120(3):425-32.

5. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol*. 2000 Feb;18(4):743-53.

6. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. *Br J Cancer*. 2004 Aug 31;91(5):822-8.

7. Tonosaki A. The long-term effects after hematopoietic stem cell transplant on leg muscle strength, physical inactivity and fatigue. *Eur J Oncol Nurs*. 2012 Dec;16(5):475-82.

8. Graef DM, Phipps S, Parris KR, Martin-Elbahesh K, Huang L, Zhang H, et al. Sleepiness, Fatigue, Behavioral Functioning, and Quality of Life in Survivors of Childhood Hematopoietic Stem Cell Transplant. *J Pediatr Psychol*. 2016 Jul;41(6):600-9.

9. Baggott C, Dodd M, Kennedy C, Marina N, Matthay KK, Cooper BA, et al. Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *J Pediatr Oncol Nurs*. 2010 Nov-Dec;27(6):307-15.

10. Collins JJ, Byrnes ME, Dunkel IJ, Lapin J, Nadel T, Thaler HT, et al. The measurement of symptoms in children with cancer. *J Pain Symptom Manage*. 2000 May;19(5):363-77.

11. Walker AJ, Gedaly-Duff V, Miaskowski C, Nail L. Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and one week after the administration of chemotherapy. *J Pediatr Oncol Nurs*. 2010 Sep-Oct;27(5):259-65.

12. Dupuis LL, Johnston DL, Baggott C, Hyslop S, Tomlinson D, Gibson P, et al. Symptom Screening in Pediatrics Tool (SSPedi) Is Reliable and Valid in Children with Cancer. *Journal of the National Cancer Institute*. 2017(in press).

13. Nowe E, Stobel-Richter Y, Sender A, Leuteritz K, Friedrich M, Geue K. Cancer-related fatigue in adolescents and young adults: A systematic review of the literature. *Crit Rev Oncol Hematol*. 2017 Oct;118:63-9.

14. Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, Barclay S. Teenage and Young Adult Cancer-Related Fatigue Is Prevalent, Distressing, and Neglected: It Is Time to Intervene. A Systematic Literature Review and Narrative Synthesis. *J Adolesc Young Adult Oncol*. 2015 Mar;4(1):3-17.

15. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014 Jun 10;32(17):1840-50.

16. Oxman AD, Fretheim A, Schunemann HJ. Improving the use of research evidence in guideline development: introduction. *Health Research Policy and Systems*. 2006;4:12.

17. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy*. 2009 May;64(5):669-77.

18. Duong N, Davis H, Robinson PD, Oberoi S, Cataudella D, Culos-Reed SN, et al. Mind and body practices for fatigue reduction in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis. *Critical Reviews in Oncology/Hematology*. 2017;120:210-6.

19. Oberoi S, Robinson PD, Cataudella D, Culos-Reid N, Davis H, Duong N, et al. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis of randomized trials. *Awaiting publication*.

20. Tomlinson D, Robinson PD, Oberoi S, Cataudella D, Culos-Reed N, Davis H, et al. Effect of pharmacological interventions on fatigue in patients with cancer and hematopoietic stem cell transplant recipients: A systematic review and meta-analysis of randomized trials *Current Oncology*. 2017(In press).

21. Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2 ed. Hillsdale, NJ,: Lawrence Erlbaum Associates Inc.; 1988.

22. Higgins JPT, S. Green, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.

23. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama*. 1995 Feb 01;273(5):408-12.

24. Hinds PS, Hockenberry M, Rai SN, Zhang L, Razzouk BI, Cremer L, et al. Clinical field testing of an enhanced-activity intervention in hospitalized children with cancer. *Journal of Pain & Symptom Management*. 2007 Jun;33(6):686-97.

25. Diorio C, Schechter T, Lee M, O'Sullivan C, Hesser T, Tomlinson D, et al. A pilot study to evaluate the feasibility of individualized yoga for inpatient children receiving intensive chemotherapy. *BMC Complement Altern Med*. 2015 Jan 24;15:2.

26. Dicato M, Plawny L. Erythropoietin in cancer patients: pros and cons. *Curr Opin Oncol*. 2010 Jul;22(4):307-11.

27. Hedley BD, Allan AL, Xenocostas A. The role of erythropoietin and erythropoiesis-stimulating agents in tumor progression. *Clin Cancer Res*. 2011 Oct 15;17(20):6373-80.

28. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage*. 2002 Dec;24(6):547-61.

29. Storebo OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2015 Nov 25(11):CD009885.

30. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011 Jul;43(7):1334-59.

31. Bastani F, Khosravi M, Borimnejad L, Arbabi N. The effect of acupressure on cancer-related fatigue among school-aged children with acute lymphoblastic leukemia. *Iran J Nurs Midwifery Res*. 2015 Sep-Oct;20(5):545-51.

32. Jacobs S, Mowbray C, Cates LM, Baylor A, Gable C, Skora E, et al. Pilot Study of Massage to Improve Sleep and Fatigue in Hospitalized Adolescents With Cancer. *Pediatr Blood Cancer*. 2016 May;63(5):880-6.

33. Mehling WE, Lown EA, Dvorak CC, Cowan MJ, Horn BN, Dunn EA, et al. Hematopoietic cell transplant and use of massage for improved symptom management: results from a pilot randomized control trial. *Evid Based Complement Alternat Med*. 2012;2012:450150.

34. Hinds PS, Nuss SL, Ruccione KS, Withycombe JS, Jacobs S, DeLuca H, et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. *Pediatr Blood Cancer*. 2013 Mar;60(3):402-8.

35. Tomlinson D, Hinds PS, Ethier MC, Ness KK, Zupanec S, Sung L. Psychometric properties of instruments used to measure fatigue in children and adolescents with cancer: a systematic review. *J Pain Symptom Manage*. 2013 Jan;45(1):83-91.

36. O'Sullivan C, Dupuis LL, Gibson P, Johnston DL, Baggott C, Portwine C, et al. Refinement of the symptom screening in pediatrics tool (SSPedi). *Br J Cancer*. 2014 Sep 23;111(7):1262-8.

37. O'Sullivan C, Dupuis LL, Gibson P, Johnston DL, Baggott C, Portwine C, et al. Evaluation of the electronic self-report Symptom Screening in Pediatrics Tool (SSPedi). *BMJ Support Palliat Care*. 2016 Nov 01.

38. Collins JJ, Devine TD, Dick GS, Johnson EA, Kilham HA, Pinkerton CR, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7-12. *J Pain Symptom Manage*. 2002 Jan;23(1):10-6.

39. Gibson F, Aldiss S, Taylor RM, Maguire R, McCann L, Sage M, et al. Utilization of the Medical Research Council evaluation framework in the development of technology for symptom management: the ASyMS-YG Study. *Cancer Nurs*. 2010 Sep-Oct;33(5):343-52.

40. Hinds PS, Schum L, Srivastava DK. Is clinical relevance sometimes lost in summative scores? *West J Nurs Res*. 2002 Jun;24(4):345-53.

**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** | **I2 (%)** | **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 recipientsStrong 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 benefitsWe 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 recipientsStrong recommendationModerate 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 childrenOther 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 fatigueStrong recommendationModerate 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 trainingAbility 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 approachesWeak recommendationModerate 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 childrenSome 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