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Patel, Priya, Robinson, Paula D, van der Torre, Patrick et al. (14 more authors) (2023) Guideline for the management of fatigue in children and adolescents with cancer or pediatric hematopoietic cell transplant recipients:2023 update. EClinicalMedicine. 102147. ISSN 2589-5370

https://doi.org/10.1016/j.eclinm.2023.102147

Guideline for the management of fatigue in children and adolescents with cancer or pediatric hematopoietic cell transplant recipients: 2023 update

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Summary

Objective was to update a clinical practice guideline (CPG) for the management of fatigue in children and adolescents with cancer or pediatric hematopoietic cell transplant recipients. We reconvened a multi-disciplinary and multi-national panel. While the previous 2018 CPG evaluated adult and pediatric randomized controlled trials (RCTs) to manage fatigue, this 2023 update revised previous recommendations based only on pediatric RCTs. Twenty RCTs were included in the updated systematic review. Physical activity significantly reduced fatigue (standardized mean difference –0.44, 95% confidence interval –0.64 to –0.24; n = 8 RCTs). Using the 2018 recommendations as a basis, the panel continued to make strong recommendations to use physical activity, and to offer relaxation, mindfulness or both, to manage fatigue in pediatric patients. Cognitive or cognitive behavioral therapies may be offered. Pharmacological approaches should not be routinely used. The panel made a new good practice statement to routinely assess for fatigue, ideally using a validated scale.

eClinicalMedicine 2023;63: 102147
Published Online 10 August 2023
https://doi.org/10.1016/j.eclinm.2023.102147

Keywords: Practice guideline; Fatigue; Pediatric oncology

Introduction

Fatigue is one of the most common severely bothersome symptoms in children and adolescents with cancer and pediatric hematopoietic cell transplant (HCT) recipients.[1–3] Fatigue can precede cancer diagnosis, emerge during cancer treatment and persist following completion of cancer therapy. Interventions for fatigue management have been evaluated[4–6]; however, they are rarely applied in routine clinical care.[7]

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Research in context

Evidence before this study

A clinical practice guideline (CPG) for the management of fatigue in children and adolescents with cancer or pediatric hematopoietic cell transplant recipients was developed in 2018.

Added value of this study

In this update of the 2018 CPG, 20 randomized controlled trials were included and formed the evidence base for this update. Using the 2018 recommendations as a basis, the panel continued to make strong recommendations to use physical activity, and to offer relaxation, mindfulness or both, to manage fatigue in pediatric patients. Cognitive or cognitive behavioral therapies may be offered. Pharmacological approaches should not be routinely used. The panel made a new good practice statement to routinely assess for fatigue, ideally using a validated scale.

Implications of all the available evidence

There is an increasing number of randomized trials conducted in pediatric cancer and HCT recipients, providing direct evidence to support recommendations. The new good practice statement to routinely assess for fatigue, ideally using a validated scale, is an important addition to this CPG update.

One way to improve the application of evidence-based care is the development and implementation of clinical practice guidelines (CPGs).[8,9] Thus, we created a CPG for the management of fatigue in children and adolescents with cancer and pediatric HCT recipients in 2018.[10] As with all CPGs, the fatigue CPG requires updating as new studies are published. Thus, the objective was to update the 2018 CPG for the management of fatigue in children and adolescents with cancer and pediatric HCT recipients.

Methods

Panel constitution

We re-convened a multi-disciplinary and multi-national panel with representation from the following groups: pediatric oncology, exercise medicine, physical therapy, nursing, pharmacy, psychology, two pediatric cancer survivors, and two guideline methodologists (see Appendix 1). Panel members were selected according to scientific expertise or lived experience from a patient perspective. Conflicts of interest are presented as Appendix 2; none precluded participation on this panel or required recusal from voting on specific recommendations.

CPG development approach

We followed standard approaches to develop the CPG.[8] The key clinical question to be addressed by the CPG remained unchanged from the 2018 CPG as follows: What are effective interventions for the management of fatigue in children and adolescents with cancer or pediatric HCT recipients? The CPG recommendations continue to be intended for pediatric patients 18 years of age or younger with cancer or HCT recipients. The scope includes patients with cancer on and off active therapy including those in survivorship. The target users continue to be pediatric oncology and HCT physicians, nurse practitioners, physician assistants, nurses, pharmacists, social workers, psychiatrists, psychologists, child life specialists, physical therapists, and other healthcare professionals who manage fatigue in the target population. Outcomes considered critical in formulating recommendations were severity of fatigue, intervention feasibility, and adverse effects.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to describe level of evidence and to generate recommendations.[9] Evidence quality was categorized as high, moderate, low, or very low based upon the degree of certainty of intervention effects in children and adolescents with cancer or pediatric HCT recipients.[9,11] Factors that reduced this certainty were imprecision, inconsistency, bias, and indirectness. Strong or conditional recommendations were created using this evidence base.[9] When making a strong recommendation for an intervention, its benefits clearly outweigh its potential downsides. In contrast, when making a strong recommendation against an intervention, its downsides clearly outweigh its potential benefits. Conditional recommendations were made when the benefits and downsides were more closely matched, or when there was considerable uncertainty about their benefits and downsides.

The panel also made a good practice statement.[12] These statements are appropriate when there is compelling indirect evidence from multiple sources that strongly support the action. One suggested approach to determine the appropriateness of a good practice statement is to ask whether the alternative action would be absurd or clearly not conform to ethical norms.[12]

The 2018 fatigue CPG was based upon a systematic review of 462 randomized controlled trials (RCTs) conducted in both adults and children as there were few RCTs conducted in pediatric patients at that time. In the 2018 fatigue CPG, the panel made strong recommendations for physical activity, relaxation and mindfulness, a conditional recommendation for cognitive or cognitive behavioral therapies, and a strong recommendation against the routine use of systemic pharmacological approaches to manage fatigue in pediatric patients.

We took a different approach for this 2023 CPG update. Given the large number of RCTs that

contributed to the 2018 recommendations, we presumed that direct, high-quality data would be required to substantially modify them. Thus, we restricted the evidence base for the 2023 CPG update to RCTs evaluating any strategy for the management of fatigue in children and adolescents with cancer or pediatric HCT recipients.

Search strategy and selection criteria

With the assistance of a library scientist, we searched the following databases: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, APA PsycINFO (OvidSP), Cochrane Library (Wiley), and CINAHL (EBSCOHost). The search strategy included approaches to identify randomized controlled trials of patients with cancer and HCT recipients evaluating strategies to manage fatigue. We included studies if: (1) at least 75% of participants had cancer or were HCT recipients; (2) the mean or median age of participants was 16 years or younger or, in the absence of this information, the study was categorized as a pediatric trial by authors; (3) each was a fully published primary RCT with a parallel group design; (4) an intervention was evaluated for the prevention or treatment of fatigue; and (5) publication occurred in or after 1980. We excluded studies for the following reasons: (1) fatigue was not an end point or was reported as an adverse event; (2) intervention was direct cancer treatment; and (3) fewer than five participants were randomized to any study group. There was no exclusion by language. Appendix 3 shows the full search strategy that included RCTs published from January 1980 to March 9, 2023.

Titles and abstracts of articles identified by the search strategy were independently screened by two reviewers (PP, PDR or VM) and potentially relevant articles were retrieved for full text evaluation. Eligibility criteria were applied to full text by two reviewers (PP, PDR or VM). In the event of disagreement, the reviewers met to come to consensus and if it could not be achieved, arbitration was by a third reviewer (PDR or LS). Appendix 4 shows the flow diagram of study identification, selection, and reasons for exclusion. Agreement in study inclusion was described using the Kappa statistic.[13]

Two reviewers (PP, PDR or VM) abstracted the data consisting of study-level characteristics, details of the intervention and control groups, outcomes, and risk of bias assessments. In the event of disagreement, the reviewers met to come to consensus and if it could not be achieved, arbitration was by a third reviewer (PDR or LS). Study-level characteristics were as follows: year of publication, country of study conduct, age of participants, cancer diagnosis, HCT recipient, whether presence of fatigue was an eligibility criterion for enrollment, study collection of biomarkers and number of randomized participants. We also abstracted details of the intervention and control groups, including whether the intervention was delivered at the individual or group level, intervention period in weeks, intervention duration in minutes, and total number of sessions. As in our 2018 fatigue CPG, interventions were classified by intervention type 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 cognitive behavioral therapies; and (5) others. Control groups were categorized as active control group if it was a potential intervention for fatigue (for example, different prescriptions of exercise), and non-active control group if it consisted of usual care, attention control, waitlist control, or sham control.

We also abstracted outcomes considered important to recommendation formulation: fatigue scores, adverse effects, and feasibility considerations. The primary outcome was self-reported fatigue severity post-intervention. To describe this, fatigue severity instruments were rescaled as needed such that higher scores reflected more (worse) fatigue. If fatigue severity data did not appear in the publication, authors were contacted and asked to provide the information. We also described the fatigue scale used and measurement time points. Finally, we used the Cochrane Collaboration's tool for assessing risk of bias.[14]

Statistical analysis

Synthesis was performed when there were at least three studies evaluating the same intervention type or same specific intervention. In terms of synthesis across an intervention type, we synthesized across physical activity and cognitive therapy interventions if there were at least three studies in either group. However, we decided *a priori* to not synthesize across all mind and body interventions or pharmacological agents because of anticipated differences between interventions. For example, we did not think it would be reasonable to combine the effects of different medications. Rather, for these intervention types, we only synthesized by specific intervention, such as specific medication.

As we anticipated different fatigue scales would be used, we decided *a priori* to synthesize data over all scales and present results as the standardized mean difference (SMD). For SMD interpretation, a SMD of 0.20 is a small effect, 0.50 is a medium effect, and 0.80 is a large effect.[15] If synthesis was possible using the same fatigue scale, we presented results as the weighted mean difference (WMD). A SMD or WMD less than 0 indicated that the intervention was better than control. For synthesis, effects were weighted by the inverse variance and a random effects model was used for all analyses as we anticipated heterogeneity in effects. Heterogeneity was depicted using the I^2. Publication bias was explored by visual inspection of funnel plots

when at least 10 studies were available for synthesis.[14] Tests of significance were two-sided, and statistical significance was defined as $P < 0.05$. Analysis was conducted using Review Manager 5.4.[16]

Formulating recommendations

We described pediatric RCTs included in the 2018 CPG and those newly added to this 2023 CPG update. Evidence tables including synthesized results were then created. Evidence was reviewed during one videoconference call held in March 2023. The proposals to leave recommendations unchanged, modify them, add new recommendations, or add good practice statements were drafted and voted upon by panel members. Consensus required at least 80% of panel members to agree with each statement. Draft versions of the recommendations and manuscript were circulated until approved by all authors.

As in our 2018 CPG, we used the publication peer-review process as an efficient approach to external review. We will update this CPG in five years or sooner in the event of important new information.

Role of funding source

This CPG was funded and developed through the Pediatric Oncology Group of Ontario (POGO) Guidelines Program. The development process and the CPG content were editorially independent from POGO.

Results

Table 1 presents the 2023 fatigue CPG update recommendations and notes changes from the 2018 fatigue CPG. Table 2 shows the characteristics of pediatric RCTs included in the 2018 CPG (n = 6), new RCTs included in the 2023 CPG update (n = 14) and the total number of RCTs contributing to the 2023 CPG update (n = 20). Agreement in study inclusion was perfect (Kappa = 1.0). Across all included RCTs, most studies (n = 18) were conducted during cancer treatment. There were 8 RCTs evaluating physical activity, 4 RCTs evaluating mind and body interventions, and 8 RCTs that were categorized as "other" interventions. Appendix 5 shows detailed characteristics of included pediatric RCTs by intervention type. The "other" intervention type category consisted of miscellaneous single interventions (n = 5) or interventions with multiple components (n = 3). Six RCTs were new to this update. Of the three multi-component intervention studies, all involved education about fatigue and some form of mind and body intervention; one RCT also included physical activity as one of the components. Appendix 6 describes outcomes by intervention type for individual RCTs. Appendix 7 shows the most frequently used fatigue scales across studies.

Table 3 shows that across all intervention types and specific interventions, only physical activity was amenable to synthesis. Due to the number of studies, publication bias could not be assessed. Table 4 describes knowledge gaps.

Recommendation 1

Use physical activity interventions to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, high quality evidence).

The strong recommendation to use physical activity interventions from the 2018 fatigue CPG was based upon a systematic review that included 170 RCTs of physical activity,[4] only one of which was conducted in children and adolescents.[17] Specific interventions evaluated 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%). In five (2.9%) studies, the type of physical activity was not specified. Physical activity reduced the severity of fatigue when compared to all controls across all scales (SMD –0.49, 95% CI –0.60 to –0.37), and when assessed using the FACT 13-item fatigue subscale (WMD –3.40 (95% CI –5.25 to –1.55).

In this 2023 fatigue CPG update, the systematic review now includes seven additional RCTs of physical activity conducted in pediatric cancer or HCT patients, or eight pediatric RCTs total. Several studies included very young children ranging from 3 to 7 years as the youngest participant. Appendix 5 shows the different types of exercise programs that were evaluated with seven delivered to individual patients and one delivered to groups. Most intervention sessions were 30–60 min with program length ranging from 6 to 26 weeks. Table 3 shows that across all scales, physical activity significantly reduced fatigue with a medium effect size (SMD –0.44, 95% CI –0.64 to –0.24; forest plot provided in Appendix 8). In terms of adverse effects, one study described three falls that did not lead to injury and muscle soreness following 7 out of 381 sessions (Appendix 6).[18] In terms of feasibility, two studies showed that exercise sessions were often cancelled or postponed for multiple reasons including medical issues, emerging contraindications, and lack of motivation (Appendix 6).[18,19]

As in the 2018 CPG, the panel made a strong recommendation to use physical activity interventions to manage fatigue in children and adolescents with cancer or pediatric HCT recipients based on the observed benefit in reducing fatigue, easy availability, low risk of harm, low costs, and likelihood of other associated health benefits. The quality of evidence supporting this recommendation was modified from moderate in the 2018 CPG, to high in this 2023 update based on the number of direct pediatric RCTs and evidence of benefit in pediatric patients.

It is reassuring that young children were included in the studies. However, challenges were observed with session delivery or program discontinuation due to

Recommendations	2023 update status and remarks
1. Use physical activity interventions to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, high quality evidence)	The quality of evidence was increased from moderate to high based on the number of pediatric RCTs and synthesized results showing that physical activity was effective at reducing fatigue in pediatric patients.
2. Do not routinely use pharmacological approaches to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, moderate quality evidence)	No new pediatric RCTs; the 2018 recommendation was maintained.
3. Offer relaxation, mindfulness, or both to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, moderate quality evidence)	One new RCT of relaxation including 34 pediatric patients was identified. Although it did not show a difference by intervention, the recommendation was unchanged given the findings of RCTs in adults showing the efficacy of relaxation and mindfulness. Since data supporting efficacy were indirect and derived solely from adult RCTs, evidence quality remained moderate.
4. In settings where strongly recommended approaches are not feasible or were not successful, consider offering cognitive or cognitive behavioral therapies to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (conditional recommendation, moderate quality evidence)	No new pediatric RCTs; the 2018 recommendation was maintained.
Good practice statement	
1. Routinely assess for fatigue, ideally using a validated scale, in children and adolescents with cancer or pediatric HCT recipients	This is a new good practice statement reflecting the importance of routine assessment to identify fatigue. The frequency of assessment will depend on setting and patient factors. Ideally, a validated scale would be used to track fatigue severity over time.

Abbreviations: HCT, hematopoietic cell transplantation; RCT, randomized controlled trial.

Table 1: **Summary of recommendations for the management of fatigue and changes from 2018 recommendations.**

Characteristic	Previous in 2018 CPG n (%)	New in 2023 CPG update n (%)	Total number RCTs n (%)
Number of studies	6	14	20
Study population setting			
Cancer			
Leukemia	2 (33)	2 (14)	4 (20)
More than one cancer	2 (33)	8 (57)	10 (50)
HCT	1 (17)	2 (14)	3 (15)
Both cancer and HCT	1 (17)	2 (14)	3 (15)
Timing of intervention			
During cancer treatment	6 (100)	12 (86)	18 (90)
Following end of cancer treatment	0 (0)	2 (14)	2 (10)
Fatigue eligibility criterion for enrollment	0 (0)	2 (14)	2 (10)
Intervention group type			
Mind and body	3 (50)	1 (7)	4 (20)
Physical activity	1 (17)	7 (50)	8 (40)
Other (including combination)	2 (33)	6 (43)	8 (40)
Control group type			
Usual care or wait list	5 (83)	9 (64)	14 (70)
Placebo or sham	1 (17)	0 (0)	1 (5)
Attention control	0 (0)	2 (14)	2 (10)
Other	0 (0)	3 (21)	3 (15)
Biomarker measurement	0 (0)	1 (7)	1 (5)
Risk of bias adequacy			
Sequence generation	4 (66)	11 (79)	15 (75)
Allocation concealment	2 (33)	7 (50)	9 (45)
Participants, personnel blinded	1 (17)	1 (7)	2 (10)
Outcome assessors blinded	1 (17)	6 (43)	7 (35)
Lack of attrition bias	4 (66)	9 (64)	13 (65)
Free of selective reporting	6 (100)	14 (100)	20 (100)

Abbreviations: CPG, clinical practice guideline; HCT, hematopoietic cell transplant; RCT, randomized controlled trial.

Table 2: **Characteristics of included pediatric randomized controlled trials of fatigue.**

Outcome	No. studies	No. patients	Effect measure	Effect[b]	95% CI	I^2 (%)	P value
Physical activity							
All physical activity interventions vs. any control							
All scales	8	607	SMD	−0.44	−0.64 to −0.24	24%	<0.0001
Fatigue scale (Chinese version)	3	453	WMD	−4.11	−6.97 to −1.25	80%	0.005
PedsQL multidimensional Fatigue scale[c]	3	91	WMD	−2.07	−7.12 to 2.97	0%	0.42
All physical activity interventions vs. non-active control[a]							
All scales	7	560	SMD	−0.48	−0.69 to −0.27	23%	<0.0001
Fatigue scale (Chinese version)	3	453	WMD	−4.11	−6.97 to −1.25	80%	0.005

Abbreviations: SMD, standardized mean difference; WMD, weighted mean difference; CI, confidence interval. [a]Non-active control defined as usual care, attention control, waitlist control or sham control. [b]A negative SMD or WMD suggests that the intervention is better than control at reducing fatigue severity. [c]Directionality of this scale was inverted for synthesis to be consistent with the other scales for WMD and to permit calculation of SMD.

***Table 3:* Effect of strategy on self-reported fatigue by intervention type.**

Optimal approaches to implement physical activity, relaxation or mindfulness in children and adolescents with cancer or pediatric HCT recipients, particularly among those who are medically unwell.
Feasible approaches to screen and monitor for fatigue during cancer treatment and following completion of therapy
Describe the cost effectiveness of different approaches for fatigue management in children and adolescents with cancer or pediatric HCT recipients
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: HCT, hematopoietic cell transplantation.

***Table 4:* Identified knowledge gaps.**

medical and non-medical reasons. Gaps in our knowledge that remain include determining the youngest patients in whom physical activity can be encouraged and determining approaches to successfully implement physical activity in a patient population that may be limited due to temporary or permanent health circumstances.

Recommendation 2

Do not routinely use pharmacological approaches to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, moderate quality evidence).

The original 2018 CPG recommendation was based upon a systematic review that identified 117 studies of systemic pharmacological agents for fatigue.[6] Methylphenidate and modafinil or amodafinil were not effective at reducing fatigue severity.[6] The panel made a strong recommendation against using systemic pharmacological agents because of the absence of clinically important benefits in any analysis and because of the potential for harm.

No RCTs were identified either in the 2018 CPG or in the 2023 CPG update that examined systemic pharmacologic approaches in the target population and thus, the panel maintained the 2018 recommendation.

Recommendation 3

Offer relaxation, mindfulness, or both to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (strong recommendation, moderate quality evidence).

The original 2018 CPG recommendation was based upon a systematic review of mind and body interventions for fatigue.[5] Among the 55 RCTs conducted in adults and children, specific interventions found to be effective were relaxation (n = 10 RCTs) and mindfulness (n = 11 RCTs). More specifically, the effects were as follows: relaxation techniques (SMD −0.94, 95% CI −1.61 to −0.27) and mindfulness (SMD −0.50, 95% CI −0.85 to −0.15). The 2018 CPG strong recommendation to use relaxation, mindfulness, or both was based upon consistent benefits across patient and intervention characteristics in adults, very low risk of harm, and low costs.

In the pediatric systematic review of RCTs, there were no studies of mindfulness and only one small study of relaxation (n = 34)[20] (Appendix 5). Although this pediatric study did not show a reduction in fatigue (Appendix 6), the original recommendation was maintained given the large body of evidence from adult RCTs demonstrating efficacy of relaxation to reduce fatigue. The level of evidence remained moderate because of indirectness. The age range of participants in the one pediatric RCT was not reported.[20] Thus, whether relaxation and mindfulness can be delivered to young children remains a knowledge gap (Table 4).

Recommendation 4

In settings where strongly recommended approaches are not feasible or were not successful, consider offering

cognitive or cognitive behavioral therapies to manage fatigue in children and adolescents with cancer or pediatric HCT recipients (conditional recommendation, moderate quality evidence).

The original 2018 CPG recommendation was based upon 17 RCTs evaluating cognitive or cognitive behavioral therapies for the management of fatigue.[10] Synthesis showed this intervention type reduced the severity of fatigue (SMD –0.45, 95% CI –0.81 to –0.10). The 2018 CPG conditional recommendation (rather than strong recommendation) to consider offering cognitive or cognitive behavioral therapies to manage fatigue was based upon the costs and resources required for intervention delivery and the lack of pediatric specific data. No RCTs were identified either in the 2018 CPG or in the 2023 CPG update that examined cognitive or cognitive behavioral approaches in the target population and thus, the 2018 recommendation was maintained.

Good practice statement 1

Routinely assess for fatigue, ideally using a validated scale, in children and adolescents with cancer or pediatric HCT recipients.

This statement is new to the 2023 fatigue CPG. Given the well documented prevalence of fatigue in pediatric patients receiving cancer treatments, the panel felt it was important to assess for fatigue during routine clinical care. At a minimum, the assessment should inquire about the presence of fatigue during clinical encounters. However, ideally, a validated scale should be used for fatigue assessment to allow tracking of fatigue severity over time. For clinical implementation, the scale will need to be short and easy for children and adolescents to complete. There are several validated instruments available including the Symptom Screening in Pediatrics Tool (SSPedi)[3] and Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue scale.[21] For patients enrolled on a clinical trial, the Pediatric Patient-reported Outcome-Common Terminology Criteria for Adverse Events (Pediatric PRO-CTCAE) is appropriate.[22] Approaches that facilitate self-report from young children will be required. Mini-SSPedi is valid for pediatric patient self-report for children as young as 4 years of age.[23] Co-SSPedi is a novel, structured, dyadic approach to pediatric patient symptom reporting in which children voice their perspectives first, and guardians enable and support symptom reporting by confirming or clarifying articulated symptoms.[24,25]

Discussion

In the 2023 fatigue CPG update, we found that the number of RCTs conducted in pediatric cancer and HCT recipients has increased notably providing direct evidence to support recommendations. The panel maintained the strong recommendations from the 2018 CPG to use physical activity and to offer relaxation, mindfulness or both, to manage fatigue in pediatric patients. Cognitive or cognitive behavioral therapies may be offered. Pharmacological approaches should not be routinely used. The panel also made a new good practice statement to routinely assess for fatigue, ideally using a validated scale. This addition is important to ensure patients are being screened for fatigue such that it is treated expeditiously to avoid long term consequences of untreated fatigue.

The meta-analysis demonstrated that physical activity was effective at reducing fatigue, which emphasizes why systematic reviews and meta-analysis (when appropriate) are a critical component of CPG creation. Although physical activity was effective, the nature of the intervention was heterogeneous and even among similar interventions such as exercise therapy, the specific program, duration and number of sessions varied. Thus, we cannot be more specific about which types of physical activity are more effective and which types are better suited for specific patient populations. This granularity should be the focus of future research.

A primary challenge continues to be identifying effective approaches to support CPG implementation and, more specifically, a CPG focused on fatigue. It is possible that institutions are more likely to prioritize CPGs focused on life-threatening supportive care issues such as infection, compared with those focused on symptoms. Even among symptoms, fatigue may be more likely to be neglected since it may not be observable. Moreover, clinicians are often not aware of the extent to which patients are bothered by fatigue.[7] Given its prevalence, systematic evaluation and implementation of interventions for fatigue management should be prioritized by institutions and individual health care professionals.[1] Implementation plans should include strategies to deliver recommended interventions to young children and pediatric patients who are unmotivated or limited in their ability to participate due to their medical circumstances.

In conclusion, we updated a CPG for fatigue management in children and adolescents with cancer and pediatric HCT recipients. It will be important to develop and evaluate CPG implementation strategies and to measure the impact of CPG-consistent care on fatigue outcomes.

Outstanding questions

An important question is how to best implement routine screening for fatigue in children and adolescents with cancer or pediatric hematopoietic cell transplant (HCT) recipients, particularly for those who are medically unwell. Another challenge is to identify effective approaches to support fatigue clinical practice guideline (CPG) implementation. In particular, it will be important to identify strategies to deliver recommended

interventions to young children and pediatric patients who are unmotivated or limited in their ability to participate due to their medical circumstances.

Contributors

Study concepts and design: PP, PDR, LS.

Data acquisition and verification: PP, PDR, VM.

Data analysis: PP, PDR.

Data interpretation: PP, PDR, PVDT, DT, JS, SO, JEM, PSH, MG, FG, ND, HD, SNCR, DC, VM, LLD, LS.

Drafting the manuscript or revising it critically for important intellectual content: PP, PDR, PVDT, DT, JS, SO, JEM, PSH, MG, FG, ND, HD, SNCR, DC, VM, LLD, LS.

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Agreement to be accountable for all aspects of the work: PP, PDR, PVDT, DT, JS, SO, JEM, PSH, MG, FG, ND, HD, SNCR, DC, VM, LLD, LS.

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Data sharing statement

The authors declare that all of the results of the systematic review used to inform the recommendations in this clinical practice guideline are presented within the article and appendices. No original study data are presented.

Declaration of interests

PSH received grants or research support from NIH; royalties or licenses from Lippincott; consulting fees from MSKCC and participated on the REACH Board at Nemours, Delaware.

SNCR received grants from CIHR, CCS and Kids Cancer Care-IMPACT.

LS is supported by the Canada Research Chair in Pediatric Oncology Supportive Care.

No other authors declared a conflict of interest.

Acknowledgements

This CPG was funded and developed through the Pediatric Oncology Group of Ontario Guidelines Program. We would like to thank Elizabeth Uleryk for conducting the literature search and Sandra Cabral for her research assistance.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102147.

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