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REVIEW ARTICLE

Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis

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ABSTRACT

Background Our objective was to determine whether, compared with control interventions, pharmacologic interventions reduce the severity of fatigue in patients with cancer or recipients of hematopoietic stem-cell transplantation (HSCT).

Methods For a systematic review, we searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, and PsychINFO for randomized trials of systemic pharmacologic interventions for the management of fatigue in patients with cancer or recipients of HSCT. Two authors independently identified studies and abstracted data. Methodologic quality was assessed using the Cochrane Risk of Bias tool. The primary outcome was fatigue severity measured using various fatigue scales. Data were synthesized using random-effects models.

Results In the 117 included trials (19,819 patients), the pharmacologic agents used were erythropoietins ($n = 31$), stimulants ($n = 19$), L-carnitine ($n = 6$), corticosteroids ($n = 5$), antidepressants ($n = 5$), appetite stimulants ($n = 3$), and other agents ($n = 48$). Fatigue was significantly reduced with erythropoietin [standardized mean difference (SMD): −0.52; 95% confidence interval (CI): −0.89 to −0.14] and with methylphenidate (SMD: −0.36; 95% CI: −0.56 to −0.15); modafinil (or armodafinil) and corticosteroids were not effective.

Conclusions Erythropoietin and methylphenidate significantly reduced fatigue severity in patients with cancer and in recipients of HSCT. Concerns about the safety of those agents might limit their usefulness. Future research should identify effective interventions for fatigue that have minimal adverse effects.

Key Words Pharmacologic agents, fatigue, meta-analyses, drugs, cancer-related fatigue, erythropoietin, stimulants, corticosteroids

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INTRODUCTION

Cancer-related fatigue is increasingly being recognized as one of the most important symptoms in patients with cancer [1,2]. It has been described as an unexpected tiredness that is more intense and severe than the fatigue experienced in healthy people [3]. Cancer-related fatigue can affect up to 80%–90% of cancer patients, and it can occur before diagnosis, during cancer treatment, and after completion of cancer therapies [1,4–9]. The origin of cancer-related fatigue is multifactorial: it can be a result of the cancer itself, of cancer treatments, and of comorbid medical and psychological conditions [10,11]. Recipients of hematopoietic stem-cell transplantation (HSCT) also experience fatigue, likely related to similar underlying mechanisms [12,13].

Interventions including physical activity and psychological and pharmacologic approaches have been investigated for the management of fatigue in cancer patients, and several systematic reviews have been published [14–22]. The evaluation of pharmacologic interventions is particularly important, because medications can be associated with adverse effects and high costs. Thus, a good understanding of the benefits and risks are necessary to guide decision-making. However, the systematic reviews of pharmacologic interventions published to date had restrictive inclusion and exclusion criteria, limiting the number of

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studies included [18,22]. The reviews therefore lacked precision in their estimates of treatment effects and had limited power to identify effective interventions.

Our primary objective was to determine whether, compared with control interventions, pharmacologic interventions reduce the severity of fatigue in patients with cancer or in recipients of HSCT.

METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for the systematic review [23]. A search for eligible randomized trials indexed from 1980 to 11 May 2017 was conducted in the MEDLINE, MEDLINE in-process, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, and PsycINFO electronic databases. The search strategy included MESH terms and text words that identified patients with cancer or recipients of HSCT who received an intervention to reduce fatigue. Table I shows the full search strategy.

Study Selection and Data Abstraction

Inclusion and exclusion criteria were defined *a priori*. Studies were included if participants were adults or children with cancer or recipients of HSCT and if the study was a fully published primary randomized or quasi-randomized trial with a parallel-group design that evaluated a pharmacologic intervention for the management of fatigue.

Studies were excluded if fewer than 75% of the participants had cancer or were undergoing HSCT, if fatigue was not an endpoint or was reported as an adverse effect, if the intervention was direct cancer treatment, and if fewer than 5 participants were randomized to any study arm. Inclusion was not restricted by language. For the purpose of the analysis, studies were limited to those using a systemically administered pharmacologic agent. Studies using non-systemically administered pharmacologic agents were excluded, as were studies in which only education or advice was provided.

Two reviewers (PDR and SO or LS) independently evaluated the titles and abstracts of publications identified by the search. Any publication considered potentially relevant by at least one reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this meta-analysis was determined by agreement of two reviewers (PDR and SO or LS). Discrepancies between the two reviewers were resolved by consensus and adjudication by a third reviewer if required (LLD or LS). The kappa statistic was used to evaluate agreement for study inclusion between the two reviewers. Strength of agreement was defined as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00) [24].

Data were abstracted in duplicate by two reviewers (DT and PDR) and any discrepancies were resolved by consensus. We contacted authors of manuscripts when publications were missing data for the primary fatigue outcome.

Outcomes

The primary outcome was severity of self-reported fatigue using various fatigue scales. Change scores and end-of-intervention scores were both evaluated. For studies that

TABLE I Search strategies

Database	Set	History
MEDLINE, 1946 to Week 1, May 2017		
	1	fatigue/ or (fatigue or fatigued).ti,ab,kf.
	2	exp neoplasms/ or stem cell transplantation/ or cord blood stem cell transplantation/ or hematopoietic stem cell transplantation/ or mesenchymal stem cell transplantation/ or peripheral blood stem cell transplantation/ or bone marrow transplantation/ or transplantation, autologous/ or exp antineoplastic agents/ or chemotherap*.mp. or exp antineoplastic protocols/ or (cancer* or neoplas* or oncolog* or tumor* or tumour* or transplant* or chemotherap*).mp.
	3	randomized controlled trial.pt.
	4	controlled clinical trial.pt.
	5	randomized.ab.
	6	randomised.ab.
	7	randomly.ab.
	8	(trial or trials).ti,ab.
	9	or/3–8
	10	1 and 2 and 9
	11	limit 10 to yr="1980 -Current"
	12	limit 11 to humans
MEDLINE in-process and other non-indexed citations, 10 May 2017		
	1	(fatigue or fatigued).ti,ab,kw.
	2	(neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp.
	3	(hsct or bmt or chemotherap* or (antineoplas* adj2 protocol*) or (antineoplas* adj2 (agent* or drug or treatment*))).mp.
	4	or/2–3
	5	(RCT or RCTS).ti,ab.
	6	randomized.ab.
	7	randomised.ab.
	8	randomly.ab.
	9	(trial or trials).ti,ab.
	10	or/5–9
	11	1 and 4 and 10
EMBASE, 1980 to Week 19, 2017		
	1	*fatigue/ or (fatigue or fatigued).ti,ab,kw.
	2	exp neoplasm/ or exp antineoplastic agent/ or (antineoplas* adj2 protocol*).mp.
	3	(neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant* or chemotherap*).mp.
	4	or/2–3
	5	1 and 4
	6	cancer fatigue/ or (cancer* adj2 fatigue*).ti,ab,kw.
	7	5 or 6
	8	limit 7 to (randomized controlled trial or controlled clinical trial)
	9	(randomized or randomised or randomly).ab.
	10	(trial or trials).ti,ab.
	11	or/9–10
	12	8 or (7 and 11)
	13	limit 12 to conference abstract
	14	12 Not 13
	15	limit 14 to human

TABLE I Continued

Database	Set	History
PsycINFO, 1806 to Week 1, May 2017		
	1	fatigue/ or (fatigue or fatigued).ti,ab,id.
	2	exp neoplasms/ or chemotherapy/ or exp antineoplastic drugs/
	3	((“stem cell*” or “stem-cell*” or “cord blood” or “bone marrowor autologous”) adj3 transplant*).mp.
	4	(cancer* or neoplas* or oncolog* or tumor* or tumour* or transplant* or chemotherap*).mp.
	5	or/2–4
	6	1 and 5
	7	limit 6 to “0300 clinical trial”
	8	randomized.ab.
	9	randomised.ab.
	10	randomly.ab.
	11	(trial or trials).ti,ab.
	12	(RCT or CCT).ti,ab.
	13	clinical trials/
	14	or/8–13
	15	7 or (6 and 14)
	16	limit 15 to yr=“1980 -Current”
Cochrane Central Register of Controlled Trials, Issue 5, 12 May 2017		
	1	MeSH descriptor: [Fatigue] this term only
	2	(fatigue or fatigued):ti,ab
	3	(or #1-#2)
	4	MeSH descriptor: [Neoplasms] explode all trees
	5	MeSH descriptor: [Antineoplastic Agents] explode all trees
	6	MeSH descriptor: [Antineoplastic Protocols] explode all trees
	7	(neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant* or chemotherap*):ti,ab
	8	(or #4-#7)
	9	#3 and #8 Publication Year from 1980 to 2017
CINAHL, 1983 to 11 May 2017		
	1	(MH “Cancer Fatigue”) OR (MH “Fatigue”)
	2	TI (fatigue OR fatigued) OR AB (fatigue OR fatigued)
	3	1 OR 2
	4	(MH “Neoplasms+”) OR (MH “Antineoplastic Agents+”) OR (MH “Antineoplastics, ImmuNosuppressives”)
	5	TX (antineoplastic N2 protocol*)
	6	(MH “ImmuNocompromised Host”)
	7	4 OR 5 OR 6
	8	3 AND 7
	9	(MH “Double-Blind Studies”) OR (MH “Randomized Controlled Trials”) OR (MH “Triple-Blind Studies”) OR (MH “Single-Blind Studies”)
	10	AB randomized or randomised or randomly or trial or trials
	11	9 OR 10
	12	8 AND 11

used more than one fatigue scale, we *a priori* defined a hierarchy, based on prevalence, for the inclusion of scales in the analysis. Table II shows the prevalence of the scales reported in our systematic review.

The secondary outcome was the severity of self-reported fatigue using the most common fatigue scale (determined after all scales had been categorized).

Intervention and Control Groups

The intervention was any systemically administered pharmaceutical agent. In studies with more than two arms, the least “active” agent (for example, placebo, usual care, or lowest dose) was used as the control group. Where multiple pharmacologic agents were evaluated, the “intervention group” was the highest dose or the most commonly evaluated intervention (determined after all interventions had been abstracted and categorized).

We categorized the control group type as placebo, usual care, or other pharmacologic intervention.

Study Covariates

Study-level variables included age of the participants (adult or child), cancer diagnosis (breast, lung, other single cancer type, or more than one cancer type), inclusion of HSCT patients, timing of the intervention (during cancer treatment, after completion of treatment, or both during and after treatment), exclusive enrolment of palliative care patients (as defined by each study), presence of fatigue as an eligibility criterion for enrolment (as defined by each study), and duration of intervention [<8 weeks, ≥8 weeks, or variable (based on median duration reported by each study)]. We also evaluated the methodologic aspects of the studies.

Risk-of-Bias Assessment

We used the Cochrane Collaboration tool for assessing the risk of bias in randomized trials [25]. We evaluated sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, and attrition bias. Because of their potential effect on bias, adequate sequence generation and adequate allocation concealment were prioritized *a priori* for the stratified analyses [26].

Data Analysis

For this meta-analysis, we combined data at the study level and not at the individual patient level. All synthesized outcomes were continuous. For fatigue scores with missing summary measures, we made these assumptions to facilitate data synthesis: the mean can be approximated by the median; the range contains 6 standard deviations; the 95% confidence interval (CI) contains 4 standard errors; and the interquartile range contains 1.35 standard deviations. Where required, instruments were rescaled such that higher scores reflected more fatigue. We synthesized outcomes when data from at least three studies within a stratum were available.

For the primary outcome of severity of fatigue for all fatigue scales, data were synthesized using the standardized mean difference (SMD). For the secondary outcome of the most commonly used fatigue scale, data were synthesized

TABLE II Self-report fatigue assessment scales used in the included trials[a]

Fatigue scale	Studies (*n*)	Score range	Interpretation of higher score
Functional Assessment of Cancer Therapy[b] (13-item fatigue subscale)	55	0–52	Less fatigue
EORTC QLQ-C30 (fatigue subscale)	23	0–100	More fatigue
Brief Fatigue Inventory[c]	23	0–10	More fatigue
Profile of Mood States[d] (fatigue subscale)	11	0–28	More fatigue
Visual Analog Scale	8	0–10	More fatigue
Number Rating Scale	7	0–10	More fatigue
Edmonton Symptom Assessment System (fatigue subscale)	4	0–10	More fatigue
Multidimensional Fatigue Symptom Inventory–Short Form	4	NA	More fatigue
Multidimensional Assessment of Fatigue (revised Piper Fatigue Scale)	3	1–50	More fatigue
Multidimensional Fatigue Inventory-20	2	4–20	More fatigue
Others (used in 1 study each)	16	—	—

[a] Some studies used more than one fatigue scale.
[b] FACIT.org, Elmhurst, IL, U.S.A.
[c] MD Anderson Cancer Center, Houston, TX, U.S.A.
[d] MHS Assessments, Toronto, ON.
EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = 30-question core Quality of Life Questionnaire; NA = not available.

using the weighted mean difference (WMD). A SMD or WMD less than 0 indicates that the mean fatigue scores were lower (better) in the intervention group than in the control group. Effect sizes were weighted using the inverse variance method. Given an anticipation of heterogeneity between the studies, a random-effects model was used for all analyses. Statistical heterogeneity between the trials was assessed using the I^2 value, which describes the percentage total variation for all studies attributable to heterogeneity rather than to chance.

For the primary analysis, individual pharmacologic intervention groups were compared with all control groups using all fatigue severity scales. Change scores and end-of-intervention scores were both evaluated. Where possible, interventions were also evaluated against placebo. A secondary analysis evaluating the most commonly used fatigue severity scale was similarly conducted.

Potential publication bias was explored by a visual inspection of funnel plots when at least 10 studies were available for synthesis [25]. In the event of potential publication bias, the ''trim and fill'' technique was used to determine the effect of such bias [27]. In that technique, outlying studies are deleted, and hypothetical negative studies with equal weight are created.

Meta-analyses were conducted using Review Manager (version 5.2: Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). All tests of significance were two-sided, and statistical significance was defined as $p < 0.05$.

RESULTS

Figure 1 presents the flow diagram of study identification and selection. The search strategy identified 11,793 citations, of which 617 were retrieved for full-text evaluation. Within those 617 citations, 117 studies met the eligibility criteria and were included in the systematic review. Figure 1

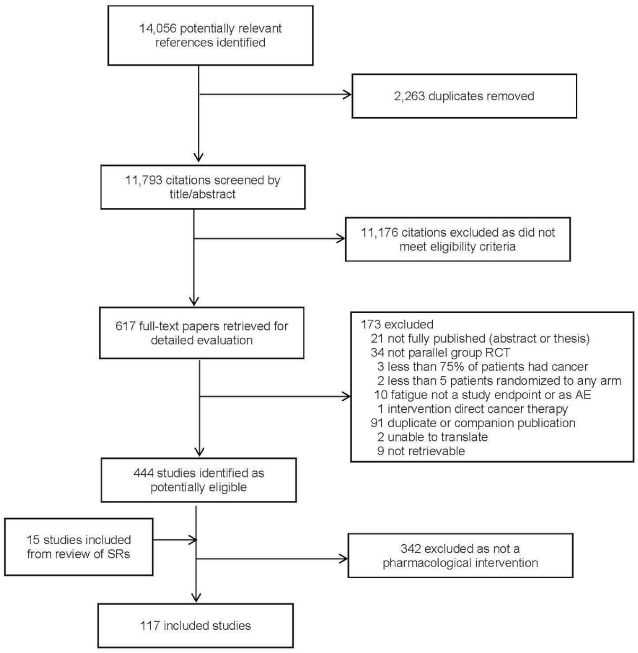

FIGURE 1 Study identification and selection, and reasons for study exclusion. RCT = randomized controlled trial; AE = adverse event; SRs = systematic reviews.

indicates the reasons for exclusions. Agreement for study inclusion was almost perfect between the two reviewers (kappa: 0.97; 95% CI: 0.95 to 0.99).

Tables III and IV present the characteristics and details of the 117 included studies, which were conducted in more than 30 countries. Most of the studies (69.2%) were published during or after 2007. All were conducted exclusively in adults; no pediatric patients were included in any study. Breast cancer (15.4%) was the most common cancer

TABLE III Characteristics of 117 studies included in the systematic review

Characteristic	Value [*n* (%)]
Study population	
Adults	117 (100)
Children	0
Cancer diagnosis	
Breast	18 (15.4)
Lung	11 (9.4)
Other single cancer type	25 (21.4)
More than one cancer type	63 (53.8)
Included HSCT recipients	2 (1.7)
Timing of intervention	
During cancer treatment	80 (68.4)
After treatment completion	15 (12.8)
Both during and after treatment	18 (15.4)
Not reported	4 (3.4)
Palliative care setting only	20 (17.1)
Required fatigue for eligibility	28 (23.9)
Pharmaceutical company sponsor	42 (35.9)
Duration of intervention	
<8 Weeks	43 (36.8)
≥8 Weeks	57 (48.7)
Variable	17 (14.5)
Intervention type	
Erythropoietins	31 (26.5)
Stimulants	19 (16.2)
L-Carnitine	6 (5.1)
Corticosteroids	5 (4.3)
Antidepressants	5 (4.3)
Appetite stimulants	3 (2.6)
Other agents	48 (41.0)
Route of administration	
Oral	67 (57.3)
Subcutaneous	36 (30.8)
Intravenous	13 (11.1)
Intramuscular	1 (0.9)
Control group type	
Placebo	75 (64.1)
Usual care	26 (22.2)
Other pharmacologic	16 (13.7)
Low risk of bias	
Adequate sequence generation	68 (58.1)
Adequate allocation concealment	41 (35.0)
Participants and personnel blinded	44 (37.6)
Outcome assessors blinded	55 (47.0)
Lack of attrition bias	95 (81.2)
Free of selective reporting	106 (90.6)

HSCT = hematopoietic stem-cell transplantation.

diagnosis studied. Twenty studies (17.1%) were conducted exclusively in the palliative care setting.

The pharmacologic interventions studied were erythropoietins (*n* = 31, 26.5%), stimulants (*n* = 19, 16.2%), L-carnitine (*n* = 6, 5.1%), corticosteroids (*n* = 5, 4.3%), antidepressants (*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 pharmacologic interventions (*n* = 16, 13.7%).

Table II lists all the fatigue assessment scales used in the various studies. The scale most commonly used was the Functional Assessment of Cancer Therapy (FACT) 13-item fatigue scale (FACIT.org, Elmhurst, IL, U.S.A.). Of all the studies included in our systematic review, only 35 (29.9%) could be included in any synthesis because of the requirements that an estimate of central tendency (mean or median) and a measure of variability be presented and that at least three studies with such data be included within a stratum. The pharmacologic agents for which synthesizable data were available were erythropoietins, stimulants, and corticosteroids.

Table V shows the effects of the evaluable pharmacologic agents by either change scores or end-of-intervention score. In evaluating erythropoietin, only change scores could be evaluated because too few studies reported end-of-intervention scores for any analysis. Compared with all controls and placebo, erythropoietin significantly improved fatigue. Compared with all controls, its SMD was –0.52 (95% CI: –0.89 to –0.14). When the comparison was restricted to studies that reported fatigue using the FACT, fatigue was significantly improved in patients receiving erythropoietin compared with all control patients (WMD: –2.98; 95% CI: –4.41 to –1.55).

Table V also shows the effect of stimulants compared with all control treatments and with placebo. As a group, stimulants were not effective for improving change or end-of-intervention fatigue scores. However, when stratified by specific agent, methylphenidate was associated with a significant improvement in fatigue (SMD: –0.36; 95% CI: –0.56 to –0.15; and WMD: –2.87; 95% CI: –4.68 to –1.07); modafinil (or armodafinil) was not effective in any comparison. Corticosteroids were not associated with improvement in fatigue (Table V).

Given the small number of studies having data available for synthesis, stratified analyses could not be conducted for L-carnitine, antidepressants, and appetite stimulants. All other agents were examined in only one or two studies, and thus data synthesis was not possible (see Table IV). Figure 2 presents the funnel plot for erythropoietin compared with all controls; no evidence of publication bias was observed.

DISCUSSION

In the present systematic review and meta-analysis, erythropoietin and methylphenidate were found to be associated with significant improvements in fatigue for patients with cancer and for recipients of HSCT; modafinil (or armodafinil) and corticosteroids were not found to be effective. Also, despite a very large number of randomized trials, data synthesis was limited. Most interventions were studied only

TABLE IV Details of the 117 included studies

Agent category and reference	Age (years)	Cancer diagnosis	Timing	HSCT	Fatigue eligibility	Intervention	Control
Erythropoietins							
Johansson *et al.*, 2001 [28]	NR	Prostate cancer	Both	No	No	Epoetin beta	Epoetin beta
Littlewood *et al.*, 2001 [29]	18.7–88.6	>1 Type	On therapy	No	No	Epoetin alfa	Placebo
Osterberg *et al.*, 2002 [30]	28–86	>1 Type	On therapy	No	No	Epoetin beta	Placebo
Vansteenkiste *et al.*, 2002 [31]	36–80	Lung cancer	On therapy	No	No	Darbepoetin alfa	Placebo
Boogaerts *et al.*, 2003 [32]	24–85	>1 Type	On therapy	No	No	Epoetin beta	Usual care
Glaspy *et al.*, 2003 [33]	NR	>1 Type	On therapy	No	No	Darbepoetin alfa	rHuEPO
Glossmann *et al.*, 2003 [34]	19–65	Lymphoma	On therapy	No	No	Epoetin beta	Placebo
Iconomou *et al.*, 2003 [35]	33–85	>1 Type	On therapy	No	No	rHuEPO	Usual care
Kotasek *et al.*, 2003 [36]	NR	>1 Type	On therapy	No	No	Darbepoetin alfa	Placebo
Smith *et al.*, 2003 [37]	NR	>1 Type	Off therapy	No	No	Darbepoetin alfa	Placebo
Chang *et al.*, 2004 [38]	27–85	Breast cancer	On therapy	No	No	Epoetin alfa	Usual care
Leyland Jones *et al.*, 2005 [39]	24–84	Breast cancer	On therapy	No	No	Epoetin alfa	Placebo
O'Shaughnessy *et al.*, 2005 [40]	42–64	Breast cancer	On therapy	No	No	Epoetin alfa	Placebo
Witzig *et al.*, 2005 [41]	20–88	>1 Type	On therapy	No	No	Epoetin alfa	Placebo
Littlewood *et al.*, 2006 [42]	NR	Lymphoma	On therapy	No	No	Darbepoetin alfa	Placebo
Morishima *et al.*, 2006 [43]	22–79	>1 Type	On therapy	No	No	Epoetin beta	Epoetin beta
Norager *et al.*, 2006 [44]	59–68	Colon cancer	On therapy	No	No	Darbepoetin alfa	Placebo
Savonije *et al.*, 2006 [45]	46–68	>1 Type	On therapy	No	No	Epoetin alfa	Usual care
Straus *et al.*, 2006 [46]	20–88	>1 Type	On therapy	No	No	Epoetin alfa	Usual care
Wilkinson *et al.*, 2006 [47]	30–87	Ovarian cancer	On therapy	No	No	Epoetin alfa	Usual care
Charu *et al.*, 2007 [48]	NR	>1 Type	On therapy	No	No	Darbepoetin alfa	Placebo
Charu *et al.*, 2007 [49]	NR	>1 Type	On therapy	No	No	Darbepoetin alfa	Usual care
Zemelka *et al.*, 2007 [50]	46–72	Lung cancer	On therapy	No	No	Erythropoietin	Usual care
Heras *et al.*, 2008 [51]	35–70	>1 Type	On therapy	No	No	Epoetin beta	Epoetin beta
Hoskin *et al.*, 2009 [52]	35–99	Head-and-neck	On therapy	No	No	Epoetin alfa	Usual care
Tsuboi *et al.*, 2009 [53]	NR	>1 Type	On therapy	No	No	Epoetin beta	Placebo
Auerbach *et al.*, 2010 [54]	27–97	>1 Type	On therapy	No	No	Darbepoetin alfa	Darbepoetin alfa
Engert *et al.*, 2010 [55]	18–60	Lymphoma	On therapy	No	No	Epoetin alfa	Placebo
Ichinose *et al.*, 2010 [56]	NR	>1 Type	On therapy	No	No	Darbepoetin alfa	Darbepoetin alfa
Pronzato *et al.*, 2010 [57]	27–77	Breast cancer	On therapy	No	No	Epoetin alfa	Usual care
Milroy *et al.*, 2011 [58]	34–83	Lung cancer	On therapy	No	No	Epoetin alfa	Usual care
Stimulants							
Bruera *et al.*, 2006 [59]	22–85	>1 Type	On therapy	No	Yes	Methylphenidate	Placebo
Butler *et al.*, 2007 [60]	28–83	Brain tumours	On therapy	No	No	D-Methylphenidate	Placebo
Mar Fan *et al.*, 2008 [61]	36–74	Breast cancer	On therapy	No	No	D-Methylphenidate	Placebo
Auret *et al.*, 2009 [62]	NR	>1 Type	NR	No	Yes	Dexamphetamine	Placebo
Lower *et al.*, 2009 [63]	NR	>1 Type	On therapy	No	Yes	D-Methylphenidate	Placebo
Moraska *et al.*, 2010 [64]	NR	>1 Type	On therapy	No	Yes	Methylphenidate	Placebo
Roth *et al.*, 2010 [65]	NR	Prostate cancer	On therapy	No	Yes	Methylphenidate	Placebo
Gehring *et al.*, 2012 [66]	NR	Brain tumours	On therapy	No	No	Modafinil	Methylphenidate
Kerr *et al.*, 2012 [67]	51–90	>1 Type	Off therapy	No	Yes	Methylphenidate	Placebo
Bruera *et al.*, 2013 [68]	32–83	>1 Type	Off therapy	No	Yes	Methylphenidate	Placebo
Suh *et al.*, 2013 [69]	NR	>1 Type	Off therapy	No	No	Caffeine	Placebo
Hovey *et al.*, 2014 [70]	NR	>1 Type	On therapy	No	Yes	Modafinil	Placebo

TABLE IV Continued

Agent category and reference	Age (years)	Cancer diagnosis	Timing	HSCT	Fatigue eligibility	Intervention	Control
Stimulants continued							
Spathis *et al.*, 2014 [71]	NR	Lung cancer	On therapy	No	Yes	Modafinil	Placebo
Berenson *et al.*, 2015 [72]	43–85	Multiple myeloma	On therapy	No	Yes	Armodafinil	Placebo
Page *et al.*, 2015 [73]	20–79	Brain tumours	On therapy	No	No	Armodafinil	Placebo
Richard *et al.*, 2015 [74]	NR	Prostate cancer	On therapy	No	Yes	Methylphenidate	Placebo
Heckler *et al.*, 2016 [75]	NR	>1 Type	Off therapy	No	No	Armodafinil	Placebo
Jean-Pierre *et al.*, 2016 [76]	18–90	>1 Type	Both	No	Yes	Modafinil	Placebo
Lee *et al.*, 2016 [77]	19–79	Brain tumours	On therapy	No	No	Armodafinil	Placebo
Corticosteroids							
Inoue *et al.*, 2003 [78]	28–78	>1 Type	On therapy	No	No	Dexamethasone	Placebo
Zarger-Shoshtari *et al.* 2009, [79]	34–92	Colorectal cancer	On therapy	No	No	Dexamethasone	Placebo
Yennurajalingam *et al.*, 2013 [80]	29–89	>1 Type	Both	No	Yes	Dexamethasone	Placebo
Paulsen *et al.*, 2014 [81]	NR	>1 Type	Both	No	Yes	Methylprednisolone	Placebo
Eguchi *et al.*, 2015 [82]	46–84	>1 Type	Off therapy	No	No	Methylprednisolone	Placebo
L-Carnitine							
Cruciani *et al.*, 2009 [83]	53.7–84.6	>1 Type	Both	No	Yes	L-Carnitine	Placebo
Mantovani *et al.*, 2010 [84]	NR	>1 Type	Both	No	No	L-Carnitine	Nutritional supplement
Cruciani *et al.*, 2012 [85]	NR	>1 Type	Both	No	Yes	L-Carnitine	Placebo
Kraft *et al.*, 2012 [86]	NR	Pancreatic cancer	Both	No	No	L-Carnitine	Placebo
Hershman *et al.*, 2013 [87]	26–80	Breast cancer	On therapy	No	No	Acetyl-L-carnitine	Placebo
Iwase *et al.*, 2016 [88]	22–70	Breast cancer	Both	No	Yes	L-Carnitine	Usual care
Antidepressants							
Capuron *et al.*, 2002 [89]	25–74	Malignant melanoma	On therapy	No	No	Paroxetine	Placebo
Morrow *et al.*, 2003 [90]	23–87	>1 Type	On therapy	No	Yes	Paroxetine	Placebo
Roscoe *et al.*, 2005 [91]	31–79	Breast cancer	On therapy	No	Yes	Paroxetine	Placebo
Stockler *et al.*, 2007 [92]	NR	>1 Type	On therapy	No	No	Sertraline	Placebo
Heras *et al.*, 2013 [93]	32–89	>1 Type	On therapy	No	Yes	Paroxetine	Placebo
Appetite stimulant							
Simons *et al.*, 1996 [94]	NR	>1 Type	Off therapy	No	No	Medroxyprogesterone acetate	Placebo
De Conno *et al.*, 1998 [95]	NR	>1 Type	Off therapy	No	No	Megestrol	Placebo
Westman *et al.*, 1999 [96]	37–89	>1 Type	On therapy	No	No	Megestrol acetate	Placebo
American ginseng							
Barton *et al.*, 2010 [97]	NR	>1 Type	On therapy	No	Yes	American ginseng	Placebo
Barton *et al.*, 2013 [98]	NR	>1 Type	Both	No	Yes	American ginseng	Placebo
Adenosine 5′-triphosphate (ATP)							
Agteresch *et al.*, 2000 [99]	NR	Lung cancer	Off therapy	No	No	ATP	Usual care
Beijer *et al.*, 2010 [100]	NR	>1 Type	Both	No	No	ATP	Usual care
Celecoxib							
Cerchietti *et al.*, 2007 [101]	44–90	Lung cancer	Off therapy	No	No	Celecoxib	Placebo and fish oil
Maccio *et al.*, 2012 [102]	NR	>1 Type	Both	No	No	Celecoxib, megestrol acetate, L-carnitine, and antioxidants	Megestrol acetate

TABLE IV Continued

Agent category and reference	Age (years)	Cancer diagnosis	Timing	HSCT	Fatigue eligibility	Intervention	Control
Donepezil							
Bruera *et al.*, 2007 [103]	NR	>1 Type	NR	No	Yes	Donepezil	Placebo
Lawrence *et al.*, 2016 [104]	39–79	Breast cancer	Both	No	No	Donepezil	Placebo
Traditional Chinese Medicine[a]							
Sun *et al.*, 2010 [105]	18–80	>1 Type	On therapy	No	No	Traditional Chinese medicines	Usual care
Kuo *et al.*, 2012 [106]	NR	Breast cancer	Off therapy	No	No	Tien-Hsien liquid practical	Placebo
Zhao *et al.*, 2012 [107]	NR	Breast cancer	On therapy	No	Yes	Spore powder of *Ganoderma lucidum*	Placebo
Xue *et al.*, 2015 [108]	NR	Lung cancer	On therapy	No	No	Decoctions and patent medicines	Usual care
Others (agents used in only 1 study)							
Young *et al.*, 1993 [109]	20–49	>1 Type	On therapy	HSCT	No	TPN plus glutamine	TPN
Borghardt *et al.*, 2000 [110]	20–70	Head-and-neck cancer	On therapy	No	Yes	Splenic peptides	Placebo
Martin *et al.*, 2002 [111]	NR	>1 Type	On therapy	No	No	Proteolytic enzymes	Placebo
Bruera *et al.*, 2003 [112]	NR	>1 Type	Off therapy	No	No	Fish oil	Placebo
Diel *et al.*, 2004 [113]	27–97	Breast cancer	On therapy	No	No	Ibandronate	Placebo
Monk *et al.*, 2006 [114]	25–83	>1 Type	On therapy	No	No	Etanercept	Usual care
Semiglazov *et al.*, 2006 [115]	25–55	Breast cancer	On therapy	No	No	Mistletoe preparation	Placebo
Berk *et al.*, 2008 [116]	23–91	>1 Type	On therapy	No	No	β-Hydroxyl β-methyl butyrate (HMB), glutamine, and arginine	Isonitrogenous, isocaloric
Troger *et al.*, 2009 [117]	NR	Breast cancer	On therapy	No	No	Iscador M special[b]	Usual care
Jeong *et al.*, 2010 [118]	NR	>1 Type	On therapy	No	Yes	Bojungikki-tang (TJ-41)	Usual care
Tian *et al.*, 2010 [119]	NR	Lung cancer	Off therapy	No	No	Feiji recipe	Usual care
Anthony *et al.*, 2011 [120]	NR	>1 Type	On therapy	No	No	Iron sucrose plus ESA	ESA
Barton *et al.*, 2011 [121]	NR	>1 Type	On therapy	No	No	Valerian	Placebo
Dimsdale *et al.*, 2011 [122]	NR	>1 Type	On therapy	Both	No	Eszopiclone	Placebo
Ikeguchi *et al.* 2011, [123]	NR	Colorectal cancer	On therapy	No	No	Fucoidan	Usual care
Chen *et al.*, 2012 [124]	NR	>1 Type	Both	No	Yes	*Astragalus membranaceus*	Placebo
Zhang *et al.* 2012, [125]	NR	Lung cancer	On therapy	No	No	Buckangling	Placebo
Del Fabbro *et al.*, 2013 [126]	NR	>1 Type	On therapy	No	No	Testosterone	Placebo
del Giglio *et al.*, 2013 [127]	NR	>1 Type	On therapy	No	Yes	*Paullinia cupana*	Placebo
Lesser *et al.*, 2013 [128]	28–85	Breast cancer	On therapy	No	No	Coenzyme Q10	Placebo
Wen *et al.*, 2013 [129]	NR	>1 Type	On therapy	No	No	Thalidomide and megestrol acetate	Megestrol
Hansen *et al.*, 2014 [130]	46–68	Breast cancer	On therapy	No	No	Melatonin	Placebo
Hui *et al.*, 2014 [131]	27–75	>1 Type	On therapy	No	No	Fentanyl	Placebo
Law *et al.*, 2014 [132]	30–73	Breast cancer	On therapy	No	No	Virgin coconut oil	Usual care
Lee *et al.*, 2014 [133]	NR	Colorectal cancer	Off therapy	No	No	Probiotic preparation	Placebo
Sanchez-Lara *et al.*, 2014 [134]	NR	Lung cancer	On therapy	No	No	Eicosapentaenoic	Usual care
Terkawi *et al.*, 2014 [135]	NR	Breast cancer	On therapy	No	No	Lidocaine	Placebo
Wang *et al.*, 2014 [136]	NR	Lung cancer	On therapy	No	No	rHuBNP	Usual care
Liu *et al.*, 2015 [137]	40–74	>1 Type	On therapy	No	No	Olanzapine	Usual care
Birgegard *et al.*, 2016 [138]	21–87	>1 Type	On therapy	No	No	Iron isomaltoside	Iron sulphate

TABLE IV Continued

Agent category and reference	Age (years)	Cancer diagnosis	Timing	HSCT	Fatigue eligibility	Intervention	Control
Others (agents used in only 1 study) continued							
Jeon *et al.,* 2016 [139]	NR	Colon cancer	On therapy	No	No	Vitamin C	Placebo
Mofid *et al.* 2016, [140]	NR	>1 Type	On therapy	No	Yes	Royal jelly and honey	Honey
Faramarzi *et al.,* 2017 [141]	NR	Rectal cancer	On therapy	No	No	Conjugated linoleic acid	Placebo
Martins *et al.,* 2017 [142]	NR	Head-and-neck cancer	On therapy	No	No	Guarana	Placebo
Ribeiro *et al.,* 2017 [143]	NR	Colorectal cancer	Both	No	No	Zinc supplement	Placebo
Sun *et al.,* 2017 [144]	18–90	Gastric cancer	Off therapy	No	No	Jinlongshe granule	Placebo

[a] Studies included differing agents within Traditional Chinese Medicines.
[b] Iscador Ltd., Lörrach, Germany.
HSCT = hematopoietic stem-cell transplantation; NR = not reported; SC = subcutaneous; rHuEPO = recombinant human erythropoietin; PO = oral; IV = intravenous; CTx = chemotherapy; TPN = total parenteral nutrition; ESA = erythropoiesis stimulating agents; IM = intramuscular; CFU = colony-forming units; rHuBNP = recombinant human B-type natriuretic peptide.

once or twice; and even for agents that were studied more often, the data could not be synthesized because of limited data reporting from many of the studies.

Erythropoietin was found to be effective in reducing fatigue, but the size of the effect—a WMD of 2.49 compared with placebo according to the FACT 13-item fatigue subscale—was small. The minimal clinically important difference for the FACT 13-item fatigue subscale has been reported to be 3–3.5 [145], which suggests that, although statistically significant, the observed effect is not meaningful to patients. Combined with concerns about the tumour protection, venothrombotic events, and worse survival potentially associated with erythropoietin [146,147], that minimal change in outcome suggests that this agent should not routinely be used in clinical practice for fatigue reduction.

The other pharmacologic agent that was found to be effective for fatigue was methylphenidate. However, the WMD of methylphenidate also did not meet the threshold for clinical importance. Further, a Cochrane review of methylphenidate for attention deficit hyperactivity disorder suggested that this agent is associated with an increased risk of non-serious adverse events—sleep problems and decreased appetite being most common [148]. Those issues suggest that methylphenidate should not routinely be used to manage fatigue in patients with cancer and in recipients of HSCT, but could selectively be used in specific patients for whom the potential benefits outweigh the disadvantages.

None of the studies found during the systematic review of literature included children. That omission is important, because patients with childhood cancer experience severe fatigue [149,150] and are vulnerable to long-term side effects of treatments [151]. Pharmacologic interventions might not have been applied in children because dosing considerations and safety concerns add complexity. However, future studies should consider the pediatric population when formulating eligibility criteria.

An interesting observation was that, despite the large number of randomized trials, relatively few studies had data available for meta-analysis. Although the FACT 13-item fatigue subscale was used in many of the trials, publications were inconsistent in whether they reported FACT change scores or end-of-intervention scores. Additionally, many of the studies did not report a measure of central tendency and a measure of variability for either of the two fatigue outcomes (change or end-of-intervention score). The lack of well-reported fatigue data raises potential concerns about a form of publication bias in which negative endpoints are not reported or the data are not shown. Future randomized studies focused on fatigue reduction should be encouraged to explicitly report data that could be combined for analysis in systematic reviews.

The present systematic review complements two previously published meta-analyses evaluating the effects of pharmacologic agents on fatigue in cancer patients [18,152]. Our review adds important insights, given that the review by Mustian *et al.* [18] reported many types of interventions, citing 14 studies of pharmacologic interventions that were analyzed as a single group. To inform practice, studies must evaluate pharmacologic agents separately. The review by Minton and Stone [152], which analyzed specific pharmacologic interventions, is now outdated, being based on a literature search conducted in 2009.

The strengths of the present review are its broad eligibility criteria, its inclusion of publications in all languages, and its focus on systemically administered pharmacologic agents. However, our meta-analysis was limited because of the data reporting in the primary studies. Furthermore, wide variations in dose and schedule were noted for the individual pharmacologic agents studied, and the limited number of studies available for synthesis meant that stratified analyses were not possible.

CONCLUSIONS

Erythropoietin and methylphenidate significantly reduce fatigue severity in patients with cancer and recipients of HSCT; however, the magnitude of the benefit is of questionable clinical significance. Use of those agents is potentially further limited by concerns about safety. Pharmacologic interventions should not routinely be used to reduce fatigue

TABLE V Effect of erythropoietins, stimulants, and corticosteroids on fatigue using all fatigue scales and the FACT scale[a]

Agent and comparators	Outcome											
	Fatigue change score						End-of-intervention fatigue score					
	Studies (*n*)	Pts (*n*)	Effect	95% CL (%)	I^2	*p* Value	Studies (*n*)	Pts (*n*)	Effect	95% CL (%)	I^2	*p* Value
Erythropoietins												
All scales												
All interventions vs. all controls	14	3,037	–0.52 SMD	–0.89, –0.14	96	0.007	2			NSP		
All interventions vs. placebo	6	1,057	–0.19 SMD	–0.32, –0.07	0	0.003	1			NSP		
FACT scale												
All interventions vs. all controls	12	2,587	–2.98 WMD	–4.41, –1.55	79	<0.001	0			NSP		
All interventions vs. placebo	4	683	–2.49 WMD	–4.06, –0.92	0	0.002	0			NSP		
Stimulants												
All scales												
All interventions vs. all controls	9	1,240	–0.16 SMD	–0.34, 0.02	42	0.08	13	1,287	–0.09 SMD	–0.28, 0.11	50	0.51
All interventions vs. placebo[b]	9	1,240	–0.16 SMD	–0.34, 0.02	42	0.08	12	1,263	–0.08 SMD	–0.28, 0.12	53	0.44
Stratified by agent for all scales												
Methylphenidate vs. all controls	5	369	–0.36 SMD	–0.56, –0.15	0	<0.001	6	305	–0.32 SMD	–0.80, 0.17	73	0.20
Modafinil/armodafinil vs. all controls	4	871	0.01 SMD	–0.21, 0.22	36	0.94	5	905	–0.04 SMD	–0.17, 0.09	0	0.51
FACT scale												
All interventions vs. all controls	7	596	–1.35 WMD	–3.47, 0.78	50	0.21	7	424	0.80 WMD	–1.57, 3.18	0	0.51
All interventions vs. placebo[b]	7	596	–1.35 WMD	–3.47, 0.78	50	0.21	7	424	0.80 WMD	–1.57, 3.18	0	0.51
Methylphenidate vs. all controls	4	346	–2.87 WMD	–4.68, –1.07	0	0.002	3	150	0.71 WMD	–3.18, 4.59	0	0.72
Modafinil/armodafinil vs. all controls	3	250	1.24 WMD	–2.19, 4.68	49	0.48	4	274	0.89 WMD	–2.17, 3.94	3	0.57
Corticosteroids												
All interventions vs. all controls	3	165	–0.43 SMD	–1.00, 0.14	67	0.14	2			NSP		
All interventions vs. placebo[b]	3	165	–0.43 SMD	–1.00, 0.14	67	0.14	2			NSP		

[a] Outcomes using the FACT (FACIT.org, Elmhurst, IL, U.S.A.) were rescaled (multiplied by –1) such that higher scores reflect more fatigue. One study contributed twice: results were reported separately for the lymphoma and multiple myeloma groups (Littlewood *et al.*, 2001[29] and Littlewood *et al.*, 2006[42]).

[b] All synthesized studies were placebo-controlled.

FACT = Functional Assessment of Cancer Therapy; Pts = patients; CL = confidence limits; SMD = standardized mean difference; NSP = no synthesis possible (too few studies); WMD = weighted mean difference.

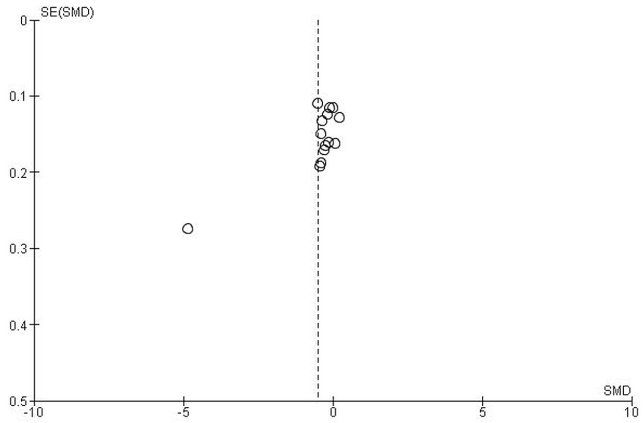

FIGURE 2 Funnel plot comparing erythropoietins with all control medications. SE = standard error; SMD = standardized mean difference.

severity. Future meta-analyses should obtain individual data from trials to better understand how pharmacologic interventions affect fatigue. Research is required to identify interventions for fatigue that are effective and have minimal adverse effects.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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