Supplementary materials

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Table 1. Explanations that have been proposed for placebo response[1,2,3]

		Examples
Patients characteristics	Factors related to recruitment	Methods, source, types
	Severity of symptoms	Participants with mild symptoms are more likely to experience spontaneous recovery
	Duration of symptom	Chronic conditions, acute conditions, fluctuations
	Psychological phenomena	Patient expectations, conditional responses
Investigator factors	Experience	Clinical and conducting trials
	Methods to accelerate enrolment	Financial incentives
	Their availability	Attention perceived by patient
	The degree of positivity which a treatment is presented	Psychological
	Rosental effect	If investigators communicate their expectations to participants, this can alter their behaviour to conform to these expectations
Research design and statistical	Duration of the trial	Participants with recent symptoms are more likely to experience spontaneous recovery
	Number of treatment arms	
	Flexible vs fixed dosage	
	Outcome measurement	Reliability, validity, type and extent of assessments
	Hawthorne effect	Clinical trial participation may alter the behaviour and experience of participants
	Unidentified parallel interventions	
	Regression to the mean	Symptoms that fluctuate and are at their most severe at the initiation of the study may improve spontaneously as a part of their natural history
Placebo related	Use of equipment	Infusions pumps
	Appearance	Shape, colour, number of pills

[1]Sanderson, C., Hardy, J., Spruyt, O. & Currow, D. C. Placebo and Nocebo Effects in Randomized Controlled Trials: The Implications for Research and Practice. (2013).

[2]Dworkin, R. H., Katz, J. & Gitlin, M. J. Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. *Neurology* **65,** S7-19 (2005).
[3]Miro Jakovljevic, The placebo–nocebo response: Controversies and challenges from clinical and research perspective, *European Neuropsychopharmacology*, **24**, 3, (333), (2014).

Box 1. Search strategies used

Embase

1 fatigue.mp. or cancer fatigue/ or fatigue/
2 neoplasm/co, dt, rt, rh, si, th [Complication, Drug Therapy, Radiotherapy, Rehabilitation, Side Effect, Therapy]
3 malignant neoplasm/co, dm, dt, rt, rh, si, th , [Complication, Disease Management, Drug Therapy, Radiotherapy, Rehabilitation, Side Effect, Therapy]
4 clinical trial/
5 controlled study/
6 random*.mp.
7 placebo/ct, ad, cm, dt [Clinical Trial, Drug Administration, Drug Comparison, Drug Therapy]
8 2 or 3
9 4 or 5 or 6 or 7
10 1 and 8 and 9
11 Limit 10 to human

Medline

1 FATIGUE/ or fatigue.mp.
2 Neoplasms.mp or NEOPLASMS/
3 Cencer.mp. or Neoplasms/
4 Malignan*.mp.
5 Clinical trial/
6 RANDOM ALLOCATION/
7 Placebo.mp.
8 2 or 3 or 4
9 5 or 6 or 7
10 1 and 8 and 9
11 Limit 10 to humans
12 Limit 11 to “all adult (19 plus years)”

PsychInfo

1 exp FATIGUE/
2 exp NEOPLASMS/
3 cancer.mp. or exp Neoplasms/
4 exp Clinical Trials/
5 exp RANDOM SAMPLING/
6 exp Drug Therapy/ or exp Placebo/ or exp Clinical Trials/ or exp Drugs
7 2 or 3
8 4 or 5 or 6
9 1 and 7 and 8
10 Limit 9 to human
11 Limit 10 to adulthood <18+ years>

CINAHL plus

S1 fatigue
S2 fatigue management
S3 neoplasms or oncology or cancer
S4 clinical trials or randomized controlled trials
S5 S1 or S2
S6 S3 and S4 and S5, S7 limits

Box 2. Rejected studies with reason per study

Studies rejected	Reason for rejection
Barton 2011[1]	Secondary outcome using BFI.
Beijer 2010 [2]	Not placebo arm. ATP vs usual care.
Beniwal 2015[3]	Only Abstract, not published, not data enough.
Boele 2013[4]	Abstract of full paper included in review.
Bruera 2013[6]	Mixed design intervention.
Butler 2007[7]	Prophylactic.
Conley 2016[8]	Secondary analysis of paper included in review
Cornish 2015[10]	Capacity and function related to exercise +BFI.
Cruciani 2004[11]	No placebo controlled.
Cruciani 2006[12]	No placebo controlled.
daCostaMiranda 2009[13]	Prophylactic treatment.
DelFabbro 2011[14]	Abstract of full paper included in review.
DelFabbro 2012[16]	Abstract of full paper included in review.
delFabbro 2013[17]	Fatigue as a secondary outcome.
deSouza 2007[18]	Prophylactic.
Dimsdale 2011[19]	Secondary outcome.
Djalali 2013[20]	No abstract available.
Heckler 2016l[21]	Fatigue as a secondary outcome.
Heim 2012[22]	Abstract, and some results posted in German, no published.
Hovey 2012[23]	Abstract of full paper included in review.
Kamath 2012[25]	Abstract of full paper included in review.
Lai 2013[27]	Same study that Chen[28].
Lesser 2012[29]	Prophylactic. And both arms have vit E.
Littlewood 2006D[30]	EPO.
MarFan 2008[31]	Prophylactic.
Mitchell 2015[32]	N-of-1.
Norager2006[33]	EPO.
Page2015[34]	Prophylactic. Fatigue as a secondary outcome.
Palesh2012[35]	No fatigue, secondary analysis of Morrow2003Paroxetine[36].
Paulsen2014[37]	Fatigue as a secondary outcome (ESAS+QoLC30).
Ribeiro2017[38]	Prophylactic treatment.
Richard2014[39]	Abstract of full paper included in review.
Roscoe2005P [41]	Report of paper included in review
Schmidt2012[42]	Abstract not published as an article.
Tanioka2018[43]	Prophylactic treatment.
Yennu2015G[44]	Preliminary report of paper included in review.

Refeences of excluded studies

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3. Beniwal, S., et al. (2015). 'A Phase III randomized, placebo-controlled trial evaluating cancer-related fatigue in patients with advanced cancer treated with dexamethasone.' *Support. care cancer. 23(1 SUPPL. 1) S85.*
4. Boele, F., et al. (2013). ". The effect of modafinil on fatigue, cognitive functioning and mood in primary brain tumor patients: a multi-center RCT.". *Support. care cancer. 21 S148-S149.*
5. Boele, F. W. *et al.* The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro. Oncol.* **15,** 1420–8 (2013).
6. Bruera, E. *et al.* Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *J. Clin. Oncol.* **31,** 2421–2427 (2013).
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15. Del Fabbro, E. *et al.* Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial. *Support. Care Cancer* **21,** 2599–2607 (2013).
16. Del Fabbro, E., et al. 'Testosterone replacement for fatigue in male hypogonadic patients with advanced cancer: a preliminary double-blind, placebo-controlled trial.' *Support. care cancer. 20 S249-S250.*
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results of a double-blind randomized crossover trial. *Am. J. Clin. Oncol.* **30,** 432–436 (2007).
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trial. *J. Clin. Oncol.* **32,** (2014).

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Table 2. Descriptive summary of study characteristics

Continuous Variables	N studies	Min.	1st quartile	Median	Mean	3rd quartile	Max.
Participants in placebo arm	23	12	19	50	68.65	70	316
Number of trial centres	17	1	2	2	8.94	18	40
Mean age of participants	15	53.2	56.15	62	61.96	67.4	71
Percentage of male participants	21	0	34.1	43	49.53	60	100
Duration (in weeks) of intervention	23	1	2	4	4.43	6	10

Table 3 .Details of categorical and binary variables used in meta-regression

	n	%
Subjects in placebo arm		
<=50	12	52.2
51-199	9	39.1
>=200	2	8.7
total	23	100
Type of Intervention		
psychostimulants	11	47.8
dietary supplements	2	8.7
antidepressants	2	8.7
herbs	4	17.4
Hormones	1	4.3
Others	2	8.7
steroids	1	4.3
total	23	100
Type of Study		
2 arms, no X-over	18	78.3
3 arms	0	0
4 arms	1	4.3
X-over, endpoint before x-over	2	8.7
X-over with washout period	2	8.7
total	23	100
Tool		
FACIT-F	11	47.8
BFI	6	26.1
MFSI-SF	1	4.3
CSI	1	4.3
FACT-An	1	4.3
item 3 of BFI	1	4.3
MFI-20	1	4.3
MAF	1	4.3
total	23	100
Tool Item		
one item	2	9.1
multidimensional	20	90.9
total	22	100
Placebo Dosage		
Less than once a day	1	4.5
Once a day	6	27.3
Twice a day	10	45.5
3 a day	0	0
progressive dosage	4	18.2
prn	1	4.5
total	22	100
Placebo administration via		
Oral	21	95.5
intravenous	0	0
IM	1	4.5
total	22	100
Stage		
curative	9	47.4
palliative	10	52.6
survivors	0	0
total	19	100
Placebo dosage regimen		
fixed-dose	15	68.2
flexible-dose	7	31.8
total	22	100
Drug placebo significant difference?		
yes	4	22.2
no	14	77.8
total	18	100
Risk of Bias RoB2		
low	9	39.1
unclear	8	34.8
high	6	26.1
total	23	100

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