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Interventions for the management of fatigue in adults with a primary brain tumour (Review)

Day J, Yust-Katz S, Cachia D, Wefel J, Tremont Lukats IW, Bulbeck H, Rooney AG

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[Intervention Review]

Interventions for the management of fatigue in adults with a primary brain tumour

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ABSTRACT

Background

Fatigue is a common and disabling symptom in people with a primary brain tumour (PBT). The effectiveness of interventions for treating clinically significant levels of fatigue in this population is unclear. This is an updated version of the original Cochrane Review published in Issue 4, 2016.

Objectives

To assess the effectiveness and safety of pharmacological and non-pharmacological interventions for adults with PBT and clinically significant (or high levels) of fatigue.

Search methods

For this updated review, we searched CENTRAL, MEDLINE and Embase, and checked the reference lists of included studies in April 2022. We also searched relevant conference proceedings, and ClinicalTrials.gov for ongoing trials.

Selection criteria

We included randomised controlled trials (RCTs) that investigated any pharmacological or non-pharmacological intervention in adults with PBT and fatigue, where fatigue was the primary outcome measure. We restricted inclusion specifically to studies that enrolled only participants with clinically significant levels of fatigue to improve the clinical utility of the findings.

Data collection and analysis

Two review authors (JD, DC) independently evaluated search results for the updated search. Two review authors (JD, SYK) extracted data from selected studies, and carried out a risk of bias assessment. We extracted data on fatigue, mood, cognition, quality of life and adverse events outcomes.

Main results

The original review identified one study and this update identified a further two for inclusion. One study investigated the use of modafinil, one study the use of armodafinil and one study the use of dexamfetamine. We identified three ongoing studies.

In the original review, the single eligible trial compared modafinil to placebo for 37 participants with a high- or low-grade PBT. One new study compared two doses of armodafinil (150 mg and 250 mg) to placebo for 297 people with a high-grade glioma. The second new study compared dexamfetamine sulfate to placebo for 46 participants with a low- or high-grade PBT. The evidence was uncertain for both modafinil and dexamfetamine regarding fatigue outcome measures, compared to controls, at study endpoint. Two trials did not reach the planned recruitment target and therefore may not, in practice, have been adequately powered to detect a difference. These trials were at a low risk of bias across most areas. There was an unclear risk of bias related to the use of mean imputation for one study because the investigators did not analyse the impact of imputation on the results and information regarding baseline characteristics and randomisation were not clear. The certainty of the evidence measured using GRADE was very low across all three studies.

There was one identified study awaiting classification once data are available, which investigated the feasibility of 'health coaching' for people with a PBT experiencing fatigue. There were three ongoing studies that may be eligible for an update of this review, all investigating a non-pharmacological intervention for fatigue in people with PBT.

Authors' conclusions

There is currently insufficient evidence to draw reliable and generalisable conclusions regarding potential effectiveness or harm of any pharmacological or non-pharmacological treatments for fatigue in people with PBT. More research is needed on how best to treat people with brain tumours with high fatigue.

PLAIN LANGUAGE SUMMARY

Interventions for the management of fatigue in adults with a primary brain tumour

Key message

We do not know whether any treatments are effective in the management of people with primary brain tumour and high fatigue due to finding only three trials each with a low number of participants.

What is a primary brain tumour?

A primary brain tumour is a cancer that began in the brain rather than spreading from other parts of the body. Brain tumours are graded as high grade and low grade; high-grade tumours are made up of very abnormal cells that grow quickly, whereas low-grade tumours are made up of abnormal cells that grow slowly. Fatigue (tiredness) is common in people with a primary brain tumour. This may be due to the tumour, its treatment or the use of other medicines, such as antiepileptic medicines (which are used to treat seizures (fits)). It may also occur with other symptoms such as sleep disturbance, thinking problems and emotional distress.

What did we want to find out?

We wanted to find out if treatments to help manage fatigue may improve a person's quality of life, their ability to tolerate cancer treatment (which in itself is associated with fatigue), and their ability to carry out social and day-to-day activities.

What did we do?

In April 2022, we searched four medical databases. We found three clinical trials that were eligible for inclusion. The three trials investigated the use of three medicines (modafinil, armodafinil and dexamfetamine sulfate) in adults with a primary brain tumour and high levels of fatigue. These medicines promote wakefulness.

What did we find?

The three included trials found no evidence of a difference between the medicine and placebo (a dummy treatment) in treating fatigue at the point the trials ended. It is possible that this could be due to two trials not reaching their planned number of participants.

What were the limitations of the evidence?

With only three included trials, and the lack of positive findings, we do not currently know whether any treatments are effective in the management of people with primary brain tumour and high fatigue. Further, there were no included studies of non-medicine interventions, such as talking therapy and exercise. More high-quality studies are needed that enrol adults with primary brain tumours and high fatigue. We found three ongoing studies that are investigating non-medicine interventions that might offer some helpful results.

How up-to-date is this evidence?

The evidence is current to April 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Boele 2013: modafinil compared with placebo for fatigue in people with a primary brain tumour

Modafinil compared with placebo for fatigue in people with a primary brain tumour

Patient or population: people with a primary brain tumour

Settings: hospital, outpatient

Intervention: modafinil

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Modafinil				
Fatigue – concentration problems Subscale from CIS range: 0–35 (follow-up: 6 weeks)	The mean concentration problem score ranged across control groups from 15.91 to 23.91 points	The mean concentration problem score in the intervention groups was **1.06 lower** (3.18 lower to 1.06 higher)	—	37 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate a higher level of concentration problems.
Fatigue – reduced motivation Subscale from CIS range: 0–28 (follow-up: 6 weeks)	The mean reduced motivation score ranged across control groups from 10.22 to 19.48 points	The mean reduced motivation score in the intervention groups was **0.48 lower** (2.93 lower to 1.97 higher)	—	37 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate lower motivation.
Fatigue – reduced activity Subscale from CIS range: 0–21 (follow-up: 6 weeks)	The mean reduced activity score ranged across control groups from 3.84 to 21.34 points	The mean reduced activity score in the intervention groups was **1.01 lower** (5.64 lower to 3.62 higher)	—	37 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate lower activity.

Fatigue – severity Subscale from CIS range: 0–56	The mean fatigue severity score ranged across control groups from 34.06 to 36.22 points	The mean fatigue severity score in the intervention groups was **0.22 lower** (0.79 lower to 0.35 higher)	—	37 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate a higher level of fatigue.
Adverse events (follow-up: 6 weeks)	**Low-risk population**		**RR 2.79** (0.59 to 13.16)	37 (1)	⊕⊖⊖⊖ **Very low**[a]	—
	—	**30 per 100** (1 to 180)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CIS: Checklist Individual Strength; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded three levels; there was very low-certainty evidence due to low accrual, such that recruitment did not meet the estimated power requirement to detect a true effect.

Summary of findings 2. Laigle-Donadey 2019: dexamfetamine sulfate compared with placebo for fatigue in primary brain tumour

Dexamfetamine sulfate compared with placebo for fatigue in primary brain tumour

Patient or population: people with a primary brain tumour

Settings: hospital, outpatient

Intervention: dexamfetamine sulfate

Comparison: placebo

Outcomes	Median change from baseline (IQR)	Between-group comparison	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	**dexamfetamine sulfate**			
Fatigue MFI-20 scale	The median difference in fatigue score between baseline and 3-month follow-up in the control	The median difference in fatigue score between baseline and 3-month fol-	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate a higher level of fatigue.

(follow-up: 3 months)	group was 14 points (IQR 4.5 to 24.25)	low-up in the dexamfetamine sulfate group was **4 points lower** (IQR 4 to 13)			
Fatigue ('asthenia') Norris Scale	The median difference in fatigue score between baseline and 3-month follow-up in the control group was 4.25 points (IQR −0.06 to 12.16)	The median difference in fatigue score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **2.31 points lower** (IQR −10.88 to 13.96)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate a higher level of fatigue.
Cognition Trail Making Test A	The median difference in score between baseline and 3-month follow-up in the control group was 6.5 points (IQR −0.75 to 17.5)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **7.5 points lower** (IQR −4 to 10)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate poorer cognition.
Cognition Trail Making Test B	The median difference in score between baseline and 3-month follow-up in the control group was −2 points (IQR −16 to 21.75)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **18 points higher** (IQR −37 to 39)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate poorer cognitive performance.
Cognition Semantic Fluency	The median difference in score between baseline and 3-month follow-up in the control group was 1 points (IQR −1 to 3)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **1 point lower** (IQR −5 to 3)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better cognitive performance.
Cognition Lexical Fluency	The median difference in score between baseline and 3-month follow-up in the control group was 1 point (IQR −0.75 to 2.75)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **2 points lower** (IQR −4 to 4)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better cognitive performance.
Cognition Episodic memory (Grober and Buschke test)	The median difference in score between baseline and 3-month follow-up in the control group was −0.5 points (IQR −4.25 to 2.5)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **0.5 points higher** (IQR −4.5 to 4)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better cognitive performance.
Cognition Mattis Scale	The median difference in score between baseline and 3-month follow-up in the control group was −2 (IQR −7 to 1)	The median difference in fatigue score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **1point higher** (IQR −4 to 0)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better cognitive performance.
Affectivity Norris Scale	The median difference in score between baseline and 3-month follow-up in the control group was 8.25 (IQR 2.34 to 18.09)	The median difference in score between baseline and 3-month follow-up in the dexamfetamine sulfate group was **5.87 points lower** (IQR −10.78 to 10)	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate higher affectivity.
Apathy Marin Scale	The median difference in score between baseline and 3-month fol-	The median difference in score between baseline and 3-month follow-up in the	41 (1)	⊕⊖⊖⊖	Higher scores indicated higher apathy.

	low-up in the control group was 0.5 (IQR –6 to 2.75)	dexamfetamine sulfate group was **1.5 points higher** (IQR –2 to 11)		**Very low**[a]	
Depression HADS	—	—	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate more severe depression symptoms.
Quality of life EORTC QLQ-C30	—	—	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better quality of life.
Quality of life EORTC QLQ-BN 20	—	—	41 (1)	⊕⊖⊖⊖ **Very low**[a]	Higher scores indicate better quality of life.

EORTC QLQ-BN 20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Brain Neoplasm; **EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; **HADS:** Hospital Anxiety and Depression Scale; **IQR:** interquartile range; **MFI-20:** 20-item Multidimensional Fatigue Inventory.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded three levels; there was very low-certainty evidence due to low accrual, such that recruitment did not meet the estimated power requirement to detect a true effect.

Summary of findings 3. Porter 2020: armodafinil compared with placebo for fatigue in high-grade glioma

Armodafinil (150 mg and 250 mg) compared with placebo for fatigue

Patient or population: people with primary brain tumour

Settings: hospital, outpatient

Intervention: armodafinil (150 mg and 250 mg)

Comparison: placebo

Outcomes	Group comparisons			No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Armodafinil 150 mg	Armodafinil 250 mg			

Fatigue Brief Fatigue Inventory (number of participants with an improvement in 2 points from baseline at 8 weeks (%))	29 (29.9%)	27 (27.8%)	29 (28.2%)	297 (1)	⊕⊕⊖⊖ **Low**[a]	Higher scores indicate higher fatigue.
Cognition Symbol Digit Modalities Test (median (range))	0.0 (–3.4 to 4.9)	0.0 (–1.6 to 2.5)	0.3 (–3.4 to 2.5)	180 (1)	⊕⊕⊖⊖ **Low**[a]	Higher scores indicate better performance.
Quality of life Linear Analogue Self Assessment (median (range))	2.0 (–15.0 to 27.0	4.0 (–32.0 to 26.0)	3.0 (–16.0 to 27.0)	232 (1)	⊕⊕⊖⊖ **Low**[a]	Higher scores indicate better quality of life.
Adverse events Grade 3 or higher (number of participants (%))	3 (2.8%)	6 (5.5%)	8 (7.3%)	328 (1)	⊕⊕⊖⊖ **Low**[a]	—

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded two levels; there was low-certainty evidence due to the level of unclear risk of bias relating to selection, detection and attrition.

BACKGROUND

Description of the condition

Fatigue is one of the most common symptoms experienced by people with cancer. The reported prevalence rates for cancer-related fatigue in the clinical trial setting is about 70% to 80% (Lawrence 2004; Lovely 1999; van Coevorden-van Loon 2017). Cancer-related fatigue is "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer that is not proportional to recent activity and interferes with usual functioning" (NCCN 2018). Fatigue is also a common adverse effect of cancer treatment (Roscoe 2002; van Coevorden-van Loon 2017), occurs across various cancer types (Stone 2000), and persists in disease-free survivors (Servaes 2007). As the scientific knowledge about cancer-related fatigue expands, there is increasing recognition on the importance of its effective management (Coomans 2019; Goedendorp 2009).

Prevalence of fatigue in primary brain tumours

Prevalence estimates suggest that, as in other cancer populations, fatigue is an extremely common problem in people with a primary brain tumour (PBT; van Coevorden-van Loon 2017). In one study, 96% of people with high-grade glioma reported moderate or severe fatigue (Fox 2007). Studies enrolling mixed high-grade and low-grade tumour populations estimated that up to 42% of people with PBT had fatigue (Pelletier 2002). Fatigue remains troublesome throughout the course of survivorship, from the 12 months following PBT diagnosis (Molassiotis 2010), to more than eight years after diagnosis (Struik 2009). Fatigue in PBT has been studied both as a primary outcome (Armstrong 2010; Lovely 1999), and as a secondary outcome related to symptoms such as depression (Rooney 2011), poor quality of life (Kvale 2009), and sleep-wake disturbances (Miaskowski 2011).

Associated clinical variables

Fatigue in the setting of PBT has multiple potential causes including primary treatments of the tumour, secondary symptomatic treatments, and the physical and emotional consequences of the diagnosis (Armstrong 2012; Coomans 2019). Up to 80% of people undertaking cranial radiotherapy report fatigue (Lovely 1999). Although it is rarely the only possible cause, radiotherapy in particular may exacerbate fatigue by endocrine (hormone) dysfunction when the irradiated area encroaches upon the hypothalamus or pituitary gland. The hypothalamic-pituitary-adrenal axis feedback system is responsible for controlling the secretion of many hormones that regulate many body processes, including sleep (Arlt 1997; Taphoorn 1995).

Fatigue is also a recognised adverse effect of numerous medications that people with PBT may receive, including chemotherapy, anticonvulsant drugs (Lu 2009; Maschio 2008; Struik 2009), and corticosteroids (Drappatz 2007; Hinds 2007). Fatigue is further associated with sleep disturbance, cognitive complaints, depression and anxiety (Armstrong 2010; Fox 2007; Pelletier 2002), and this cluster of symptoms may significantly influence people's quality of life (Fox 2007). Symptom clustering can make the presence of fatigue difficult to distinguish from other symptoms such as depression (Rooney 2011).

The relationship between histological tumour grade and fatigue remains unclear. Some authors find fatigue is more common in high-grade than in low-grade tumours (Salo 2002), whereas other authors do not (Armstrong 2010; Pelletier 2002). Regardless, the wide range of possible causes suggest that fatigue is best investigated as a multifactorial symptom alongside these other associated issues (Armstrong 2010).

Methods of measuring fatigue

Many tools have been developed to measure fatigue in people with cancer (Jean-Pierre 2007); each instrument relies on subjective patient report. The Brief Fatigue Inventory (BFI; Mendoza 1999) has been used in several studies including brain tumour correlation studies (Kim 2012), and clinical trials (Gehring 2012). Other measurement tools validated for use in cancer include the Functional Assessment of Cancer Therapy – Fatigue (FACT-F; Yellen 1997), the Cancer-Related Fatigue Distress Scale (Holley 2000), the Fatigue Assessment Questionnaire (Glaus 1998), the Revised Piper Fatigue Scale (Piper 1998), and the Multidimensional Fatigue Symptom Inventory (Stein 2004). Several general and brain tumour-specific quality of life measures also assess fatigue, such as the Functional Assessment of Cancer Therapy – Brain (FACT-Br) (Cella 1993), the MD Anderson Symptom Inventory Brain Tumour Module (MDASI-BT) (Armstrong 2006), the European Organization of Research and Treatment Quality of Life Questionnaire-C30 (EORTC QLQ-C30) (Ringdal 1993), and the World Health Organization Quality of Life assessment (WHOQOL; WHOQOL Group 1995). With many different tools available, caution is needed when synthesising data in a systematic review or meta-analysis.

Description of the intervention

In this review, we included pharmacological and non-pharmacological interventions for fatigue in adults with PBT. We defined pharmacological interventions as a drug, given by any route, at any therapeutic dose, with the primary intention of treating fatigue. Such drugs could include psychostimulants and antidepressants. We defined non-pharmacological interventions and general strategies as any psychological or behavioural treatment with the primary aim of improving fatigue in PBT. These interventions could include physical activity, cognitive or behavioural therapies, and psychosocial interventions.

How the intervention might work

Studies have explored pharmacological and non-pharmacological interventions aimed at improving and alleviating symptoms of fatigue (e.g. Cramp 2012; Goedendorp 2009; Minton 2013).

Pharmacological interventions

Pharmacological treatments might reduce fatigue by acting on critical neurotransmitter pathways. For example, the central nervous system (CNS) stimulant, methylphenidate, could enhance neural signal processing by increasing concentrations of dopamine and noradrenaline (norepinephrine) (Volkow 2002). Similarly, the CNS stimulant, modafinil, may enhance the effect of dopamine associated with wakefulness and motivation (Young 2010).

Non-pharmacological interventions

Psychological interventions may improve fatigue by introducing and reinforcing adaptive coping strategies (Armstrong 2012). This approach can be effective through the use of cognitive therapy, which identifies negative or maladaptive thoughts/beliefs,

challenges them, and replaces them with more helpful and realistic alternatives (Beck 1979).

These strategies could be used alongside behavioural interventions such as exercise. Exercise may improve fatigue in people with PBT by increasing mental and physical stamina. A reduction in fatigue could be achieved through a balance between activity and rest (Winningham 1992). Excessive rest could promote muscle wasting and decreasing cardiorespiratory fitness, adding to the perception of fatigue (Dimeo 2001). By increasing functional capacity, exercise could reduce fatigue (NCCN 2018), while alleviating anxiety and improving mood (Dimeo 2001).

Interventions may also improve fatigue by improving associated factors, such as sleep. Sleep interventions have been suggested to significantly improve fatigue in people with other cancer types, associated with improving circadian rhythm and cytokine balance to improve CNS function (Dun 2021).

Why it is important to do this review

Fatigue is consistently the single most frequently reported symptom in studies of people with PBT. Therefore, there is a pressing need to search for trials in this area systematically to generate a high-quality review of interventions for fatigue in people with PBT. With survival times for low-grade PBT typically measured in years, and survival times for certain subgroups of people with high-grade PBT gradually increasing, there is great potential benefit in establishing which interventions are effective for fatigue. Effective interventions could improve quality of life, yet the multifactorial nature of fatigue (potentially including neuroendocrine, neuroimmune and psychosocial causes) makes it a symptom that can be particularly difficult to treat (Bowe 2012).

A clear synthesis of the evidence for the effectiveness of managing fatigue in PBT is currently lacking. This review will answer a clinically useful research question: what are the effective interventions for managing fatigue in adults with a PBT?

OBJECTIVES

To assess the effectiveness and safety of pharmacological and non-pharmacological interventions for adults with PBT and clinically significant (or high levels) of fatigue.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of any intervention for the management of fatigue in adults with PBT, in which fatigue was (one of) the primary or secondary therapeutic outcomes. Due to the prediction that there may currently be few RCTs that satisfy the inclusion criteria, we planned to include a narrative description of relevant excluded RCTs in the Excluded studies section. This was intended to provide valuable information about interventions that may warrant further investigation.

Types of participants

We included studies that evaluated the effect of interventions on adults (aged 18 years or older) with high self-reported fatigue (defined by a pre-established cut-off using a questionnaire, validated measure or presence/absence report), and with a histological diagnosis of PBT at any stage in their illness. Following discussion, we excluded studies that recruited non-fatigued participants. As per the original review, we reasoned that the clinically relevant question of how to treat high fatigue required a strict focus on studies that enrolled people with high fatigue, which has been emphasised in an editorial considering the design of clinical trials for fatigue interventions (Grant 2016).

Types of interventions

Pharmacological interventions

For pharmacological interventions, we investigated the effectiveness of any drug, given by any route and at any therapeutic dose, with the intention of treating fatigue in PBT. For ethical reasons, RCTs of psychoactive drugs may not necessarily include a placebo arm. In order to increase the relevance of the review, we included studies without a placebo arm, provided that the study randomly allocated participants to a control group (e.g. treatment as usual, another active drug or allocation to a waiting list).

Non-pharmacological interventions

For psychological interventions, we aimed to include any cognitive treatment given with the aim of improving fatigue in PBT. For behavioural interventions, we aimed to investigate the effectiveness of any behavioural or social treatment given for the improvement of fatigue in PBT; this may have included exercise and energy management techniques. We included RCTs in which the control group was allocated to treatment as usual or to a waiting list.

Types of outcome measures

We aimed to summarise the following outcome measures.

Primary outcomes

- Fatigue at study endpoint.

Due to potential differences in effectiveness endpoints between the different interventions, we aimed to analyse both short-term and long-term effects of these interventions, where the data were available.

High fatigue may be summarised categorically as 'present' or 'absent' (e.g. in response to a clinical interview), or else quantified ordinally on a rating scale assessing fatigue using cut-offs defined by the measure used. Such rating scales can be specific to fatigue, or may assess fatigue as part of a wider symptom screen (e.g. as part of quality of life). We included studies in which fatigue was self-reported using any validated method. Due to the subjective nature of fatigue, we excluded studies using clinician-reported or relative- or carer-reported measures, because these may not be a true reflection of the person's symptoms.

If fatigue was measured by a rating scale, we aimed to quantify its improvement with respect to the recommended scale threshold for clinical significance (or 'caseness'). If possible, we also aimed to record the total number of people reaching 'non-fatigued' status.

Secondary outcomes

- General functioning, including quality of life measurements, and depression (e.g. Hospital Anxiety and Depression Scale

(HADS) and cognitive outcomes (e.g. Addenbrooke's Cognitive Examination – 3rd version (ACE-III)) according to validated measures.
- Overall survival (OS) and progression-free survival (PFS).
- Adverse events as described by Katz 2012. Adverse event occurrence: clinical adverse events; any serious adverse event as defined by any medical occurrence in any participant that resulted in a dose reduction or treatment discontinuation, which did not necessarily have causal relationship with the treatment. The International Conference on Harmonisation Guidelines defines serious adverse events as any event that may jeopardise the person or require an intervention to prevent it (ICH-GCP 1997). This includes any important medical event that: was life-threatening, led to death, resulted in significant or persistent disability or congenital anomaly/birth defect, or required hospitalisation or prolongation of existing hospitalisation, which may have jeopardised the person or required intervention to prevent it.

We aimed to combine outcomes in a meta-analysis. The secondary outcomes were not criteria for eligibility for this review, but were outcomes that we noted and reviewed.

Search methods for identification of studies

Electronic searches

In the original review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2), MEDLINE (1950 to March 2016), Embase (1980 to March 2016), PsycINFO (1974 to March 2016) and CINAHL (1982 to March 2016).

For this review update, we searched the following databases on 7 April 2022:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 4);
- MEDLINE via Ovid (February 2016 to March week 5 2022);
- Embase via Ovid (February 2016 to week 13 2022).

See Appendix 1; Appendix 2; and Appendix 3 for search strategies.

Searching other resources

Unpublished and grey literature

We searched ClinicalTrials.gov to identify ongoing trials using the search term "fatigue". We also approached the major co-operative trial groups active in this area (e.g. Edinburgh Centre for Neuro-Onocology and MD Anderson Cancer Center).

Handsearching

We handsearched the reference lists of included studies and previous systematic reviews. We handsearched the latest journal and conference materials from the following sources:

- Annual Meeting of the European Society of Medical Oncology (ESMO);
- Annual Meeting of the European Association of Neuro-Oncology (EANO);
- Annual Meeting of the World Federation of Neuro-Oncology (WFNO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Annual Meeting of the Society for Neuro-Oncology (SNO);
- Annual Meeting of the Society for Behavioral Medicine (SBM);
- Annual Meeting of the American Psychosocial Oncology Society (APOS);
- Annual Meeting of the International Psycho-Oncology Society (IPOS);
- Annual Meeting of the Multinational Association of Supportive Care in Cancer (MASCC).

Data collection and analysis

We completed the following data collection and analysis.

Selection of studies

We downloaded the titles and abstracts retrieved by electronic searches and removed duplicates. Three review authors (JD, DC, SYK) independently examined the remaining references in the original review; for the updated search, two review authors (JD, DC) independently examined references. The review authors were not blinded to the authors or affiliations of the studies. We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of the full text of potentially relevant references. Three review authors (JD, DC, SYK) independently assessed the eligibility of retrieved papers for the original review, and two review authors independently assessed eligibility for the updated review (JD, DC). We resolved disagreements by discussion and documented the reasons for exclusion.

Data extraction and management

Data extraction

We extracted data as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Three review authors (JD, DC, SYK) independently extracted data onto a data extraction form specially designed for the review for both the original review, and two review authors (JD, SYK) completed this for the update. For the cross-over trial identified in the original review, we extracted data as published, which included data for those that had completed both arms.

We extracted data on the following:

- article details (author, year of publication, journal citation, country and language);
- intervention (characteristics, e.g. drug name, dose and duration);
- study design and methodology (including inclusion and exclusion criteria, assignment process and timing of measurements);
- population demographics (e.g. age, gender and marital status) and total number involved;
- details of participants' health status (including tumour pathology and treatment details);
- dichotomous and continuous outcome measures (fatigue, cognitive functioning, quality of life, depression and adverse events);
- risk of bias.

Where possible, we extracted all data relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.

Data management

We collated and entered data into Review Manager 5 (Review Manager 2020).

Continuous data

Where possible, for continuous outcomes (e.g. fatigue scales, cognitive tests and measures, depression measures, quality of life measures), we expressed the treatment effect as a mean difference (MD) with 95% confidence interval (CI) when studies used the same scales or standardised mean difference (SMD) with 95% CI when studies used different scales. We extracted postintervention data to calculate the MD, the final value and standard deviation (SD) of the outcome of interest, and the number of participants assessed in each treatment arm at the end of follow-up. Where this was not possible, following guidance sought from the Cochrane Neuro-Oncology Group team, we presented the data in tables in the format published (e.g. medians and interquartile ranges (IQR)).

Dichotomous data

Where possible, for dichotomous outcomes (e.g. high or low fatigue), we extracted the number of participants in each treatment arm who experienced the outcome of interest, at baseline and at study endpoint. We aimed to dichotomise fatigue using validated thresholds. We noted the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using Cochrane's RoB 1 tool (Higgins 2011). This included assessment of:

- selection bias: random sequence generation and allocation concealment;
- performance bias: blinding of participants and personnel (participants and treatment providers);
- detection bias: blinding of outcome assessment;
- performance bias: participants received similar care outside of the intervention they received;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting of outcomes;
- other possible sources of bias.

See Appendix 4 for full description of each risk of bias area. Three review authors (JD, DC, SYK) in the original review and two review authors (JD, SYK) in the updated review applied the risk of bias tool independently and resolved differences by discussion. We summarised results in a risk of bias summary table. We aimed to interpret the results of any meta-analyses in light of the findings with respect to risk of bias. We judged and reported all bias criteria in terms of low, high or unclear risk of bias. We classified criteria as having an unclear risk of bias where there was insufficient information provided, or when there was uncertainty over the potential for bias. We contacted authors to clarify uncertainties, if possible. We noted that blinding may not have been possible for all treatment comparisons, particularly with respect to any non-pharmacological interventions such as exercise.

Measures of treatment effect

For continuous data, we used MDs or SMDs as appropriate, or as reported by the studies where MDs were not available from the authors. For dichotomous data, where possible, we calculated the risk ratio (RR) with 95% CIs.

Unit of analysis issues

Where applicable, we reported details where analysis was not associated with randomisation at the participant level or where individuals underwent more than one intervention. For example, where studies used a cluster-randomised or cross-over trial design.

Dealing with missing data

We did not impute missing outcome data for the primary outcome. Instead, if data were missing, or trial authors reported only imputed data, we contacted them to request data on the outcomes among participants who were assessed, where possible.

We included details of missing data in the narrative summary and risk of bias table, and stated whether authors examined the extent to which the missing data could have altered the results of the review.

Assessment of heterogeneity

We planned to assess heterogeneity between studies by visual inspection of forest plots (including the presence of outliers and a poor overlap of CIs), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). We planned to investigate and report heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, due to the differences in methodology regarding both the intervention and analyses, assessment of heterogeneity was not possible.

Assessment of reporting biases

Two review authors (JD, SYK) reviewed and recorded reporting biases.

We aimed to examine funnel plots to assess the potential for small-study effects, such as publication bias, if the meta-analysis included more than 10 trials.

Data synthesis

We planned to pool data for meta-analysis using Review Manager 5 if studies were comparable with respect to participants, interventions and outcomes (Review Manager 2020). We intended to combine studies at the level of the intervention itself (e.g. psychostimulant, cognitive behavioural therapy, exercise) rather than broad categories (e.g. pharmacological, psychological, behavioural). Had a meta-analysis been possible, we planned to carry it out the following.

- We planned to pool the MDs between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale and at the same primary study endpoint, otherwise we planned to pool SMDs.
- For dichotomous data, we intended to use RRs and 95% CIs.
- We intended to use random-effects models with inverse variance weighting for all meta-analyses, with 95% CIs (DerSimonian 1986).

- For dichotomous data for adverse events, we planned to pool RRs.
- We intended to note the time points at which outcomes were collected and reported.

However, data synthesis was not possible due to the heterogeneity between studies included in the review.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses comparing changes in scale score studies using identical scales, where appropriate. We also intended to perform subgroup analyses according to World Health Organization (WHO) tumour grade (low grade/high grade) and interventions delivered only during treatment/only during follow-up (Louis 2021). However, due to the differences in methodology regarding both the intervention and analyses, subgroup analysis and investigation of heterogeneity was not possible.

Sensitivity analysis

We planned to involve all review authors in determining whether sensitivity analysis would be required, under the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We intended to consider the following factors as possible sources of heterogeneity across studies.

- Differing study quality (high or low levels of risk of bias).
- Different classes of drugs.
- Dosage or scheduling differences.

We planned to identify additional possible types of sensitivity analyses during the conduct of the review. However, due to the differences in methodology regarding both the intervention and analyses, sensitivity analysis was not possible.

Summary of findings and assessment of the certainty of the evidence

Due to the heterogeneity in analysis approaches between studies, we created separate summary of findings tables using guidance from the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011), alongside correspondence with the Cochrane Neuro-Oncology Group team. We used the Cochrane risk of bias tool and GRADE approach to assess the certainty of the evidence.

RESULTS

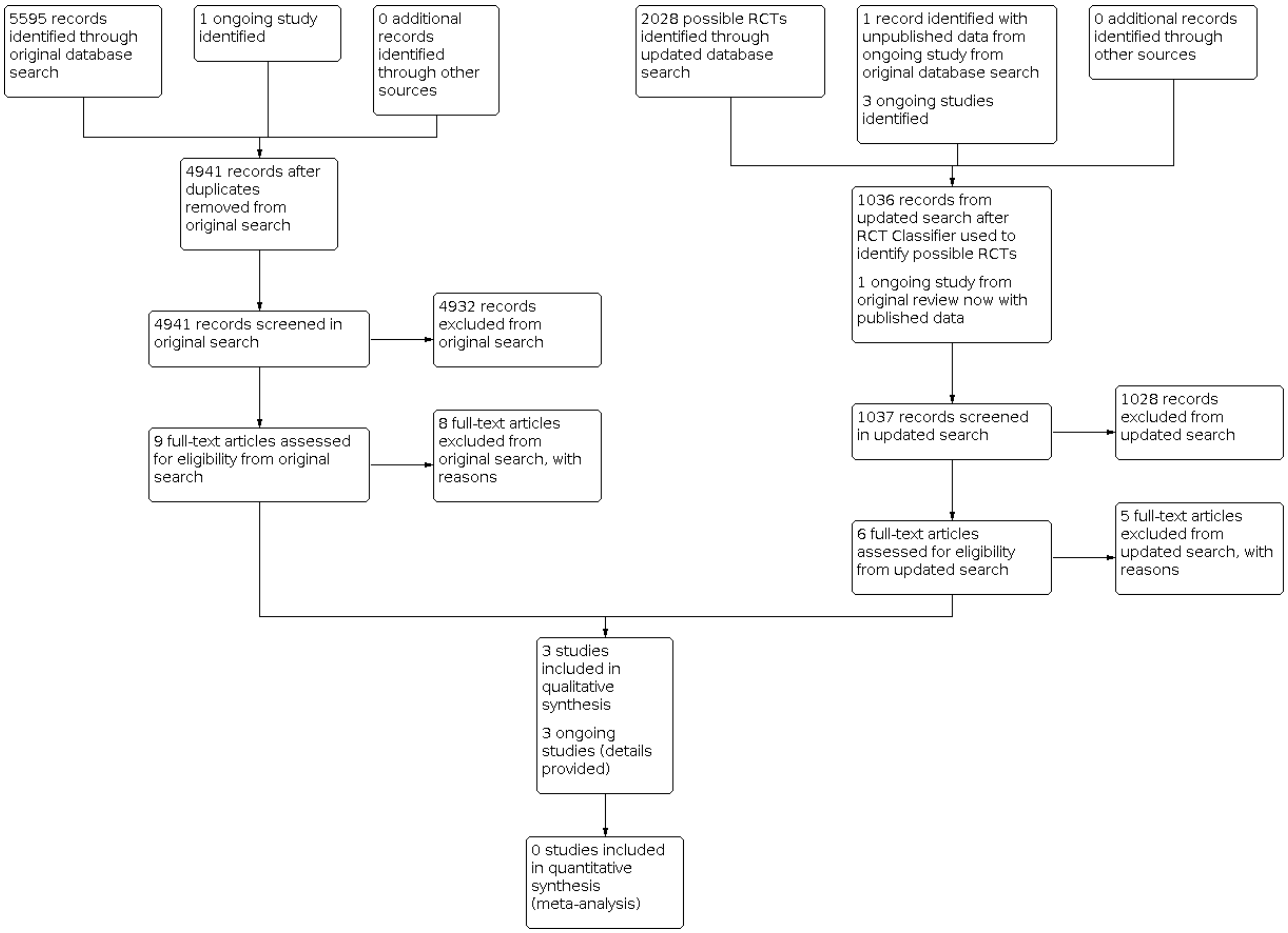
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

Figure 1 shows details of the search, including details of both the original review (Day 2016), and this updated search.

Figure 1. Study flow diagram. RCT: randomised controlled trial.



The original database search identified 5595 records and one ongoing study; the updated database search identified 2028 possible RCTs. Deduplication of the original search results identified 4941 citations, and the updated search identified 1036 records after using RCT Classifier to identify possible RCTs. We narrowed the original results to nine full-text articles upon screening of the titles and abstracts, and identified an additional six full-text articles were identified from the updated search. One trial was eligible for inclusion in the original review (Boele 2013), and two further studies were eligible for inclusion in the update (Laigle-Donadey 2019; Porter 2020). Thirteen studies did not meet our inclusion criteria for analysis due to the lack of high self-reported fatigue as a necessary inclusion criterion (Bigatão 2016; Boele 2018; Butler 2007; Gehring 2009; Gehring 2012; Gehring 2020; Hansen 2020; Kaleita 2006; Lee 2016; Locke 2008; Naughton 2018; Page 2015; Shaw 2006). We identified no additional studies when searching conference proceedings and the reference list of the single included trial in the original review (Day 2016). We identified no additional studies when contacting experts in the field. The updated search identified one trial awaiting classification (Rooney 2020), and three ongoing studies potentially eligible for a future update (Cordier 2019; NCT03259438; Röttgering 2020).

Included studies

For detailed information, see Characteristics of included studies table.

The original review identified one eligible trial (Boele 2013), the updated search identified two additional trials (Laigle-Donadey 2019; Porter 2020). Boele 2013 investigated the use of modafinil, Porter 2020 the use of armodafinil and Laigle-Donadey 2019 the use of dexamfetamine in treating fatigue in people with PBT compared with placebo.

Participant demographics

Boele 2013 recruited 37 of the estimated 64 required participants from three neuro-oncology centres in the Netherlands. Their mean age was 48.16 (SD 12.02) years. Participants had a meningioma (32.4%), low-grade glioma (37.8%) or high-grade glioma (29.7%), with most having had surgery (94.6%), without further radiotherapy (56.8%) or chemotherapy (78.4%). There were more women (62.2%) than men (37.8%). All participants were required to have experienced high fatigue, determined using a cut-off above 27 on the Checklist Individual Strength (CIS). The authors obtained ethical approval and registered the trial with a clinical trials database. All participants gave informed consent. The study recorded adverse events.

Laigle-Donadey 2019 recruited 46 of the estimated 58 required participants from seven centres in France; 41 participants were retained and included in the analyses. The mean age for those in the intervention arm was 55 years and in the control arm was 49 years. Participants had a high-grade glioma (75.6%), low-grade glioma (7.3%), CNS lymphoma (9.7%) and medulloblastoma

(7.3%). Thirty-four participants were treated with radiotherapy and chemotherapy, with three treated with radiotherapy alone and four treated with chemotherapy alone. Median time since initial treatment was 3.92 years (IQR 0.96 to 7.58) (intervention), and 3.78 years (IQR 1.04 to 8.41) (control), since last treatment. There were a similar number of men (51.2%) and women (48.8%). All participants were required to have experienced severe fatigue, determined using a cut-off of 60 or above on the 20-item Multidimensional Fatigue Inventory (MFI-20); without concomitant suspected depression, determined using a cut-off above 8 on the HADS. The authors obtained ethical approval and participants gave informed consent. The study recorded adverse events.

Porter 2020 recruited 328 participants; 297 were retained and included in the analyses. The mean age was 57.3 years (SD 12.3). There were more men (58.8%) than women (41.2%). As per the inclusion criteria, all participants had a clinically stable high-grade glioma with completed radiotherapy but ongoing chemotherapy was allowed; no further tumour or treatment characteristics were provided. All participants were required to experience high fatigue, determined used a cut-off equal to or above 6 on the 'worst' fatigue item of the BFI. The authors obtained ethical approval and registered the trial with a clinical trials database. All participants gave informed consent. The study recorded adverse events.

Intervention characteristics

Boele 2013 investigated the use of modafinil (2-benzhydrylsulfinylethanamide), a wakefulness-promoting drug that targets fatigue, cognitive functioning and mood. The study used a dose escalation, washout and cross-over method for both arms and participants received either modafinil then placebo or placebo then modafinil. It included a dose reduction and withdrawal technique if participants experienced adverse events. Laigle-Donadey 2019 investigated the use of dexamfetamine, a cognitive enhancer and wakefulness promoting drug. The study used dose escalation for both intervention and placebo arms. Where tolerance was not achieved at the next dose escalation level, a lower dose was maintained or of the drug was discontinued. Porter 2020 investigated two doses of armodafinil (150 mg and 250 mg) compared to placebo, given for eight weeks.

Primary and secondary outcomes

Boele 2013 assessed the primary outcome measure of fatigue using the CIS. It included secondary subjective measures of depression, health-related quality of life and everyday cognitive functioning. Cognitive functioning was assessed using a neuropsychological test battery to assess verbal memory, working memory, attention, executive function and psychomotor speed. Assessments were carried out at baseline, six weeks and 12 weeks.

Laigle-Donadey 2019 assessed the primary outcome measure of fatigue using the MFI-20, alongside the Norris Visual Analog Scale for fatigue. It included secondary outcome measures of depression, anxiety, cognitive function and quality of life. Cognitive function was assessment using a neuropsychological test battery to assess verbal memory, speed of mental processing, attention, verbal fluency and executive functions. The study also included a measure of toxicity and adverse events. Assessments were carried out at baseline and three months.

Porter 2020 assessed the primary outcome measure of fatigue using the BFI. It included secondary outcome measures of cognitive function and quality of life. Cognitive functioning was assessed using the Symbol Digit Modalities Test. The study also included a measure of adverse events. Assessments were carried out at baseline, four weeks and eight weeks.

Data collection

Boele 2013 used a cross-over trial design, therefore they collected data for each participant at baseline, six weeks, and on completion of the modafinil and placebo treatment schedules. Of 155 eligible participants, 39 participants met the inclusion criteria and agreed to participate. Two participants dropped out prior to randomisation leaving 37 participants in the trial, of whom 25 completed both treatment schedules and had all outcomes measured. Imputation was carried out for missing values for those who completed questionnaires and neuropsychological assessments.

Laigle-Donadey 2019 used a parallel design and collected data for each participant at baseline and on completion of the dexamfetamine and placebo treatment schedules. Of 50 eligible participants, 46 met the inclusion criteria and agree to participate. Of the 46 that started the treatment schedule, 23 in each arm, 19 completed the placebo arm and 22 completed the dexamfetamine arm. There was no imputation for missing data.

Porter 2020 used a parallel design and collected data for each participant at baseline, four weeks, and on completion of the armodafinil and placebo treatment schedules. A total of 109 participants completed the armodafinil 150 mg arm, 110 completed the armodafinil 250 mg arm and 109 completed the placebo arm. There was no imputation for missing data.

Statistical analyses

Boele 2013 used a within-participant design to determine differences between modafinil and placebo test scores. They used Wilcoxon signed-rank tests as no data were normally distributed. There were no corrections to account for multiple statistical testing.

Laigle-Donadey 2019 used a between-participant design to determine the differences between dexamfetamine sulfate and placebo test scores. They used Mann-Whitney tests for the primary analysis of continuous data and Chi^2 or Fisher's exact tests for dichotomous data. There were no corrections carried out to account for multiple statistical testing.

Porter 2020 used a between-participant design to determine the differences between the armodafinil arms and the placebo arm test scores. It used Fisher's exact tests for dichotomous data and Kruskal-Wallis test for continuous data. There were no corrections to account for multiple statistical testing.

Excluded studies

See Characteristics of excluded studies table. We found 13 studies (eight in the original search; five in the updated search) that included fatigue as a primary or secondary outcome measure, but we excluded them as high fatigue was not a necessary inclusion criterion for participation. Five studies investigated an intervention in people with brain tumours undergoing radiotherapy (Bigatão 2016; Butler 2007; Hansen 2020; Lee 2016; Page 2015). Eight studies evaluated an intervention in people with brain tumours not on active treatment (Boele 2018; Gehring 2009; Gehring 2012; Gehring 2020; Kaleita 2006; Locke 2008; Naughton 2018; Shaw 2006).

Studies of people undergoing radiotherapy

Bigatão 2016 evaluated the effectiveness of an educational programme (information leaflet and tailored guidance) to improve fatigue in an RCT with 23 participants with a high-grade glioma undergoing radiotherapy and chemotherapy. Participation was not limited to people with high fatigue. There was no difference in fatigue between groups, assessed via the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) questionnaire, compared to control.

Butler and co-authors evaluated the use of d-threo-methylphenidate hydrochloride in a double-blind, placebo-controlled RCT in people with primary metastatic brain tumours receiving radiotherapy. Participation was not limited to people with fatigue. The study enrolled 68 participants. Using the FACT-F, there were no differences between groups in measures of fatigue eight weeks after the completion of radiotherapy (P = 0.64) (Butler 2007).

Hansen 2020 assessed the effectiveness of a physical therapy and occupational therapy rehabilitation programme for people with glioma undergoing active treatment for cancer compared to rehabilitation as usual for quality of life. Participation was not limited to people with fatigue. A total of 64 participants were randomly assigned to each group. Participants were required to be functionally independent but participation was not limited to people with fatigue. There was a reduction in fatigue in the intervention group, compared to control (P = 0.04), assessed via the EORTC QLQ-C30; however, the study was limited by insufficient power.

Since the original review summarised initial data reported in conference proceedings, Lee and co-authors completed and published a placebo-controlled pilot RCT of armodafinil, which included 81 people undergoing radiotherapy (Lee 2016). Participation was not limited to people with fatigue. Using several measures of fatigue, the authors concluded armodafinil had no effect on fatigue comparing the change in scores from baseline to study endpoint at 55 days between intervention and control group (FACIT-F: P = 0.97; BFI: P = 0.30; Cancer Fatigue Scale: P = 0.40).

Page and co-authors conducted a double-blind placebo-controlled study of armodafinil on fatigue in people undergoing cranial irradiation. Fatigue was not a necessary inclusion criterion. The study enrolled 54 participants, and measured fatigue and day-time sleepiness. There were no differences in outcome measures between groups at the end of radiotherapy or at a four-week follow-up compared to baseline. However, in a post-hoc analysis, there was an improvement in fatigue in participants with higher baseline fatigue measured using the FACIT-F (Page 2015).

Studies of people not on active tumour treatment

Boele 2018 evaluated the effectiveness of a five-week Internet-based self-help programme for people with a glioma with depressive symptoms. Participants with glioma were randomised to the self-help programme or a waiting list group. The analysis compared all participants with glioma after completing the self-help programme to participants with non-CNS cancer controls who also received the intervention. The study included 89 people with glioma (35% of whom completed the intervention) and 26 non-CNS cancer controls (54% of whom completed the intervention). Participation was restricted to people with depressive symptoms, rather than fatigue. There were no differences between intervention and waiting list groups at 12-week follow-up for the primary outcome measure of depression (P = 0.61) or fatigue (P = 0.24).

Gehring and co-authors investigated the use of a cognitive rehabilitation programme in people with glioma in a randomised waiting list controlled trial. Participation was restricted to people with subjective and objective cognitive deficits, rather than fatigue. The study enrolled 140 adults, and measured cognition, fatigue, quality of life and community integration. Using the MFI, people in the intervention arm reported lower mental fatigue at six months compared to baseline (P = 0.026), but not activity (P = 0.82) or motivation (P = 0.063) (Gehring 2009).

Gehring and co-authors enrolled 24 people with brain tumours in an open-label randomised pilot trial comparing methylphenidate and modafinil. Participation was not limited to people with fatigue. The primary outcome measure was cognitive function. Other outcome measures included fatigue, sleep disturbance, mood and quality of life. In a post-hoc analysis that combined the treatment groups, there was a beneficial effect on fatigue at four weeks compared to baseline measured using the BFI (P = 0.04) (Gehring 2012).

Gehring 2020 completed a pilot RCT to evaluate an exercise programme to improve cognitive performance in participants with a stable glioma. Participants were randomly assigned to the exercise programme (21 participants) or control group (11 participants), and results found small- to medium-effect sizes across measures of cognition, fatigue, sleep, mood and mental-health related quality of life.

Kaleita and co-authors conducted a double-blind dose-controlled RCT of modafinil on cognition, mood and fatigue in people with brain tumours. The study did not restrict participation to people with fatigue. There were 30 participants in the study. There were improvements in fatigue, using the Fatigue Severity Scale, at eight (P < 0.0001) and 12 weeks (P = 0.0003) after modafinil initiation compared to baseline (Kaleita 2006).

Locke and co-authors reported the feasibility of a cognitive rehabilitation and problem-solving programme in 19 people with PBT. Participation was not restricted to people with fatigue. The study included measures of fatigue, cognition, mood and quality of life. The study used the BFI to assess fatigue. There were no statistical analyses, but most participants in both groups had only mild fatigue (Locke 2008).

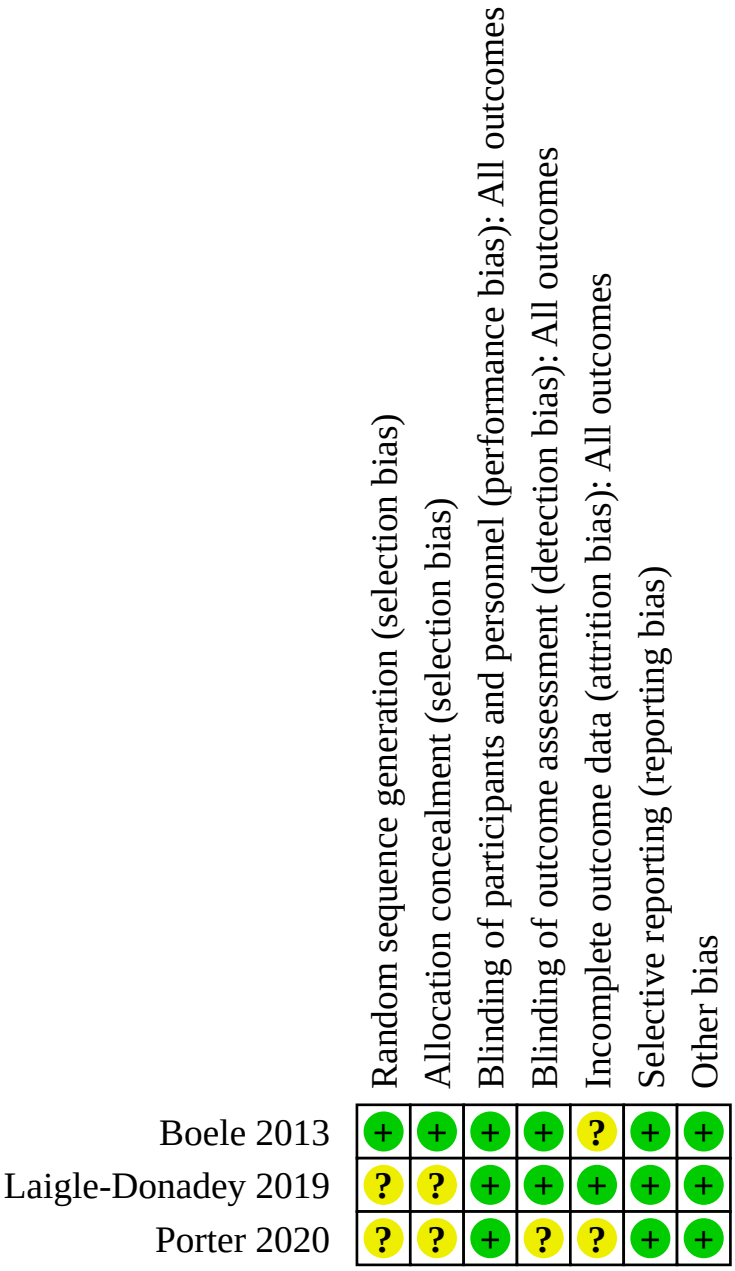
Naughton 2018 evaluated the effectiveness of donepezil compared with placebo for improving quality of life in people with a brain tumour who had received greater than 30 Gy fractionated whole or partial brain irradiation more than six months prior to study enrolment. The study randomised 198 participants to the two groups, and participation was not limited to those with fatigue. At study endpoint of 24 weeks, there was no difference between groups for fatigue assessed using the FACIT-F (P = 0.59).

Shaw and co-authors evaluated 24 people with a brain tumour enrolled to a single-arm open-label study of donepezil. Participation was not limited to people with fatigue. The study recorded cognition, mood, fatigue and quality of life. There was an improvement in fatigue at 24 weeks using the Profile of Mood States Fatigue Subscale (P = 0.03) (Shaw 2006).

Risk of bias in included studies

We assessed the included trials using the Cochrane risk of bias tool (Higgins 2011). Where risk of bias was unclear, we contacted the author for clarification. Following discussion, we reached agreement on risk of bias scores. Figure 2 shows the risk of bias summary.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Boele 2013 was at low risk of selection bias, using a pharmacy randomisation system to allocate participants to each treatment arm. This was confirmed via correspondence to be through the use of a computer randomisation system. Laigle-Donadey 2019 and Porter 2020 were at an unclear risk of bias, as there was no mention of how the randomisation was performed and there was no analysis to assess whether the two groups were different in baseline characteristics.

Blinding

Boele 2013 was at a low risk of bias for both performance and detection bias. Participants, treating physicians and researchers were blind to treatment allocation. Laigle-Donadey 2019 was at a low risk of bias for both performance and detection bias as they used identical-appearing tablets and scheduled doses, with a double-blind methodology reported. Porter 2020 was at a low risk of bias for performance bias, with a double-blind methodology reported. There was an unclear risk of detection bias as they provided no details.

Incomplete outcome data

Boele 2013 was at unclear risk of attrition bias. The study reported that 12 participants dropped out: a similar number of participants dropped out between baseline and six-week follow-up (modafinil arm: four participants; placebo arm: three participants); more participants dropped out of the placebo arm (four) than the modafinil arm (one) between six-week follow-up and 12-week follow-up. It was unclear why participants dropped out; therefore, we contacted the author of correspondence to request clarification. Five participants dropped out of the trial due to adverse events while receiving modafinil; three participants received modafinil first, two participants received modafinil second. Two participants dropped out of the trial due to adverse events while receiving placebo. The study used mean imputation where there were missing values in attempted questionnaires or neuropsychological assessments. They did not carry out an analysis to determine whether imputation or missing data could have altered the results of the study.

Laigle-Donadey 2019 was at low risk of bias as there was a high retention rate of 89% with details provided regarding reasons for drop-out.

Porter 2020 was at an unclear risk of bias, with no details provided for missing data.

Selective reporting

Boele 2013 and Porter 2020 were at low risk of reporting bias as all outcomes appear to have been reported. Laigle-Donadey 2019 was at low risk of bias with all outcomes reported, except the non-analysed data, where 50% of data were missing.

Other potential sources of bias

We identified no additional sources of bias.

Effects of interventions

See: **Summary of findings 1** Boele 2013: modafinil compared with placebo for fatigue in people with a primary brain tumour; **Summary of findings 2** Laigle-Donadey 2019: dexamfetamine sulfate compared with placebo for fatigue in primary brain tumour; **Summary of findings 3** Porter 2020: armodafinil compared with placebo for fatigue in high-grade glioma

In the original search, found one eligible trial that investigated the use of modafinil in treating fatigue in people with PBT compared to placebo (Boele 2013; see Summary of findings 1). In the updated search, we found one study investigating the use of dexamfetamine sulfate for treating fatigue in people with PBT compared with placebo (Laigle-Donadey 2019; see Summary of findings 2), and one trial investigating the use of armodafinil in treating fatigue in people with a high-grade glioma compared to placebo (Porter 2020; see Summary of findings 3).

Primary outcome

Fatigue at study endpoint

Boele 2013 found no evidence of a difference in fatigue measures between modafinil and placebo score for concentration problems, reduced motivation, reduced activity or fatigue severity (concentration problems: MD −1.06, 95% CI −3.18 to 1.06; reduced motivation: MD −0.48, 95% CI −2.93 to 1.97; reduced activity: MD −1.01, 95% CI −5.64 to 3.62; fatigue severity: MD −0.22, 95% CI −0.79 to 0.35; 55 participants; Analysis 1.1).

Laigle-Donadey 2019 (41 participants) found no evidence of a difference in fatigue between dexamfetamine sulfate and placebo groups, assessed via the MFI-20 (P = 0.17) and the asthenia subscale of the Norris Scale (P = 0.97).

Porter 2020 (297 participants) found no evidence of a difference in fatigue between the two armodafinil and placebo arms, comparing groups on the number of clinically significant improvement in fatigue (measured as a 2-point increase on the BFI) at four (P = 0.79) or eight (P = 0.96) weeks.

Secondary outcomes

Cognitive functioning

Boele 2013 found a difference between modafinil and placebo using neuropsychological test battery scores in attentional functioning favouring modafinil (MD −0.03, 95% CI −0.05 to −0.01; 53 participants). There were no differences in objective cognitive functioning (verbal memory: MD 0.26, 95% CI −0.05 to 0.57; working memory: MD 0.07, 95% CI −0.04 to 0.18; information processing: MD 0.17, 95% CI −1.19 to 1.53; executive function: MD 0.14, 95% CI −9.33 to 9.61; psychomotor speed: MD 0.10, 95% CI −0.26 to 0.46; 53 participants; Analysis 1.2), and subjective cognitive functioning (MD 1.62, 95% CI −0.74 to 3.98; 55 participants; Analysis 1.3).

Laigle-Donadey 2019 (41 participants) found no evidence of a difference between dexamfetamine and placebo scores in Semantic Fluency, (P = 0.41) Lexical Fluency (P = 0.64), the Grober and Buschke test (P = 0.76), the Trail Making Test A (P = 0.29) and B (P = 0.61), and subjective cognitive functioning assessed via the Mattis Scale (P = 0.34) (Summary of findings 2). Data regarding the modified Wisconsin Card Sorting Test were not analysed due to missing data.

Porter 2020 found no evidence of a difference between the two armodafinil and placebo arms on the Symbol Digit Modalities Test comparing group median z-score differences between baseline and eight weeks (P = 0.33; 297 participants; Summary of findings 3).

Quality of life

Boele 2013 found no evidence of a difference between modafinil and placebo scores for subjective measures of depression (MD 0.19, 95% CI −1.33 to 1.71; Analysis 1.4), or quality of life (physical: MD 1.34, 95% CI −20.11 to 22.79; mental: MD −1.40, 95% CI −4.84 to 2.04) (Analysis 1.5).

Laigle-Donadey 2019 (41 participants) found no evidence of a difference between dexamfetamine sulfate and placebo groups for affectivity (P = 0.06), apathy (P = 0.46), anxiety and depression (P = 0.77) or quality of life (P = 0.10, assessed using the EORTC QLQ-C30; P = 0.06, assessed via the EORTC QLQ-BM 20).

Porter 2020 found no evidence of a difference between the two armodafinil and placebo arms for subjective measures of quality of life assessed using the Linear Analogue Self Assessment (P = 0.91; 297 participants).

Adverse events

Boele 2013 reported adverse events included tingling sensations, depressive feelings or behaviours, nervousness, dizziness, vertigo, headaches, loss of appetite and seizures. Five participants dropped out of the trial due to adverse events while receiving modafinil; two participants dropped out of the trial due to adverse events while receiving placebo. There was no difference in adverse events reported between groups (RR 2.79, 95% CI 0.59 to 13.16; 55 participants; Analysis 1.6).

Laigle-Donadey 2019 reported 41/46 (89%) randomised participants with at least one adverse event related to treatment. More participants reported adverse events with dexamfetamine sulfate (100% with dexamfetamine sulfate versus 78% with placebo; P = 0.049). Most adverse events were considered grade 1 toxicities (81% with dexamfetamine sulfate versus 82% with placebo), with few grade 2 and 3 toxicities. Further analysis identified more participants in the dexamfetamine sulfate arm, compared to the placebo arm, reported psychological adverse effects (including anxiety, irritability, hyperactivity and sleep disorder; P = 0.018).

Porter 2020 reported adverse events including vertigo, gastrointestinal symptoms, fatigue, sepsis, urinary tract infection, injury, metabolic investigations, muscle weakness, neurological symptoms (e.g. dizziness, seizure), confusion, respiratory symptoms and vascular symptoms. Seventeen participants in the armodafinil 150 mg arm had a serious adverse event, 19 in the armodafinil 250 mg arm and 17 in the placebo arm. Three participants died during the eight-week intervention period; two in the armodafinil 250 mg arm and one in the placebo arm.

DISCUSSION

The aim of this review was to determine the effectiveness of interventions to treat high fatigue in people with PBT. We included three RCTs, one comparing the effect of modafinil with placebo (Boele 2013), one comparing armodafinil with placebo (Porter 2020), and one comparing dexamfetamine sulfate with placebo (Laigle-Donadey 2019).

Summary of main results

Boele 2013 recruited 37 participants and used a cross-over design to compare modafinil and placebo across three centres in the Netherlands. The washout period between treatments was one week. Since the half-life of modafinil is 10 hours to 12 hours, the washout period was likely adequate. There was no evidence of a difference in fatigue between modafinil and placebo groups. This finding was difficult to interpret because the trial failed to reach its recruitment target and may have lacked power to exclude a false-negative result. There were improvements in fatigue severity and motivation in both modafinil and placebo conditions compared with baseline.

Laigle-Donadey 2019 recruited 46 participants and used a parallel design to compare dexamfetamine and placebo across seven centres in France. There was no evidence of a difference in fatigue or other outcome measures between groups and there was a significantly higher number of adverse events in the dexamfetamine arm compared to placebo.

Porter 2020 recruited 328 participants and used a parallel design to compare two doses of armodafinil and placebo; there were no details regarding recruitment location. There was no evidence of a difference in fatigue or other outcome measures between groups.

Overall completeness and applicability of evidence

We could only include three RCTs examining the effectiveness of an intervention to treat fatigue in adults with PBT. Two trials included people with glioma and meningioma tumours (Boele 2013; Laigle-Donadey 2019), and one trial included people with a high-grade glioma (Porter 2020), and, therefore, may be representative across these brain tumour types. All participants were fatigued at baseline and, therefore, results could potentially generalise to people with fatigue. However, the heterogeneity of the trials suggests that, overall, conclusions regarding the applicability of the evidence was limited.

We excluded 13 studies that reported fatigue outcomes, but which enrolled a general population of people with brain tumours or where another symptom was required for inclusion (e.g. depression, cognitive impairment) rather than restricting eligibility to people who were highly fatigued. We excluded these studies in order that our conclusions could be readily applied to a clinically relevant problem. However, we recognised that the excluded studies contained valuable data. More research is needed into whether the interventions investigated specifically benefit highly fatigued people with PBT, who are the ones most likely to require treatment in clinic.

Quality of the evidence

See Summary of findings 1; Summary of findings 2; Summary of findings 3.

This review summarised the current evidence for the effect of pharmacological and non-pharmacological interventions for the treatment of fatigue in adults with PBT. There were only three trials eligible for inclusion. Two trials were at a low risk of bias across most areas and one trial was at unclear risk of bias across most areas; most unclear risk of bias assessments were selection and attrition biases. Due to issues with incomplete outcome data and low accrual, the overall certainty of the evidence was very low. As such, further evidence is very likely to have an important impact on our confidence in possible pharmacological and non-pharmacological interventions for improving fatigue in people with a PBT. We found one feasibility RCT assessing a

non-pharmacological intervention for the treatment of fatigue in people with a PBT that is awaiting classification as data are not yet published. This study compared participants receiving 'health coaching', 'health coaching plus patient activation' and fatigue management information (Rooney 2020). There are also three ongoing studies that may be eligible for a further update, all investigating a non-pharmacological intervention for participants with fatigue, including cognitive behavioural therapy and exercise (see Characteristics of ongoing studies table). These studies will hopefully offer more evidence for inclusion in a future update.

Potential biases in the review process

We searched four databases extensively, which included published studies and the most recent conference proceedings. We also searched the reference list of the trial included in the original review. Though we thoroughly handsearched the literature and searched online databases for unpublished and grey literature, we may have nevertheless failed to identify all eligible studies, specifically those that have not been published.

Agreements and disagreements with other studies or reviews

Authors of two narrative reviews on this topic also highlighted the lack of high-certainty evidence for treatment, noting favourable effectiveness of interventions in the general cancer population (Armstrong 2012; Schiff 2015). One editorial by Grant 2016 highlighted the importance of an agreed definition of high fatigue for future studies investigating interventions.

In other cancer populations, one Cochrane Review evaluating drug therapy for the management of cancer-related fatigue estimated the effect of several drugs including psychostimulants, haematopoietic growth factors, antidepressants and progestational steroids (Minton 2010). Psychostimulants showed a small but significant improvement in fatigue over placebo ($z = 2.83$; $P < 0.01$). The conclusions were based on small samples. The differences in these results from this review may be due to the inclusion in our review of only people with PBT, that only three studies met our predefined inclusion criteria, and that modafinil and dexamfetamine sulfate were included in the cancer-related review.

AUTHORS' CONCLUSIONS

Implications for practice

At present, the effectiveness of any treatment for high fatigue in people with primary brain tumours is unclear. Only three trials met our predefined inclusion criteria. This limits the conclusions that can be drawn.

Given the relative lack of high-certainty evidence for both efficacy and adverse effects, if a person with a primary brain tumour and high fatigue starts pharmacological treatment for fatigue, it would be advisable to use close follow-up. Nevertheless, high-certainty research remains important to identify the most effective interventions for fatigue following a brain tumour**.**

Implications for research

Adequately powered randomised controlled trials are provide the best evidence to address the benefits and risks of using pharmacological and non-pharmacological interventions. Further, other trials that have enrolled a general population of people with brain tumour (i.e. those not limited to high fatigue) suggest a potential benefit of certain treatments, but these data are difficult to generalise to clinical practice and require further study. Therefore, important research questions may include whether any intervention focusing on decreasing fatigue in people with primary brain tumours:

- is effective in treating high fatigue;
- has clinically significant effects on depression and cognition;
- has clinically significant pharmacokinetic interactions with tumour-related treatment (antiepileptic drugs, chemotherapy);
- has clinically significant effects on activity, role and participation outcomes for the individual patient.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boele 2013

Study characteristics	
Methods	Double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria:** aged ≥ 18 years; diagnosed with a histologically confirmed glioma or meningioma; no signs of tumour recurrence in last 6 months; fatigue self-reported CIS score > 27 **Exclusion criteria:** history of psychiatric disease or symptoms; expected adverse interactions between prescribed medications and modafinil; unable to communicate in Dutch **Number randomised:** modafinil: 20; placebo: 17 **Age:** 48.16 (SD 12.02) years **Sex:** 62.2% women; 37.8% men **Tumour type:** meningioma (32.4%), low-grade glioma (37.8%) or high-grade glioma (29.7%) **Previous treatment:** surgery (94.6%), without further radiotherapy (56.8%) or chemotherapy (78.4%) **Follow-up:** 6 weeks and 12 weeks **Setting:** 3 centres in the Netherlands
Interventions	2 treatment arms for 6 weeks' duration **Arm I treatment schedule** Week 1: oral modafinil 200 mg per day in 2 divided does (100 mg upon waking, 100 mg at lunchtime) Week 2–6: oral modafinil 400 mg per day in 2 divided doses (200 mg upon waking, 200 mg at lunchtime) Week 7: washout period Week 8–12: matched placebo **Arm II treatment schedule** Week 1–6: matched placebo Week 7: washout period Week 8: oral modafinil 200 mg per day in 2 divided does (100 mg upon waking, 100 mg at lunchtime) Week 9–12: oral modafinil 400 mg per day in 2 divided doses (200 mg upon waking, 200 mg at lunchtime)
Outcomes	Fatigue (CIS) Depression (Center for Epidemiologic Studies Depression Scale)

Boele 2013 *(Continued)*

	Health-related quality of life (Medical Outcomes Study Short-Form Health Survey) Subjective cognitive functioning (Medical Outcomes Study subjective cognitive functioning scale) Objective cognitive functioning (Rey Auditory Verbal Learning Test, Memory Comparison Test, Stroop Colour Word Test, Letter Digit Substitution Test, Concept Shifting Test, Categorical Word Fluency Test, Concept Shifting Test)
Notes	Mean imputation used where missing values were present in questionnaires or neuropsychological assessments. No corrections for multiple statistical testing carried out.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A pharmacy randomization system was used to assign participants". Comment: confirmed via correspondence.
Allocation concealment (selection bias)	Low risk	Quote: "A pharmacy randomization system was used to assign participants". Comment: confirmed via correspondence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, treating physicians, and researchers were blind to treatment allocation". Comment: confirmed via correspondence.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, treating physicians, and researchers were blind to treatment allocation". Comment: confirmed via correspondence.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how much imputation may have affected the result as sensitivity analysis was not carried out to determine whether missing data altered the results of the review. Similar number of participants dropped out between time points baseline and 6-week follow-up (modafinil arm: 4 participants; placebo arm: 3 participants), more participants dropped out of placebo arm (4 participants) than modafinil arm (1 participant) between 6-week follow-up and 12-week follow-up. Mean imputation was used where missing values were present in questionnaires or neuropsychological assessments. Details of adverse events per group confirmed through correspondence with the lead author. 5 participants dropped out due to adverse events while receiving modafinil. Details per participant were: • tingling sensations, depressive feelings, feeling nervous/fidgety, dizziness; • depressive feelings, crying without a clear cause; • vertigo, feeling as if about to get a seizure, 'light feeling' in head; • increased headaches, feeling nervous, tingling sensations, feeling anxious; • reduced appetite, nausea, sometimes vomiting, stuffy feeling in head, feeling fidgety. 2 participants dropped out of the trial due to adverse events while receiving placebo. Details per participant were: • vertigo, nausea;

Boele 2013 *(Continued)*

		• seizures, fatigue.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Laigle-Donadey 2019

Study characteristics	
Methods	Double-blind, randomised placebo-controlled trial
Participants	**Inclusion criteria:** aged ≥ 18 years; KPS > 60; diagnosed with a histologically confirmed and stable PBT; ≥ 3 months since radiotherapy with or without (concurrent) chemotherapy; severe self-reported fatigue on the 20-item Multidimensional Fatigue Inventory (score ≥ 60) **Exclusion criteria:** treatable fatigue; other symptoms impacting test completion (e.g. severe aphasia); contraindications for amphetamines; co-occurring depression (assessed as a HADS score > 8) **Number randomised:** dexamfetamine: 23; placebo: 23 **Age (mean):** intervention: 55 years; control: 49 years **Sex:** women (48.8%); men (51.2%) **Tumour type:** high-grade glioma (75.6%), low-grade glioma (7.3%), CNS lymphoma (9.7%) and medulloblastoma (7.3%) **Previous treatment:** radiotherapy + chemotherapy: 34 participants; radiotherapy alone: 3 participants; chemotherapy alone: 4 participants **Follow-up:** 3 months **Setting:** multi-institutional in France
Interventions	2 arms for 3 months' duration **Arm 1 treatment schedule** Day 1–10: dexamfetamine 10 mg in divided doses (5 mg in the morning, 5 mg at noon) Day 11–20: if previous dose tolerated, dexamfetamine 20 mg in divided doses (2 × 5 mg in the morning, 2 × 5 mg at noon) Day 21–30: if previous dose tolerated, dexamfetamine 30 mg taken in divided doses (3 × 5 mg in the morning, 3 × 5 mg at noon) Day 31: if previous dose tolerated, dexamfetamine 30 mg dose continued to 3-month endpoint. If not tolerated, dexamfetamine 10 mg taken in divided doses until 3-month endpoint **Arm II placebo schedule** Day 1–10: 2 × identical-appearing tablets (1 × in the morning, 1 at noon) Day 11–20: if previous dose tolerated, 4 × identical-appearing tablets (2 × in the morning, 2 at noon) Day 21–30: if previous dose tolerated, 6 × identical-appearing tablets (3 × in the morning, 3 at noon) Day 31: if previous dose tolerated, 6 × identical-appearing tablets continued to 3-month endpoint

Laigle-Donadey 2019 *(Continued)*

Outcomes	Fatigue (20-item Multidimensional Fatigue Inventory) Depression (HADS) Quality of Life (EORTC QLQ-C30/EORTC QLQ-BN 20) Cognition (Mattis Dementia Rating Scale, Verbal Fluency-Category test, Trail Making Test Parts A and B, Wisconsin Card Sorting Test, Marin Apathy Scale, Grober and Buschke test Toxicity and adverse events (Norris Scale)
Notes	Did not state any use of imputation for missing data. No corrections for multiple statistical testing carried out.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Manuscript did not mention how the randomisation was performed and there was no reported analysis to assess whether the 2 groups were different at baseline.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing tablets and dose schedule.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated double-blind methodology used. Probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High retention rate 89% with reasons for drop-out specified: • "progression of disease (n = 1 in the placebo arm), • refusal of further therapy (n = 1 in the placebo arm), • exclusion criteria discovered only after inclusion because they had previously been masked by the patients themselves (depression and hyperthyroid disease, 2 patients in the placebo arm), • and loss to follow-up (1 participant in the DXA [dexamfetamine] arm)"
Selective reporting (reporting bias)	Low risk	Data not analysed for 1 cognitive test due to about 50% missing data. All other outcomes reported.
Other bias	Low risk	None.

Porter 2020

Study characteristics

Methods	Double-blind randomised placebo-controlled trial
Participants	**Inclusion criteria:** adults diagnosed with a high-grade glioma; ≥ 4 weeks following radiotherapy; previous surgery or biopsy with concurrent radiotherapy and chemotherapy; clinically stable or im-

Porter 2020 *(Continued)*

	proved KPS compared to previous month; stable dose of corticosteroids; fatigue self-reported > 6 on the 'worst' item of the BFI **Exclusion criteria:** pregnancy **Number randomised:** armodafinil 150 mg: 103; armodafinil 250 mg: 97; placebo: 97 **Age:** 57.3 (SD 12.3) years **Sex:** women: 41.2%; men: 58.8% **Tumour type:** clinically stable high-grade glioma; no further details **Previous treatment:** completed radiotherapy but ongoing chemotherapy was allowed; no further details **Follow-up:** 4 weeks and 8 weeks **Setting:** USA
Interventions	2 treatment arms, 1 placebo arm, for 8 weeks' duration **Arm I treatment schedule** Oral armodafinil 150 mg taken in the morning for 8 weeks **Arm II treatment schedule** Oral armodafinil 250 mg taken in the morning for 8 weeks **Arm III placebo schedule** Oral placebo taken in the morning for 8 weeks
Outcomes	Fatigue (BFI) Health-related quality of life (Linear Analogue Self-Assessment) Objective cognitive functioning (Symbol Digit Modalities Test) Adverse events (Common Terminology Criteria for Adverse Events Version 4.0)
Notes	Data not yet published – data available via ClinicalTrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There was no mention how the randomisation was performed and there was no reported analysis to assess whether the 2 groups were different at baseline.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind methodology reported. Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.

Porter 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of reasons missing data.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

BFI: Brief Fatigue Inventory; CIS: Checklist Individual Strength; EORTC QLQ-BN 20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Brain Neoplasm; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; HADS: Hospital Anxiety and Depression Scale; KPS: Karnofsky Performance Scale; PBT: primary brain tumour.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bigatão 2016	Fatigue was not a necessary inclusion criterion.
Boele 2018	Fatigue was not a necessary inclusion criterion.
Butler 2007	Fatigue was not a necessary inclusion criterion.
Gehring 2009	Fatigue was not a necessary inclusion criterion.
Gehring 2012	Fatigue was not a necessary inclusion criterion.
Gehring 2020	Fatigue was not a necessary inclusion criterion.
Hansen 2020	Fatigue was not a necessary inclusion criterion.
Kaleita 2006	Fatigue was not a necessary inclusion criterion.
Lee 2016	Fatigue was not a necessary inclusion criterion.
Locke 2008	Fatigue was not a necessary inclusion criterion.
Naughton 2018	Fatigue was not a necessary inclusion criterion. No control group.
Page 2015	Fatigue was not a necessary inclusion criterion.
Shaw 2006	Fatigue was not a necessary inclusion criterion. No control group.

Characteristics of studies awaiting classification *[ordered by study ID]*

Rooney 2020

Methods	Randomised controlled feasibility trial
Participants	**Inclusion criteria:** adults aged ≥ 18 years diagnosed with a primary brain tumour; ≥ 3 months since radiotherapy or chemotherapy (or both); clinically and radiologically stable; self-reported fatigue > 4 on Brief Fatigue Inventory

Rooney 2020 *(Continued)*

	Exclusion criteria: inability to give informed consent; clinically unstable; radiological progression; significant cognitive or sensory impairment **Number randomised:** 46 **Follow-up:** after interventions and at 16 weeks **Setting:** 4 centres across the UK
Interventions	2 treatment arms and 1 self-guided support arm, of 16 weeks **Arm I 'Health Coaching' schedule** Participants received an information leaflet and 'Health Coaching', which involved an individualised programme based on physical measurements and lifestyle information. Participants wore an activity monitoring device and recorded information in a diary. Participants were offered 5 × 45-minute Health Coaching sessions (delivered remotely or in person) focused on setting personal goals to change lifestyle factors contributing to fatigue. **Arm II 'Health Coaching plus Patient Activation' schedule** Participants received the same intervention as in arm I plus Patient Activation. Participants were offered 2 × 1-hour Patient Activation sessions, delivered by a trained coach, focused on improving their approach to managing fatigue. **Arm III control schedule** Participants were given fatigue management information alongside treatment as usual.
Outcomes	Feasibility (participant recruitment and retention, acceptability, manageability) Fatigue (Brief Fatigue Inventory) Depression (Hospital Anxiety and Depression Scale) Quality of Life (Psychological Outcome Profiles)
Notes	Data not yet published

Characteristics of ongoing studies *[ordered by study ID]*

Cordier 2019

Study name	Effects of two types of exercise training on psychological well-being, sleep, quality of life and physical fitness in patients with high-grade glioma (WHO III and IV): study protocol for a randomized controlled trial
Methods	Randomised controlled clinical trial Participants randomly assigned to receive 1 of 2 exercise courses or to a control group
Participants	**Inclusion criteria:** adults aged 18–75 years with a diagnosis of high-grade glioma, following treatment (surgery with radiotherapy or chemotherapy, or both) **Exclusion criteria:** diagnosis of severe psychiatric disorder or severe health comorbidities (e.g. severe diabetes, severe cardiovascular disease)
Interventions	**Arm 1:** endurance training for 2 × 40- to 60-minute sessions per week for 6 weeks **Arm 2:** resistance training for 2 × 40- to 60-minute sessions per week for 6 weeks

Cordier 2019 *(Continued)*

	Arm 3: control group – individualised counselling "not intended to actively improve participants' well-being" (taken from clinicaltrials.gov/ct2/show/NCT03775369)
Outcomes	Self-reported fatigue (Functional Assessment of Cancer Therapy – Fatigue, Fatigue Severity Scale) Self-reported depression (Hamilton Depression Rating Scale) Self-reported intolerance of uncertainty (Intolerance of Uncertainty Scale) Self-reported measure of insomnia (Insomnia Severity Index) Self-reported stress (Perceived Stress Scale) Self-reported mental toughness (Mental Toughness Questionnaire) Self-reported physical activity (International Physical Activity Questionnaire) Objective walking capacity (6-minute walking test) Objective grip strength (grip force) Other measures: Change in sleep continuity and sleep architecture (assessed by electroencephalogram) Change in C reactive protein (assessed by blood test)
Starting date	2018
Contact information	Serge Brand: serge.brand@upkbs.ch Dominik Cordier: dominik.cordier@usb.ch Tel: 161-2074-782
Notes	ClinicalTrials.gov identifier: NCT03775369 Current status: recruiting

NCT03259438

Study name	The Vitality Project for fatigued female cancer survivors
Methods	Double-blind randomised controlled trial Participants randomly assigned to receive 1 of 2 courses: 2 hours and 15 minutes twice weekly of qigong (mind–body movement) or healthy living (nutrition and exercise) classes
Participants	**Inclusion criteria:** women aged 18–70 years; cancer treatment completed ≥ 8 weeks prior to enrolment, including chemotherapy, radiotherapy, surgery, or a combination of these; ≥ 3/10 on self-reported measure of fatigue interference in daily life; understands English; willingness to complete EEG, ECG, EMG and fMRI, and questionnaires, and have blood drawn; able to pass basic physical movement assessment to verify safety for enrolment into the study **Exclusion criteria:** history of coronary artery or coronary heart disease, myocardial infarction or heart murmur; pacemaker implant; peripheral neuropathy in hands; history of a major psychiatric disorder, not including depression or anxiety; active substance misuse; tobacco use; pregnancy; consumption of caffeine or cocoa products within 2 hours prior to data collection; inability to complete gentle exercise **Follow-up:** after 10-week intervention, and 3 months after intervention

NCT03259438 *(Continued)*

	Setting: USA
Interventions	**Arm 1:** 2 hours and 15 minutes twice weekly qigong classes, focusing on mind–body movement, for 10 weeks **Arm 2:** 2 hours and 15 minutes twice weekly healthy living counselling focusing on nutrition, and aerobic and strengthening exercise, for 10 weeks
Outcomes	Self-reported fatigue (FACIT-Fatigue Scale, Fatigue Symptom inventory) Physical measurements (ECG, impedance cardiography, EEG, tactile acuity, EMG, precision grip, electrodermal activity, mechanical lung function, inflammatory cytokines, resting state fMRI, muscle strength, 6-minute walk test) Objective measure of cognition (short-form OSpan (operation span)) Self-reported anxiety and depression (Patient Health Questionnaire, Profile of Mood States Questionnaire) Self-reported emotional dysregulation (Difficulties in Emotion Regulation Scale) Self-reported physical, social, emotional and functional well-being (FACT-G) Self-reported quality of life (Rand 36-item Short Form Health Survey) Self-reported sleep quality, habits and patterns (Pittsburgh Sleep Quality Index) Heart rate and step count (via Apple watch) Self-reported stress (Perceived Stress Scale) Self-reported social support (Multidimensional Scale of Perceived Social Support) Self-reported tendency to care for others before themselves (Unmitigated Communion Scale) Self-reported quantity of exercising and relaxing (Godin Leisure time questionnaire)
Starting date	2017
Contact information	Ellen Flynn Miriam Hospital Outpatient, Providence, RI, USA Tel: +1 401-793-7020; email: eflynn@lifespan.org
Notes	ClinicalTrials.gov Identifier: NCT03259438 Current status: unknown as of November 2021

Röttgering 2020

Study name	Cognitive behavioral therapy in treating severe fatigue in patients with primary brain tumors – a randomized controlled clinical trial
Methods	Randomised controlled trial Psychological intervention or control group
Participants	**Inclusion criteria:** adults aged > 18 years with a histological diagnosis of PBT; with stable disease; ≥ 2 months since active treatment; expected survival ≥ 3 months; able to read, write and speak Dutch; and scoring over a clinical cut-off score for severe fatigue on the CIS-20

Röttgering 2020 *(Continued)*	
	Exclusion criteria: other causes of fatigue not related to brain tumour treatment or receiving pharmacological treatment for fatigue in the past 3 months. Those experiencing depression, primary sleep disorders, receiving psychological intervention for a psychiatric disorder, currently (or within 3 months of being) pregnant or a KPS score < 70
Interventions	**Arm 1:** cognitive behaviour therapy involving therapist sessions and online modules, for 12 weeks **Arm 2:** control group (details unknown)
Outcomes	Self-reported fatigue (CIS – Fatigue score) Self-reported depression, anxiety and health-related quality of life Objective measure of neurocognitive functioning
Starting date	2020
Contact information	Jantine Röttgering Tel: +31 020-4448-453; email: j.rottgering@amsterdamumc.nl
Notes	Netherlands Trial Register identifier: NL8711 Current status: unknown

CIS-20: 20-item Checklist Individual Strength; ECG: electrocardiogram; EEG: electroencephalogram; EMG: electromyography; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-G: Functional Assessment of Cancer Therapy – General; fMRI: functional magnetic resonance imaging; KPS: Karnofsky Performance Scale; PBT: primary brain tumour; WHO: World Health Organization.

DATA AND ANALYSES

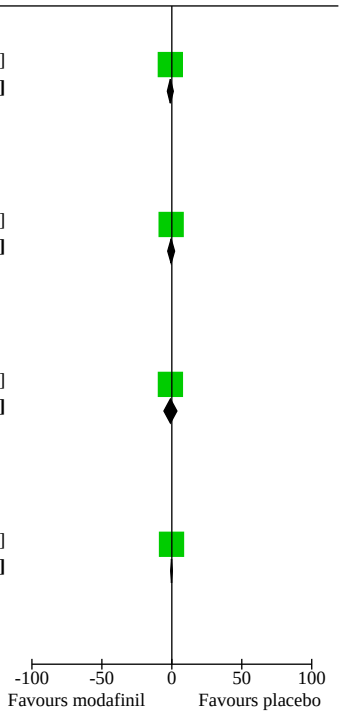
Comparison 1. Boele 2013: modafinil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Fatigue	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Concentration problems	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-3.18, 1.06]
1.1.2 Reduced motivation	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-2.93, 1.97]
1.1.3 Reduced activity	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-5.64, 3.62]
1.1.4 Fatigue severity	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.79, 0.35]
1.2 Objective cognitive functioning	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Verbal memory	1	53	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.05, 0.57]
1.2.2 Working memory	1	53	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.04, 0.18]
1.2.3 Attentional functioning	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.05, -0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.4 Information processing	1	53	Mean Difference (IV, Fixed, 95% CI)	0.17 [-1.19, 1.53]
1.2.5 Executive functioning	1	53	Mean Difference (IV, Fixed, 95% CI)	0.14 [-9.33, 9.61]
1.2.6 Psychomotor speed	1	53	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.26, 0.46]
1.3 Subjective cognitive functioning	1	55	Mean Difference (IV, Fixed, 95% CI)	1.62 [-0.74, 3.98]
1.4 Depression	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5 Health-related quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 Physical	1	55	Mean Difference (IV, Fixed, 95% CI)	1.34 [-20.11, 22.79]
1.5.2 Mental	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-4.84, 2.04]
1.6 Adverse events	1	55	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.59, 13.16]

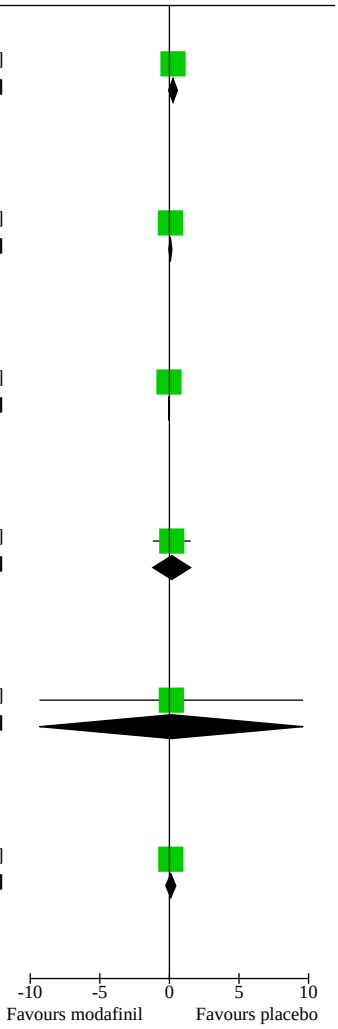
Analysis 1.1. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 1: Fatigue

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Concentration problems								
Boele 2013	18.85	4	26	19.91	4	29	100.0%	-1.06 [-3.18 , 1.06]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**-1.06 [-3.18 , 1.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.1.2 Reduced motivation								
Boele 2013	14.38	4.62	26	14.86	4.62	29	100.0%	-0.48 [-2.93 , 1.97]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**-0.48 [-2.93 , 1.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
1.1.3 Reduced activity								
Boele 2013	11.58	8.75	26	12.59	8.75	29	100.0%	-1.01 [-5.64 , 3.62]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**-1.01 [-5.64 , 3.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.1.4 Fatigue severity								
Boele 2013	34.92	1.08	26	35.14	1.08	29	100.0%	-0.22 [-0.79 , 0.35]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**-0.22 [-0.79 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.75 (P = 0.45)								



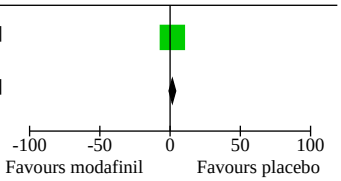
Analysis 1.2. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 2: Objective cognitive functioning

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Verbal memory								
Boele 2013	0.14	0.58	25	-0.12	0.58	28	100.0%	0.26 [-0.05 , 0.57]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**0.26 [-0.05 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.63 (P = 0.10)								
1.2.2 Working memory								
Boele 2013	0.24	0.2	25	0.17	0.2	28	100.0%	0.07 [-0.04 , 0.18]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**0.07 [-0.04 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
1.2.3 Attentional functioning								
Boele 2013	0.15	0.04	25	0.18	0.04	28	100.0%	-0.03 [-0.05 , -0.01]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**-0.03 [-0.05 , -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.73 (P = 0.006)								
1.2.4 Information processing								
Boele 2013	0.36	2.52	25	0.19	2.52	28	100.0%	0.17 [-1.19 , 1.53]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**0.17 [-1.19 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.81)								
1.2.5 Executive functioning								
Boele 2013	0.19	17.56	25	0.05	17.56	28	100.0%	0.14 [-9.33 , 9.61]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**0.14 [-9.33 , 9.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.03 (P = 0.98)								
1.2.6 Psychomotor speed								
Boele 2013	0.26	0.66	25	0.16	0.66	28	100.0%	0.10 [-0.26 , 0.46]
Subtotal (95% CI)			**25**			**28**	**100.0%**	**0.10 [-0.26 , 0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								



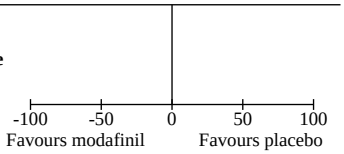
Analysis 1.3. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 3: Subjective cognitive functioning

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Boele 2013	29.11	4.46	26	27.49	4.46	29	100.0%	1.62 [-0.74 , 3.98]
Total (95% CI)			**26**			**29**	**100.0%**	**1.62 [-0.74 , 3.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								
Test for subgroup differences: Not applicable								



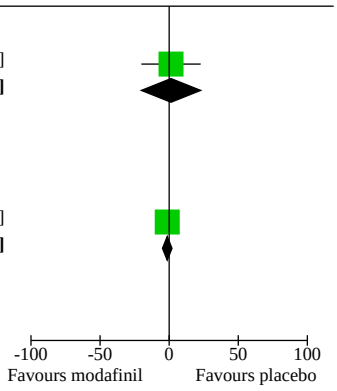
Analysis 1.4. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 4: Depression

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



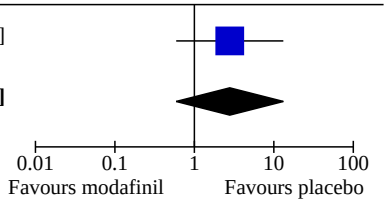
Analysis 1.5. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 5: Health-related quality of life

Study or Subgroup	Modafinil Mean	Modafinil SD	Modafinil Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Physical								
Boele 2013	46.05	40.52	26	44.71	40.52	29	100.0%	1.34 [-20.11 , 22.79]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**1.34 [-20.11 , 22.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
1.5.2 Mental								
Boele 2013	44.36	6.5	26	45.76	6.5	29	100.0%	-1.40 [-4.84 , 2.04]
Subtotal (95% CI)			**26**			**29**	**100.0%**	**-1.40 [-4.84 , 2.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.80 (P = 0.43)								
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.80), $I^2 = 0\%$								



Analysis 1.6. Comparison 1: Boele 2013: modafinil versus placebo, Outcome 6: Adverse events

Study or Subgroup	Modafinil Events	Modafinil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boele 2013	5	26	2	29	100.0%	2.79 [0.59 , 13.16]
Total (95% CI)		**26**		**29**	**100.0%**	**2.79 [0.59 , 13.16]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.20)						
Test for subgroup differences: Not applicable						



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Fatigue] explode all trees
#2 MeSH descriptor: [Lethargy] explode all trees
#3 MeSH descriptor: [Asthenia] explode all trees
#4 (fatigue* or lassitude or weary or weariness or tired or exhausted or exhaustion or lethargy or asthenia or ((lack* or loss*) near/5 energy))
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Brain Neoplasms] explode all trees
#7 MeSH descriptor: [Glioma] explode all trees
~#8 MeSH descriptor: [Meningioma] this term only
#9 (brain near/5 (tumor* or tumour* or carcinoma* or malignan* or neoplas* or cancer*))

#10 (glioma* or astrocytoma* or oligodendroglioma* or ependymoma* or medulloblastoma* or meningioma*)
#11 #6 or #7 or #8 or #9 or #10
#12 #5 and #11

Appendix 2. MEDLINE search strategy

1 exp Fatigue/
2 Lethargy/
3 Asthenia/
4 (fatigue* or lassitude or weary or weariness or tired or exhausted or exhaustion or lethargy or asthenia or ((lack* or loss*) adj5 energy)).mp.
5 1 or 2 or 3 or 4
6 exp Brain Neoplasms/
7 exp Glioma/
8 Meningioma/
9 (brain adj5 (tumor* or tumour* or carcinoma* or malignan* or neoplas* or cancer*)).mp.
10 (glioma* or astrocytoma* or oligodendroglioma* or ependymoma* or medulloblastoma* or meningioma*).mp.
11 6 or 7 or 8 or 9 or 10
12 5 and 11

Key:

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Appendix 3. Embase search strategy

1 exp fatigue/
2 lethargy/
3 asthenia/
4 (fatigue* or lassitude or weary or weariness or tired or exhausted or exhaustion or lethargy or asthenia or ((lack* or loss*) adj5 energy)).mp.
5 1 or 2 or 3 or 4
6 exp brain tumor/
7 exp glioma/
8 exp meningioma/
9 (brain adj5 (tumor* or tumour* or carcinoma* or malignan* or neoplas* or cancer*)).mp.
10 (glioma* or astrocytoma* or oligodendroglioma* or ependymoma* or medulloblastoma* or meningioma*).mp.
11 6 or 7 or 8 or 9 or 10
12 5 and 11

Key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. Risk of bias assessment tool

Random sequence generation

- Low risk of bias, for example, participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
- High risk of bias, for example, participants assigned to treatments on basis of date of birth, clinic identity number or surname, or no attempt to randomise participants.
- Unclear risk of bias, for example, not reported, information not available.

Allocation concealment

- Low risk of bias, for example, where the allocation sequence could not be foretold.
- High risk of bias, for example, allocation sequence could be foretold by patients, investigators or treatment providers.
- Unclear risk of bias, for example, not reported.

Blinding of participants and personnel

Assessment of blinding was restricted to pharmacological interventions, since it would not be possible to blind participants and treatment providers to the non-pharmacological interventions.

- Low risk of bias, if participants and personnel were adequately blinded.

- High risk of bias, if participants were not blinded to the intervention that the participant received.
- Unclear risk of bias, if this was not reported or unclear.

Blinding of outcomes assessors

- Low risk of bias, if outcome assessors were adequately blinded.
- High risk of bias, if outcome assessors were not blinded to the intervention that the participant received.
- Unclear risk of bias, if this was not reported or unclear.

Performance bias

- Low risk of bias, for example, both groups were followed on similar schedules of neurological examinations and brain imaging.
- High risk of bias, for example, each group was followed according to different schedules.
- Unclear risk of bias, for example, not reported or incomplete reporting of outcome data.

We recorded the proportion of participants whose outcomes were not reported at the end of the study.

Incomplete outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome according to the following.

- Low risk of bias, if less than 20% of participants were lost to follow-up, and reasons for loss to follow-up were similar in both treatment arms.
- High risk of bias, if more than 20% of participants were lost to follow-up, or reasons for loss to follow-up differed between treatment arms.
- Unclear risk of bias, if loss to follow-up was not reported.

Selective reporting of outcomes

- Low risk of bias, for example, review reported all outcomes specified in the protocol.
- High risk of bias, for example, it was suspected that outcomes were selectively reported.
- Unclear risk of bias, for example, it was unclear whether outcomes were selectively reported.

Other bias

- Low risk of bias, if we did not suspect any other source of bias and the trial appeared to be methodologically sound.
- High risk of bias, if we suspected that the trial was prone to an additional bias.
- Unclear risk of bias, if we were uncertain whether an additional bias may have been present.

WHAT'S NEW

Date	Event	Description
18 May 2022	New citation required but conclusions have not changed	Two new additional studies identified and included in update
7 April 2022	New search has been performed	Updated to include studies up to 13 April 2022

HISTORY

Protocol first published: Issue 11, 2014
Review first published: Issue 4, 2016

CONTRIBUTIONS OF AUTHORS

Contribution	Author

Draft the review	All review authors
Develop and run the search strategy	JD, SYK and Cochrane staff
Obtain copies of trial reports	JD, SYK, DC
Select which trials to include (3 people)	JD, SYK, DC, with advice from all review authors as needed
Extract data from trials (3 people)	JD, SYK, DC
Enter data into Review Manager 5	JD, SYK, DC
Carry out the analysis	JD, SYK, DC
Interpret the analysis	All review authors
Draft the final review	All review authors
Run the updated search	Cochrane Staff
Obtain copies of trial reports for update	JD, DC
Select which trials to include for update	JD, DC
Extract data from trial reports	JD, SYK
Carry out the analysis for the update	JD, SYK
Interpret the analysis for the update	All review authors
Draft the final review update	All review authors

DECLARATIONS OF INTEREST

JD: none known.

SYK: none known.

DC: none known.

JW: none known.

IT: none known.

HB: none known.

AGR: none known.

SOURCES OF SUPPORT

Internal sources

- Internal sources of support, Other

  No sources of support provided

External sources

- NIHR, Other

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For clarification, in the original review, we changed the following sentence "We include details of missing data in the narrative summary and 'Risk of bias' table, alongside an assessment of the extent to which the missing data could have altered the results of the review" in the protocol, to "We included details of missing data in the narrative summary and risk of bias table, and stated whether authors examined the extent to which the missing data could have altered the results of the review" in the full review. This was to clarify that we had not planned to carry out any formal analyses but to assess the extent to which the missing data could have altered the results by reviewing any assessments carried out by the included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Brain Neoplasms [complications]; Dextroamphetamine [therapeutic use]; Fatigue [etiology] [therapy]; *Glioma; Modafinil [therapeutic use]

MeSH check words

Adult; Humans