Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation

Kirkman, Matthew A; Day, Julia; Gehring, Karin; Zienius, Karolis; Grosshans, David; Taphoorn, Martin J B; Li, Jing; Brown, Paul D

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD011335.pub3

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation (Review)

Kirkman MA, Day J, Gehring K, Zienius K, Grosshans D, Taphoorn M, Li J, Brown PD

Kirkman MA, Day J, Gehring K, Zienius K, Grosshans D, Taphoorn M, Li J, Brown PD.
Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation.
Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD011335.
DOI: 10.1002/14651858.CD011335.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation

Matthew A Kirkman[1], Julia Day[2], Karin Gehring[3,4], Karolis Zienius[5], David Grosshans[6], Martin Taphoorn[7], Jing Li[6], Paul D Brown[8]

[1]Department of Neurosurgery, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK. [2]Community Rehabilitation and Brain Injury Service (CRABIS), Strathbrock Partnership Centre, West Lothian, UK. [3]Department of Neurosurgery, Elisabeth-TweeSteden Hospital, Tilburg, Netherlands. [4]Department of Cognitive Neuropsychology, Tilburg University, Tilburg, Netherlands. [5]Edinburgh Centre for Neuro-Oncology (ECNO), Western General Hospital, Edinburgh, UK. [6]Radiation Oncology, MD Anderson Cancer Center, Houston, Texas, USA. [7]Department of Neurology, Haaglanden Medical Center, PO Box 432, Netherlands. [8]Radiation Oncology, Mayo Clinic, Rochester, MN, USA

Contact: Matthew A Kirkman, matthew.kirkman@gmail.com.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2022.

Citation: Kirkman MA, Day J, Gehring K, Zienius K, Grosshans D, Taphoorn M, Li J, Brown PD. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database of Systematic Reviews* 2022, Issue 11. Art. No.: CD011335. DOI: 10.1002/14651858.CD011335.pub3.

ABSTRACT

Background

Cognitive deficits are common in people who have received cranial irradiation and have a serious impact on daily functioning and quality of life. The benefit of pharmacological and non-pharmacological treatment of cognitive deficits in this population is unclear. This is an updated version of the original Cochrane Review published in Issue 12, 2014.

Objectives

To assess the effectiveness of interventions for preventing or ameliorating cognitive deficits in adults treated with cranial irradiation.

Search methods

For this review update we searched the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE via Ovid, Embase via Ovid, and PsycInfo via Ovid to 12 September 2022.

Selection criteria

We included randomised controlled (RCTs) trials that evaluated pharmacological or non-pharmacological interventions in cranial irradiated adults, with objective cognitive functioning as a primary or secondary outcome measure.

Data collection and analysis

Two review authors (MK, JD) independently extracted data from selected studies and carried out a risk of bias assessment. Cognitive function, fatigue and mood outcomes were reported. No data were pooled.

Main results

Eight studies met the inclusion criteria and were included in this updated review. Six were from the original version of the review, and two more were added when the search was updated. Nineteen further studies were assessed as part of this update but did not fulfil the inclusion criteria.

Of the eight included studies, four studies investigated “prevention” of cognitive problems (during radiotherapy and follow-up) and four studies investigated “amelioration” (interventions to treat cognitive impairment as a late complication of radiotherapy). There were five pharmacological studies (two studies on prevention and three in amelioration) and three non-pharmacological studies (two on prevention and one in amelioration). Due to differences between studies in the interventions being evaluated, a meta-analysis was not possible.

Studies in early radiotherapy treatment phase (five studies)

Pharmacological studies in the “early radiotherapy treatment phase” were designed to prevent or ameliorate cognitive deficits and included drugs used in dementia (memantine) and fatigue (d-threo-methylphenidate hydrochloride). Non-pharmacological studies in the “early radiotherapy treatment phase” included a ketogenic diet and a two-week cognitive rehabilitation and problem-solving programme.

In the memantine study, the primary cognitive outcome of memory at six months did not reach significance, but there was significant improvement in overall cognitive function compared to placebo, with similar adverse events across groups. The d-threo-methylphenidate hydrochloride study found no statistically significant difference between arms, with few adverse events. The study of a calorie-restricted ketogenic diet found no effect, although a lower than expected calorie intake in the control group complicates interpretation of the results. The study investigating the utility of a rehabilitation program did not carry out a statistical comparison of cognitive performance between groups.

Studies in delayed radiation or late effect phase (four studies)

The “amelioration” pharmacological studies to treat cognitive complications of radiotherapy included drugs used in dementia (donepezil) or psychostimulants (methylphenidate and modafinil). Non-pharmacological measures included cognitive rehabilitation and problem solving (Goal Management Training). These studies included patients with cognitive problems at entry who had “stable” brain cancer.

The donepezil study did not find an improvement in the primary cognitive outcome of overall cognitive performance, but did find improvement in an individual test of memory, compared to placebo; adverse events were not reported. A study comparing methylphenidate with modafinil found improvements in cognitive function in both the methylphenidate and modafinil arms; few adverse events were reported. Another study comparing two different doses of modafinil combined treatment arms and found improvements across all cognitive tests, however, a number of adverse events were reported. Both studies were limited by a small sample size. The Goal Management Training study suggested a benefit of the intervention, a behavioural intervention that combined mindfulness and strategy training, on executive function and processing speed.

There were a number of limitations across studies and few were without high risks of bias.

Authors' conclusions

In this update, limited additional evidence was found for the treatment or amelioration of cognitive deficits in adults treated with cranial irradiation. As concluded in the original review, there is supportive evidence that memantine may help prevent cognitive deficits for adults with brain metastases receiving cranial irradiation. There is supportive evidence that donepezil, methylphenidate and modafinil may have a role in treating cognitive deficits in adults with brain tumours who have been treated with cranial irradiation; patient withdrawal affected the statistical power of these studies. Further research that tries to minimise the withdrawal of consent, and subsequently reduce the requirement for imputation procedures, may offer a higher certainty of evidence.

There is evidence from only a single small study to support non-pharmacological interventions in the amelioration of cognitive deficits. Further research is required.

PLAIN LANGUAGE SUMMARY

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation

Background

Problems with mental/cognitive abilities/skills (cognitive side effects) are common in people who have received radiation to the brain for a primary or secondary (metastatic) brain tumour, or for preventing a tumour from spreading to the brain from elsewhere in the body. This toxic side effect of brain radiation may be acute (during treatment) or early after treatment (one to six months) and may be reversible. However, later toxicities may occur many months or years later, and when they do occur they are generally irreversible and often slowly progressive. Late cognitive deficits, such as memory loss, problems planning tasks or behavioural changes, can have a serious impact on quality of life and the ability to carry out activities normally. Interventions to help prevent or treat these late radiation toxicities may improve a patient's well-being. Here, we review all studies on pharmacological (medical drug) and non-pharmacological (psychological) interventions that aimed to prevent or treat cognitive side effects associated with radiotherapy to the brain.

Study Characteristics

In the original review published in August 2014, we searched four literature databases, which are used to identify articles from peer-reviewed journals and other types of periodicals. Six randomised controlled trials, in which people were randomly assigned to the

intervention or a comparison group (control group), were eligible for inclusion. Each trial assessed different interventions, so results were not combined. The largest trial investigated the medical drug memantine in 508 people with a metastatic brain tumour. Another trial investigated donepezil in 198 patients with a primary or secondary brain tumour. The other trials were smaller and investigated modafinil and methylphenidate. We found one psychological intervention for preventing cognitive deficits during brain radiation.

In this update, we searched the same databases as in the original review. Two new studies were included in the review. One of these was a non-pharmacological prevention study investigating the effect of a calorie-restricted ketogenic diet and intermittent fasting. The other identified study was a non-pharmacological amelioration study evaluating Goal Management Training, a behavioural intervention that combined mindfulness and strategy training. An additional paper included in the review was the full-text article of a conference proceeding included in the original review, which investigated donepezil compared with placebo.

Key findings

Findings into the efficacy of memantine offer preliminary supportive evidence for preventing cognitive deficits in patients with a secondary brain tumour receiving brain irradiation. Findings into the efficacy of donepezil offer some initial support for its use in the amelioration of cognitive deficits in patients with a primary or secondary tumour previously treated with radiation. Further research into both drugs is important to confirm their effectiveness as well as any potential side effects. The remaining studies did not have a sufficient number of participants to provide reliable results. Side effects (adverse events) were not reported in all studies, but in studies where they were, they were most often infrequent and not severe. Recruitment and retention of trial participants for most of the pharmacological studies was difficult. Lastly, although limited support was found for non-pharmacological treatments, this does not suggest these interventions are ineffective but rather that further research is needed.

Certainty of the evidence

We found limitations in the certainty of the evidence across studies. Several of the pharmacological randomised controlled trials had a low risk of bias, although some were at high risk of bias due to, for example, an open-label design or the lack of a placebo group. The non-pharmacological interventions were at a high risk of bias as a placebo condition in these trials is difficult to employ.

BACKGROUND

Description of the condition

Cognition refers to the mental abilities that require the high-level handling of information. Such abilities include learning and memory, executive function, visuo-spatial processing, language, concentration, attention and intellectual function (Gilroy 2000). Cognitive dysfunction (or deficit) in any of these areas can have a significant impact on a person's ability to function in day-to-day life, including work performance, language and communication, social interactions and independent living (Meyers 1998).

Cognitive deficits are common among patients who have received cranial irradiation (Kirkman 2022; Lehrer 2022; Perez 2022) to treat primary or metastatic brain tumours, or as prevention (prophylaxis) of other cancers. Both the brain tumour itself and tumour treatment can cause cognitive deficits (Kirkman 2022; Taphoorn 2004), and patients with brain tumours who receive radiotherapy tend to have worse cognitive deficits than those who are radiotherapy naive, with identified neuroimaging correlates including cortical atrophy and white matter abnormalities (Correa 2007; Postma 2002; Surma-aho 2001; Sultana 2020). Over 80% of primary and metastatic brain tumour patients have self-reported cognitive concerns regarding memory or concentration (Lidstone 2003; Mukand 2001). For example, in a prospective study, cognitive functioning was assessed with neuropsychological testing in patients receiving cranial irradiation for the treatment of brain metastases. Results demonstrated cognitive deficits in the domains of learning, delayed recall and recognition six to eight weeks following radiotherapy when compared to baseline scores (Welzel 2008). In another study, patients with lung cancer receiving prophylactic cranial irradiation demonstrated declined cognitive functioning on subjective and objective measures at six- and 12-month follow-up assessments when compared to baseline scores (Gondi 2013). A randomised trial also documented significant cognitive deficits four months after whole brain radiotherapy (WBRT) compared to patients treated with radiosurgery alone (Chang 2009).

Neurotoxic effects of cranial irradiation

Radiation can be delivered to the brain tumour using large focused doses (stereotactic radiation), as part of standard fractionated treatments, or to the whole brain. Potential risk factors for cognitive decline following brain radiation include receiving fractionated radiation doses greater than 2 Gy (Klein 2002), higher total radiation dose, larger brain volume of irradiation, using a divided-dose schedule and longer overall treatment time (Lee 2002). Other risk factors may include either combined or subsequent chemotherapy use, age, with those fewer than seven years or greater than 60 years old at higher risk, and comorbid vascular risk factors such as diabetes and hypertension (Crossen 1994; Szerlip 2011). In the identification of acute treatment-related neurotoxicity it is important to distinguish symptoms from tumour progression, recurrence or metastases, since continuation of treatment may lead to irreversible central nervous system (CNS) injury (Dietrich 2008).

The neurotoxic effects of brain radiation have traditionally been divided into acute, early-delayed and late-delayed radiation encephalopathy (Sheline 1980; Wujanto 2021). Acute radiation encephalopathy occurs as a result of disruption to the blood-brain barrier leading to accumulation of fluid in the tissue (vasogenic oedema). Corticosteroids are used at this stage, and may improve symptoms of drowsiness and headache, and prevent further neurologic decline. Early-delayed radiation encephalopathy may occur at one to six months following completion of treatment, and symptoms of short-term memory and attentional deficits are seen alongside drowsiness and worsening of pre-existing neurological deficits. A return to baseline is often found within 12 months (Vigliani 1996). This phase is associated with reversible damage to the myelin sheath (Sheline 1980). In contrast to early complications, late-delayed radiation encephalopathy is viewed as irreversible. This complication occurs months to years following radiation therapy and manifests as white matter lesions (i.e. leukoencephalopathy). In more severe forms it can manifest or lead to a formation of dead brain tissue which, as a result, can lead to a pressure effect and associated neurological dysfunction (Fink 2012).

The precise relationship between initial acute changes and late/chronic radiation damage to the brain is unknown. However, more recent evidence indicates that more subtle, early forms of radiation-induced damage to the CNS could drive chronic pathophysiological processes leading to permanent cognitive decline (Makale 2017). Clinically, late radiation damage is characterised by progressive mental slowing and impairment in attention and memory, with less commonly gait ataxia, urinary incontinence, apathy, and pyramidal and extrapyramidal signs (Taphoorn 2003). The cognitive deficits increase in incidence and severity over time (Klein 2002). However the exact incidence is hard to elucidate due to the large variety of neuropsychological tests used, the heterogeneous study populations and times at which patients are followed up (Taphoorn 2004). Furthermore, deficits are likely to vary depending on the specific anatomic structures irradiated (Haldbo-Classen 2020). Historical data indicate that up to 90% of adult brain tumour patients who survive for more than six months following WBRT therapy develop (some form of) cognitive impairment (Crossen 1994), and in up to 5% of long-term survivors the cognitive impairment progresses to dementia necessitating admission to a nursing home (DeAngelis 1989; Vigliani 1996). The incidence of severe cognitive deficits/late delayed radiation encephalopathy has been shown to be even higher in patients with primary CNS lymphoma, reaching nearly 100% in patients older than 60 years old (Abrey 1998). However, improvements in treatments (including hippocampal-sparing techniques and focal radiotherapy) are likely to have reduced the cognitive effects of radiotherapy treatment (Wujanto 2021). Nevertheless, due to these adverse effects of cranial irradiation, the benefit of radiotherapy treatment for patients with a more favourable prognosis, such as with a low-grade glioma (LGG), or as prophylactic cranial irradiation for small cell lung carcinoma, has been the subject of much debate in the past decade (Gondi 2013; Xue 2022).

The mechanisms of cranial irradiation-induced cognitive impairment

The mechanisms by which radiation causes cognitive decline have been proposed to include microvascular damage, oligodendrocyte decline, loss of white matter integrity, neuroinflammation, metabolic changes, and neuronal dendritic spike damage (Makale 2017; Pazzaglia 2020; Sultana 2020). Long-term radiation-induced cognitive decline is likely to reflect changes to the white matter, hippocampus and prefrontal cortex, as well as other areas (Makale 2017). Two of the most studied mechanisms of radiation-induced cognitive impairment include white matter changes and impaired neurogenesis.

The primary mechanism of delayed radiation-induced white matter changes is associated with secondary endothelial damage and microvascular ischaemic insult (Lyubimova 2004), accompanied by apoptosis (programmed cell death) of oligodendrocyte progenitors (Makale 2017). This leads to a decrease in the volume of cerebral white matter, which is directly associated with cognitive decline (Correa 2004; Mulhern 2004; Reddick 2006). This has been confirmed in a longitudinal study that found medulloblastoma patients receiving a cranial irradiation dose of 36 Gy to show more rapid cerebral white matter volume decrease than those receiving a cranial irradiation dose of 23.4 Gy (Palmer 2002). Rarely, these white matter lesions can increase in size and may progress to frank white matter necrosis characterised by focal cavitations in the white matter within the radiated fields (Anscher 1991). Treatment of radionecrosis involves surgical excision and steroid therapy, and studies using bevacizumab, an angiogenesis inhibitor, have also reported high rates of clinical and radiological responses, albeit with small sample sizes (Gonzales 2007; Levin 2011; Torcuator 2009; Wang 2012).

Neurogenesis refers to the birth of new neurons, and occurs through the division of neural stem cells and subsequent maturation into neural progenitor cells that migrate and mature into neurons (Gage 2019). There exists compelling molecular evidence of the occurrence of neurogenesis throughout the human lifespan (Zhou 2022). A post-mortem study in patients with medulloblastoma found significantly lower neurogenesis in patients treated with radiotherapy two to 23 years prior to analysis, compared to controls matched for age and sex (Monje 2007). Radiotherapy strategies that attempt to spare the crucial areas of neurogenesis, including the hippocampus, have been shown in several studies to result in improved cognition relative to conventional radiotherapy techniques (Gondi 2014; Kim 2018), including a phase III randomised controlled trial (Brown 2020).

Measuring cognitive deficits

Use of a core battery of validated neuropsychological tests to assess cognitive function have been recommended in order to harmonise studies of cognitive function in patients with cancer (Wefel 2011). These include the Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict 1998) to assess learning and memory, Trail Making Test (TMT) (Reitan 1992) to assess processing speed and executive function, and the Controlled Oral Word Association test of the Multilingual Aphasia Examination (COWA) (Benton 1989) to assess verbal fluency. Other tests have also been used, such as digit span and digit symbol (Wechsler 1981) to assess working memory and information processing speed, respectively. Cognitive function has also been assessed by using brief mental status evaluations, such as the Mini-Mental State Examination (MMSE) (Folstein 1975). Whilst the MMSE is often shorter than neuropsychological testing, it has been associated with poor sensitivity in detecting cognitive deficits (Meyers 2003). Other studies have used subjective patient reports of cognitive concerns, such as in memory and concentration (Lidstone 2003; Mukand 2001). An additional consistent finding from the research literature is that correlations between subjectively assessed cognitive symptoms and objectively determined cognitive functioning are quite modest, with correlation coefficients generally ranging from 0.20 to 0.30 (Klein 2002). These are suggested to be confounded by some patients' lack of awareness regarding their cognitive impairments, and correlations with fatigue and depression, rather than cognitive test performance (Cull 1996; Gehring 2015).

To evaluate intervention effects, repeated neuropsychological testing is employed. However, practice effects occur resulting in improved test performance (Duff 2012). As a consequence, improvement (or stability) of test scores may be unjustly attributed to the intervention, where perhaps patients would otherwise have demonstrated a decline over time - which is not uncommon in patients with brain tumours). In preventative and ameliorative intervention trials, practice effects should thus be accounted for. The variations in tools available, use of both objective and subjective measures, differences in time points at which cognitive functioning is measured and the differences in intervention duration highlight the caution that must be taken when combining and generalising results and conclusions.

Description of the intervention

This review included all studies on interventions that aim to:

- prevent, or
- ameliorate

any cognitive deficits in people who have received therapeutic or prophylactic cranial irradiation prior to, or during, participation in the study. These may include pharmacological and non-pharmacological (medical, psychological or behavioural) interventions for the management of cognitive deficits. It is worth noting, however, that it is likely that almost all patients in the 'prevention' studies will have deficits in at least one cognitive domain, most commonly in memory and verbal fluency, due to the tumour or possibly prior neurosurgical intervention. A large proportion of patients will have been on steroid therapy and some may be recovering from craniotomy. Thus the distinction between 'prevention' and 'amelioration' is not clear cut.

Pharmacological

We defined pharmacological interventions as a drug, including herbs, given by any route at any therapeutic dose with the intention of preventing or ameliorating cognitive deficits in persons who have received cranial irradiation.

Studies investigating the pharmacological prevention of cognitive impairment have frequently been conducted in patients undergoing cranial irradiation during participation. For example, memantine, used in the treatment of Alzheimer's Disease (Robinson 2006), has been investigated for its neuroprotective role during irradiation.

Studies of pharmacological treatment for cognitive impairment after cranial irradiation have largely focused on psychostimulants, including methylphenidate (Butler 2007, Gehring 2012a) and modafinil (Gehring 2012a, Kaleita 2006). Objective cognitive functioning and patient-reported outcomes of fatigue, mood and quality of life have been used to assess the efficacy of methylphenidate and modafinil in patients with brain tumour, 83% of whom had received cranial irradiation (Gehring 2012a). Donepezil (Rapp 2015, Shaw 2006) and memantine (Brown 2013), used in the treatment of Alzheimer's Disease, have also been investigated for their use in the treatment/prevention of cognitive symptoms in brain-irradiated adults. Although the pharmacological mechanism of action is widely assumed to be through 'prevention' of cognitive failure rather than the treatment of existing cognitive impairments, the effect of drugs used in this setting is unclear and may have a 'treatment effect' as well as a

'preventative effect' in slowing the progression of cognitive failure. Chinese medicinal herbs and dietary supplements have also been investigated in irradiated brain tumour patients (Attia 2012).

Non-pharmacological

We defined non-pharmacological interventions as any non-drug intervention given with the intention of ameliorating or preventing cognitive deficits during or following cranial irradiation. These can include, but are not limited to, medical, psychological and behavioural interventions.

Medical interventions include any biomedical intervention given to a person in which the intervention is not primarily investigating cancer treatment or control. For example, one study explored the use of hyperbaric oxygen therapy in cranial irradiated brain tumour patients using 31 neuropsychological tests (Hulshof 2002).

Psychological interventions may include (but are not limited to) education, retraining and compensation strategies. Several studies have evaluated cognitive rehabilitation in patients with brain tumours (Gehring 2009, Locke 2008, Richard 2019).

Behavioural interventions can include exercise (Gehring 2020) as well as behavioural modification interventions such as mindfulness and dietary interventions.

How the intervention might work

Clinical trials have explored the prevention and treatment of cognitive deficits by targeting pharmacological, psychological or behavioural pathways.

Pharmacological

Pharmacological interventions may prevent cognitive deficits via their neuroprotective role during WBRT such as memantine, an N-Methyl-D-aspartate receptor antagonist (Brown 2013).

Pharmacological interventions may ameliorate cognitive deficits via their involvement in critical neurotransmitter pathways. Methylphenidate is a CNS stimulant found to have a positive effect on attention due to its action on the brain centre for attention control, the fronto-striatal network, by increasing dopamine and noradrenaline concentrations (Volkow 2002). Another centrally acting drug is donepezil, a reversible cholinesterase inhibitor involved in inhibiting the breakdown of the neurotransmitter acetylcholine, often prescribed for patients with Alzheimer's Disease. This may have a cognitive enhancing effect by prolonging and improving cholinergic function, associated with learning and memory (Steinberg 2011).

Non-pharmacological

Medical interventions have also been considered to help prevent or treat cognitive deficits. Hyperbaric oxygen therapy has been used to improve damage to the nervous system by stimulating angiogenesis, the process through which new blood vessels are formed from pre-existing blood vessels (Gill 2004).

Psychological interventions may help prevent and improve cognitive deficits by retraining cognitive capacities such as attention and memory, or via compensation strategies such as memory aids. These interventions target the plasticity of the brain, via restoration or reorganisation of function (Miotto 2013; Mora 2013). For example, Cicerone 2011 reviewed 370 cognitive rehabilitation interventions and found supportive evidence for its role in patients with traumatic brain injury and stroke.

Behavioural interventions, such as exercise, may also help ameliorate or prevent cognitive deficits. Exercise has been associated with increases in cerebral blood flow, increased hippocampal neurogenesis, changes in neurotransmitter release and arousal levels and brain structure, and particularly through the involvement of Brain Derived Neurotrophic Factor associated with nerve growth (Gligoroska 2012).

Other non-pharmacological interventions, such as those involving diet modifications, may also play a role in improving cognitive functioning. The dietary supplement *Ginkgo biloba* has been associated with regulating signalling pathways, cellular metabolism and gene transcription (Smith 2003).

Why it is important to do this review

As anti-cancer treatments become more effective and readily available across treatment centres, patients live longer disease-free, but with long-term sequelae of the disease and the neurotoxic side effects of treatment (Cochran 2012). Greater emphasis is now being placed on quality of life and with the establishment of neurocognitive function as a predictor of survival (Meyers 2000; van Kessel 2021) and quality of life (Mitchell 2010), cognitive functioning is an essential outcome measure. There is currently no standard policy to direct treatment. With even mild cognitive impairment leading to negative functional and psychiatric consequences, especially if persistent and untreated, it is important to identify ways to reduce the long-term impact of cranial irradiation on neuropsychological function.

OBJECTIVES

To assess the effectiveness of interventions for preventing or ameliorating cognitive deficits in adults treated with cranial irradiation.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised trials (including those described in conference abstracts) that included: (i) a group receiving an intervention for cognitive function; and (ii) a control group or comparison group receiving no intervention for cognitive function, standard care, or a comparison with a normative data control group, or comparison to another active intervention.

Types of participants

Prevention

For studies investigating the prevention of cognitive deficits, we included studies that involved adult patients (aged 18 years and over) who received an intervention aimed at the prevention of cognitive deficits and underwent cranial irradiation (whole brain or partial brain radiation) during participation in the study, for the treatment of primary or secondary brain cancer, or prophylactic treatment for other cancers.

Since these studies refer to interventions for *preventing* cognitive deficits, the presence of cognitive deficits at baseline was not an inclusion criterion. However, we only included studies where cognitive functioning was assessed via neuropsychological testing both prior to and following the start of the intervention.

Amelioration

For studies investigating the amelioration of cognitive deficits, we included studies that involved adult patients (aged 18 years and over) with impairment in at least one cognitive domain, who received an intervention aiming to ameliorate cognitive deficits and had previously undergone cranial irradiation (whole brain or partial brain radiation) prior to participation in the study for the treatment of primary or secondary brain cancer, or prophylactic treatment for other cancers. Cognitive impairment was determined prior to participation via neuropsychological testing. Participants could have received cranial irradiation during childhood, but had to be an adult (aged 18 years and over) during participation in the study.

We also included studies that involved only a subset of patients who had undergone cranial irradiation in the review, if this group formed a large majority (> 80%) of the study population or had been explored via subgroup analyses.

Types of interventions

Studies that were included could have utilised pharmacological (e.g. stimulants, or neuroprotective agents) or medical (e.g. hyperbaric oxygen therapy) approaches, or psychological (e.g. cognitive rehabilitation) or behavioural (e.g. exercise) interventions, targeted to prevent or ameliorate radiation-related cognitive deficits.

Whilst we included studies that investigated the preventative role of an intervention during cranial irradiation, we did not include those where the intervention being investigated was cranial irradiation itself, associated with treating the tumour or improving tumour control. Such excluded studies included those on:

- hippocampal sparing techniques;
- techniques limiting radiation dosage to healthy tissue (e.g. intensity-modulated radiation therapy);
- the addition of chemotherapy agents (e.g. motexafin gadolinium).

Although these techniques can be associated with reduced or limited cognitive side effects, these techniques would best fit a separate Cochrane systematic review investigating the effect of dose of radiotherapy in causing cognitive problems.

Pharmacological interventions

We investigated the effectiveness of any drug or herb given by any route for any duration, and at any therapeutic dose, with the objective of preventing or treating cognitive deficits in patients who had received, or were receiving, cranial irradiation. Such drugs are likely to include psychostimulants (e.g. methylphenidate, modafinil), and might include drugs to treat cognitive deficits in other neurological conditions (e.g. donepezil, memantine).

For ethical reasons, studies involving drugs may not automatically include a placebo arm. To increase the relevance of the review we included studies without a placebo arm if the study involved a group of participants who have been randomised to a control group of some kind (e.g. treatment as usual, another active drug or allocation to a waiting list), or that have been compared to normative control data with correction of practice effects caused by repeated neuropsychological testing.

Non-pharmacological interventions

For non-drug medical interventions, we investigated any medical intervention, such as hyperbaric oxygen therapy, which aimed to prevent or improve cognitive deficits in patients who had received, or were receiving, cranial irradiation.

For psychological and behavioural interventions, we reviewed any cognitive and/or behavioural treatment given with the intention or preventing or treating cognitive deficits in patients who had received, or were receiving, cranial irradiation; these could include, but were not limited to, retraining, education or teaching of compensation strategies, physical exercise interventions or dietary supplements. Due to the nature of these interventions, it can be difficult to blind different arms of trials. To increase the relevance of the review we included studies without a placebo arm if the study involved a group of participants who have been randomised to a control group of some kind (e.g. treatment as usual, another active treatment or allocation to a waiting list), or that have been compared to normative control data with correction of practice effects caused by repeated neuropsychological testing.

Types of outcome measures

Primary outcomes

The primary outcome for this review was cognitive performance as assessed by neuropsychological tests (and not self-report); this could be a general or composite cognitive score or individual cognitive test scores using validated neuropsychological tests (e.g. Hopkins Verbal Learning Test-Revised (HVLT-R (HVLT-R), Controlled Oral Word Association Test (COWA)). Cognitive functioning had to be measured at baseline and following intervention at any time point.

In studies involving preventative interventions, we determined efficacy as a statistically significant improvement in cognitive functioning, or no change/decline from baseline. Studies could have objective cognitive functioning as a primary outcome or include cognitive performance as the secondary outcome to an alternative primary quality of life measure (e.g. fatigue, mood).

In studies involving ameliorating interventions, we determined efficacy as a statistically significant improvement, or no change, in cognitive functioning from baseline. To increase the relevance of the review, we did not restrict eligible studies with respect to the time point at which cognitive functioning was measured at baseline or at follow-up. We noted and discussed the time points at which cognitive functioning was measured.

Secondary outcomes

- Self-reported cognitive functioning via interviews or questionnaires.
- General functioning including mood/psychiatric symptoms (e.g. Hospital Anxiety and Depression Scale (HADS)), self-reported fatigue (e.g. Brief Fatigue Inventory (BFI)) and quality of life measurements (e.g. FACT-Br).

- Adverse events (e.g. nausea, skin reactions, headache).

We noted and reviewed the secondary outcomes if recorded, but these were not eligibility criteria for this review.

Search methods for identification of studies

Electronic searches

For this review update, we searched the following databases up to 12 September 2022:

- Cochrane Register of Controlled Trials (CENTRAL, 2022, Issue 9), in the Cochrane Library;
- MEDLINE via Ovid (August 2014 to September 11 2022);
- Emase via Ovid (August 2014 to 2022 week 36);
- PsycInfo via Ovid (August 2014 to 12 September 2022).

The search strategies are listed in Appendix 1 (MEDLINE), Appendix 2 (Embase), Appendix 3 (CENTRAL), and Appendix 4 (PsycINFO). The search strategies were not restricted by year of publication, language or publication type. Following de-duplication the references were run through the Cochrane 'RCT Classifier' to identify records more than 10% likely to be a randomised controlled trial (RCT).

Original Searches

The original searches for the review of 'Interventions for preventing and ameliorating cognitive deficits in adults treatment with cranial irradiation' (Day 2014b) were as follows:

- Cochrane Register of Controlled Trials (CENTRAL, 2014, Issue 8);
- MEDLINE (1950 to August 2014);
- Embase (1980 to August 2014);
- PsycINFO (1974 to August 2014).

Searching other resources

- We searched the reference lists of included studies.
- We searched for ongoing trials using ClinicalTrials.gov (www.clinicaltrials.gov), the Physicians Data Query (www.cancer.gov/clinicaltrials) and the *meta*Register of Controlled Trials (www.controlled-trials.com/mrct).

Data collection and analysis

Selection of studies

We used the reference management database EndNote to download all titles and abstracts retrieved by electronic searching. We removed duplicates and two review authors (MK, JD) independently examined the remaining references. The review authors were not blinded to the authors or affiliations of the studies. We obtained full-text copies of potentially relevant references and excluded studies clearly not meeting the inclusion criteria. Two review authors (MK, JD) independently assessed the eligibility of retrieved papers, with disagreements planned to be resolved by discussion with a third review author (KG), which was not necessary. We documented reasons for the exclusion of studies.

Data extraction and management

Data extraction

We used the recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* to extract data from included trials using a data extraction form specifically designed for this review (Higgins 2011). Two review authors (MK, JD) completed data extraction independently. Differences between review authors were resolved by discussion.

Data extracted included the following:

- article details (author, year of publication, journal, country and language);
- aim of the study (preventative or ameliorative);
- methodology (study design, participant recruitment method, inclusion and exclusion criteria, informed consent, ethical approval, statistical analyses including corrections for practice effects);
- population demographics (geographical location, setting, age, gender, ethnicity, total number included in trial and analyses);
- details of participants health status (including disease status, tumour pathology, tumour treatment details including proportion receiving radiotherapy, antiepileptic medication, corticosteroid use);
- intervention (characteristics such as drug dose, preparation and route of administration, frequency and duration, detail of providers, timing of intervention in relation to radiotherapy);
- outcomes (primary and secondary outcomes assessed, method and timing of assessments);
- results of cognitive functioning measure (neuropsychological test performance);
- results of other outcome measures (including self-reported cognitive questionnaires on cognitive symptoms, quality of life, depression, fatigue and adverse events);
- risk(s) of bias.

Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants are analysed in the groups to which they are assigned.

Data management

We used Review Manager 5.4 to collate data (RevMan 2020). For continuous outcomes (e.g. cognitive performance and quality of life measures), we extracted the final values and standard deviations (SDs) and the number of patients assessed at endpoint for each treatment arm to estimate the mean difference (MD) between treatment arms and its standard error (SE). We noted and reviewed the time points for outcome assessment. Where participant and study details were missing, we noted these as a potential limitation of the study.

Assessment of risk of bias in included studies

We used the *Cochrane Handbook for Systematic Reviews of Interventions* risk of bias tool to assess the risk of bias in included studies (Higgins 2011), including the assessment of:

- selection bias: random sequence generation and allocation concealment;

- performance bias: blinding of participants, personnel (patients and treatment providers) and outcome assessors;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting of outcomes;
- other possible sources of bias.

A full risk of bias item list with specific criteria for each item can be found in Appendix 5.

We interpreted and reported all bias criteria as having a low, high or unclear risk of bias. We reported an unclear risk of bias when insufficient information was provided, or when uncertainty over the potential for bias was present. Two review authors (MK, JD) applied the risk of bias tool independently and resolved differences by discussion. We summarised results in a risk of bias graph and risk of bias summary and interpreted the results with respect to risk of bias.

Measures of treatment effect

For continuous outcomes, we used the between-group mean difference (MD) with 95% confidence interval (CI). We planned to use the standardised mean difference (SMD) with 95% CIs to combine trials that measured the same outcome, but used different methods. For dichotomous outcomes we used the risk ratio (RR) with 95% CI.

Unit of analysis issues

We did not identify any study designs with unit-of-analysis issues.

Dealing with missing data

We did not impute missing outcome data for any outcomes.

Assessment of heterogeneity

If a meta-analysis had been possible, we aimed to assess heterogeneity between studies by a formal statistical test to indicate 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), and via visual inspection of forest plots.

Assessment of reporting biases

Two review authors (MK, JD) reviewed and recorded any details of reporting bias. We aimed to examine funnel plots, if a meta-analysis that included more than 10 trials was possible, to assess potential small-study effects, such as publication bias.

Data synthesis

If sufficient clinically similar trials had been available, we intended to combine data for meta-analysis using the Cochrane Review Manager software 5.4 (RevMan 2020), as follows:

- for continuous outcomes, we planned to pool MDs between treatment arms at the end of follow-up if trials measured the outcome on the same scale and at the same primary study endpoint, otherwise we planned to pool SMDs;
- we intended to use random-effects models for all meta-analyses, with 95% CIs (DerSimonian 1986);
- for dichotomous data, we planned to pool RRs (RevMan 2020).

Subgroup analysis and investigation of heterogeneity

If sufficient data had been available, we would have reviewed studies separately using the following categories:

- drug dose;
- World Health Organization (WHO) tumour grade (low-grade/high-grade).

Sensitivity analysis

If sufficient data had been available, we would have considered the following factors:

- differing risk of bias profiles;
- different classes of agents, doses or scheduling differences.

We anticipated that additional types of sensitivity analyses would have been identified during the conduct of the review.

Summary of findings and assessment of the certainty of the evidence

Summary of findings tables were created where appropriate and adequate data were provided in relation to the topic of this review. If sufficient data had been available, we would have used the GRADE approach to assess certainty of the body of evidence. Table 1; Table 2.

RESULTS

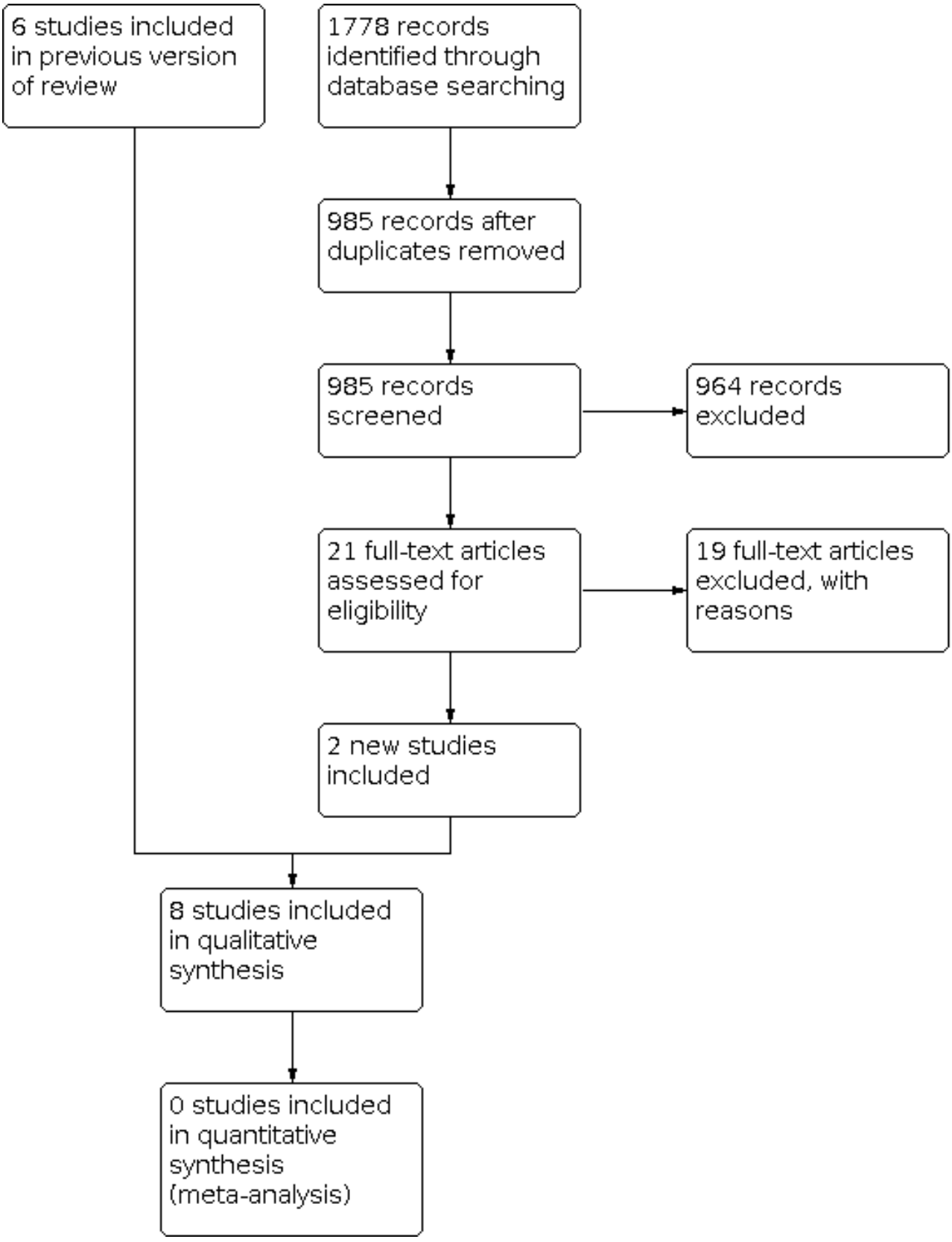
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies

Results of the search

Details can be found in Figure 1.

Figure 1.



In the original review, six studies were identified for inclusion. Four published trials met our inclusion criteria for analysis; two trials investigating the prevention of cognitive deficits and two trials investigating the amelioration of cognitive deficits. Three conference abstracts were also identified; data were available for one study (Kaleita 2006) and, following correspondence, data were obtained for another study (Rapp 2013). In addition, we identified one study when searching clinical trial databases for ongoing trials (Umphrey 2013). A further study was identified as awaiting classification (Shaw 2013).

In the updated search, an additional 1778 citations were identified through database searching, which left 985 records for screening following de-duplication of the results. Upon screening of titles, this narrowed the results to 21 articles. Of these 21 articles, the updated search identified two new additional studies for inclusion (Richard 2019; Voss 2022). In addition, the full-text article (Rapp 2015) for a conference abstract included in the original review (Rapp 2013) was identified. The full-text article of the study identified in the original review was awaiting classification (Shaw 2013) was also identified (Page 2015), which did not meet the criteria for inclusion in the review. In addition, the full-text article of a study identified in the original review as an ongoing trial (Umphrey 2013) was identified (Porter 2022), which also did not meet the criteria for inclusion in the review. An ongoing study was identified when searching clinical trial databases for ongoing trials (Chan 2018).

Included studies

For detailed information on included studies see the 'Characteristics of included studies' table.

Prevention

Two included studies investigated a pharmacological intervention (d-threo-methylphenidate hydrochloride and memantine) for the prevention of cognitive deficits during cranial irradiation (Brown 2013; Butler 2007). One included study investigated a cognitive rehabilitation and problem-solving program for the prevention of cognitive deficits in patients with primary brain tumours receiving radiotherapy (Locke 2008). Another study investigated the effect of a calorie-restricted ketogenic diet and intermittent fasting on progression-free survival in patients with glioblastoma, with cognitive outcomes as one of a number of secondary outcomes (Voss 2022).

Pharmacological Studies

Memantine versus placebo

One study recruited 554 eligible patients with brain metastases primarily from lung cancer, with breast, colon and other cancers also included; 46 patients did not meet the inclusion criteria, therefore 508 participants were allocated to intervention (*N* = 256; median age [range], 60 [31-84] years; M:F, 115:141; 84% white); placebo arm (*N* = 252; median age [range], 59 [29-86] years; M:F, 107:145; 83.3% white) (Brown 2013). This was greater than the calculated 221 participants required in each arm to reach 80% statistical power, although at eight weeks there were 129 and 139 patients in the intervention and placebo arms, respectively; of the 508 eligible patients, 55 withdrew consent and 271 died prior to completion of the study. Overall, 31% and 33% of participants completed 24 weeks of drug use as per the study protocol in the memantine and control groups, respectively. Imputation was carried out for participants still alive at the time of missed assessment. Wilcoxon rank-sum test, Gray's Test, Cox proportional hazards regression model, stratified log-rank test statistical analyses were performed.

d-threo-methylphenidate hydrochloride versus placebo

One study recruited 68 patients (intervention arm *N* = 34; median age [range], 52 [31-79] years; M:F, 20:14; 76% white; placebo arm *N* = 34; median age [range], 60 [28-83] years; M:F, 17:17; 91% white) of the 81 projected patients, calculated for a 90% statistical power, but with much fewer patients for analysis over time. Patients had a primary (*N* = 33) or metastatic brain tumour (Butler 2007); further details concerning the brain tumours were not reported. Two participants withdrew consent prior to receiving the intervention, 11 participants withdrew consent following the baseline assessment, 12 following radiation, and 11 after four weeks. Participant withdrawal of consent after eight weeks was not reported. This study was terminated early due to low accrual. Two sample t-tests, analysis of covariance, mixed-model analysis of covariance and autoregressive covariance structure statistical analyses were performed.

Comparisons between the pharmacological prevention studies

Both pharmacological prevention studies recruited participants in the USA, and both of these USA studies were multi-centre studies involving four centres (Butler 2007), and 143 centres, including Canada (Brown 2013). Both studies reported obtaining ethical approval and informed consent from participants, and described the recording of adverse events. Cranial irradiation schedule requirements varied between the two studies, with patients receiving 37.5 Gy of WBRT via 15 fractions of 2.5 Gy (Brown 2013) or partial or WBRT of at least 25 Gy in at least 10 fractions of 1.8 to 3.0 Gy/fraction (Butler 2007). Both studies reported using a randomisation method, which was confirmed via correspondence as random number generation using a computer program, and compared the interventions with a matched placebo group (Brown 2013; Butler 2007). In addition, both studies reported the use of a double-blinding and allocation concealment technique, which was confirmed via correspondence to have been through the use of a pharmaceutical company providing matched drug containers (Brown 2013; Butler 2007).

Interventions included d-threo-methylphenidate hydrochloride (d-MPH; Butler 2007) and memantine (Brown 2013). One study commenced administration of the study drug no later than three days after commencing radiotherapy (Brown 2013), and the other within five days of commencing radiotherapy (Butler 2007). Both pharmacological prevention studies included dose-escalation techniques, continued for eight (Butler 2007) or 24 (Brown 2013) weeks. Dose reduction and withdrawal techniques were included if patients experienced severe adverse events (Butler 2007), or when the patient's creatine clearance levels declined (Brown 2013).

Both studies assessed cognitive functioning using the Mini-Mental State Examination (MMSE). One study included a neuropsychological test battery that assessed memory, processing speed, executive function and verbal fluency (Brown 2013). The other study also included self-report measures of fatigue, depression and quality of life (Butler 2007). Timing of cognitive outcome assessment varied between studies, with patients assessed at baseline and then at eight, 16 and 24 weeks of drug use (Brown 2013), or at the end of radiation therapy and at eight weeks of drug use (Butler 2007). Both studies carried out a final follow-up

assessment after the drug was stopped, at 12 (Brown 2013) and 52 (Butler 2007) weeks.

Non-Pharmacological Studies

Cognitive rehabilitation versus standard care

Locke 2008 recruited 19 participants (intervention arm *N* = 12; median age [range], 47 [30 to 78] years; M:F, 7:5; ethnicity not reported; control arm *N* = 7; median age [range], 60 [31 to 71] years; M:F, 4:3) receiving cranial irradiation for the treatment of a primary brain tumour (17 glioma, two meningioma), with complete data in 14 of these participants. Six participants withdrew consent prior to completion of the study due to time commitments, tumour progression, fatigue and the unwillingness of a caregiver to attend appointments. Results were reported for 13 participants and their caregivers at post-intervention and three months follow-up. Recruitment was carried out at a single radiation oncology clinic. Ethical approval was obtained and informed consent sought. Patients were required to have a caregiver available to accompany them to each follow-up to complete a quality-of-life questionnaire. Radiation schedule requirements were not reported. The use of a randomisation method was reported, however this was abandoned due to low accrual and the final three participants were enrolled into the intervention arm. Due to the nature of the study, participants were not blinded. Blinding of personnel was not reported.

The intervention included six 50-minute sessions of cognitive rehabilitation and six 50-minute sessions of problem-solving therapy over two weeks, compared with standard medical care. The cognitive rehabilitation intervention was particularly aimed at memory. This involved the education and use of a calendar to compensate for cognitive problems. The problem-solving intervention involved the education and training of a positive problem-solving model via constructive thinking, using feelings as cues and reversed advocacy role play.

The primary aim of the study was to assess the tolerability and feasibility of the program. This was assessed through the use of the Mayo-Portland Adaptability Inventory (Malec 2003), primarily used in the evaluation of rehabilitation programmes designed for patients with acquired brain injury, and via patient feedback questionnaires. Cognitive functioning was assessed using the cognitive test battery Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph 1998). Self-reported quality of life, mood and fatigue were also assessed. Assessments were taken at baseline, following the two-week intervention, and at three months. RBANS was only reported at baseline and post-intervention as the majority of participants choosing a telephone follow-up for their final clinic appointment, and consequently cognitive assessment could not be carried out. Wilcoxon signed rank statistical tests were used to assess functional status only. Means and standard deviations for the RBANS subtest were reported for baseline and post-intervention; mean change and standard deviation of mean change were not reported.

Calorie-restricted ketogenic diet with intermittent fasting versus standard diet

Voss 2022 recruited 50 patients (intervention arm *N* = 25; median age [range], 56 [39 to 71] years; gender and ethnicity not reported; control arm *N* = 25; median age [range], 58 [26 to 75] years) with recurrent glioblastoma receiving re-irradiation from three German university hospitals. This was greater than the 42 patients necessary to have 80% statistical power. Ethical approval was obtained and informed consent provided by all participants. The radiotherapy regimen proposed by the study authors was 5 x 4 Gy from days four to eight in both groups, but other regimens were allowed. Randomisation, completed using computer software that generated random numbers, and allocation concealment were confirmed by correspondence with the study authors. Blinding of the participants and personnel were not possible due to the nature of the intervention.

The intervention comprised of three days of ketogenic diet (21–23 kcal per kg of body weight per day, with carbohydrate intake limited to 50 g per day), followed by three days of fasting and then another three days of ketogenic diet. During the fasting period, patients had an unlimited intake of fluid. From day 10 onwards, no dietary restrictions were implemented. The control group comprised a 'standard diet', with nutritional counselling in line with German Society of Nutrition guidelines, recommending a calorie intake of approximately 30 kcal per kg of body weight per day. Four participants (two from each group) withdrew consent to take part in the trial before the diet, and a further four participants stopped the diet during treatment (three from the intervention group and one from the standard diet group). There were 20 participants in the intervention group and 22 participants in the standard diet group who completed the evaluation as set by the protocol. Cognitive functioning was assessed as a secondary outcome using the MMSE and the d2 Test of Attention at baseline, day 6, day 12 and one month after radiotherapy. Of these, data on results of the d2 Test of Attention were available for 29 participants at baseline, 27 participants at day 6, 28 participants at day 12, and 27 participants at one month. The number of participants with data available for the MMSE were not specified.

The primary endpoint of the study was progression-free survival at six months, and secondary endpoints included: progression-free survival; local progression-free survival at six weeks, three months and 12 months; overall survival; frequency of epileptic seizures; extent of ketosis; quality of life; and cognitive function. Dependent and independent samples *t* tests, Wilcoxon tests, chi-squared tests, Kaplan-Meier survival analysis and log-rank tests were performed.

Amelioration

Three pharmacological studies (Gehring 2012a; Kaleita 2006; Rapp 2015) and one non-pharmacological study (Richard 2019) were included that investigated the treatment of cognitive deficits.

Pharmacological Studies

Modafinil at two different doses

One study recruited 30 of 30 expected patients (mean age [standard deviation], 45.3 [11.7] years; M:F, 19:11, ethnicity not reported) with a primary brain tumour, 87% of whom had received radiotherapy (Kaleita 2006); the distribution of tumour grade was almost equal between grade II, III and IV tumours, with two patients with a grade I tumour. Results were reported for all participants at baseline, and at eight and 12 weeks of drug use. Groups were combined for statistical analysis, and paired t-tests and Wilcoxon Signed Rank tests were used to assess change from baseline.

Methylphenidate versus modafinil

Another study recruited 34 of the 75 planned patients with a primary brain tumour, calculated to have 90% statistical power. Four participants were excluded from the study; three due to tumour progression (two methylphenidate arm; one modafinil arm), and one due to infection-related delirium requiring hospitalisation (modafinil arm). A further six participants dropped out; three due to the prescription not being filled (two methylphenidate arm; one modafinil arm), one due to nausea (modafinil arm), one due to steroid-induced hyperactivity (modafinil arm), and one missed the follow-up appointment (methylphenidate arm). Results were reported for 24 participants at four weeks of treatment (21 glioma, one medulloblastoma, one primary central nervous system (CNS) lymphoma, one hemangiopericytoma; methylphenidate arm *N* = 19; mean age [standard deviation], 42.5 [10.2] years; M:F, 8:11; ethnicity not reported; modafinil arm *N* = 5; mean age [standard deviation], 54.4 [7.7] years; M:F, 5:0); 83% of whom had received cranial irradiation prior to participation and 62.5% were receiving chemotherapy during participation (Gehring 2012a). Despite randomisation, there were significantly more males in the modafinil group, compared to the methylphenidate group (P = 0.03). An exploratory statistical analysis approach was used via t-tests and repeated measures analyses of covariance. Due to low accrual, the two methylphenidate arms were combined during analysis; further analysis also combined all interventions and compared findings with normative data. Practice effect adjusted reliable change index was used to assess individual change in cognitive test scores relative to baseline.

Donepezil versus placebo

A further study recruited 198 of the required 200 patients (intervention arm *N* = 99; median age [range], 56 [19-84] years; M:F, 43:56; 91% white; control arm *N* = 99; median age [range], 54 [19-81] years; M:F, 49:50; 91% white), required to reach 90% statistical power, from 26 sites; 130 had a primary brain tumour, 53 a metastatic brain tumour, and 15 had received prophylactic cranial irradiation (Rapp 2015). Fifty-two participants dropped out of the study; reasons were not reported. Results were presented for 146 participants at 24 weeks follow-up. Chi^2, Fisher exact and Wilcoxon rank-sum statistical tests were used. Imputation was carried out in all participants who provided at least baseline data.

Comparisons between the pharmacological amelioration studies

Two studies initially reported their results as a conference abstract (Kaleita 2006; Rapp 2015), with data from only one of these appearing in a full manuscript at the time this review was conducted (Rapp 2015). All three studies were conducted in the USA. Ethical approval and informed consent was reported for two studies (Gehring 2012a; Rapp 2015) and all reported adverse events. Two studies did not restrict patients to those receiving cranial irradiation (Gehring 2012a; Kaleita 2006). In one study, patients were eligible to participate following partial or whole brain irradiation of 30 Gy or greater (Rapp 2015). The use of a randomisation method was reported by all studies, and correspondence confirmed this and was through the use of a computer program in two studies (Gehring 2012a; Rapp 2015). Two studies used double-blinding (Kaleita 2006; Rapp 2015), and one study also reported an allocation concealment method via a pharmaceutical company (Rapp 2015). One study used an open-label design, although all treatment arms were experimental (Gehring 2012a).

Intervention arms varied between studies. Kaleita 2006 compared two dosages of modafinil followed by an extended treatment phase using a titrated dose between 50 mg and 600 mg/day for eight weeks. Gehring 2012a included three intervention arms using two forms of methylphenidate (immediate release and sustained release, combined for analysis), compared to a modafinil arm. Rapp 2015 included one intervention arm of donepezil, with an increasing dosage from 5 mg/day for six weeks and 10 mg/day for 18weeks if tolerated, compared with placebo.

All studies assessed cognitive functioning using neuropsychological testing, and one also calculated a cognitive composite score (Rapp 2015). All studies included self-reported measures of mood and fatigue, and one also included a measure of quality of life (Gehring 2012a). Assessments were taken at baseline and at four weeks of drug use (Gehring 2012a), at baseline, 12 and 24 weeks of drug use (Rapp 2015), or at baseline and at one, three, four, eight and 12 weeks of drug use (Kaleita 2006). Gehring 2012a used alternate test forms when possible and statistical corrections to minimise re-test effects. Assessments were not carried out following withdrawal of the drug, but were recorded in one study during a washout period prior to the extension phase (Kaleita 2006).

Non-Pharmacological Studies

Goal Management Training versus active control and wait-list control

Richard 2019 recruited 26 patients with meningioma, low-grade glioma or high-grade glioma, one of whom experienced disease progression before baseline testing and was thus excluded, leaving 25 patients (demographic data not reported by group allocation; overall median age [range], 48 [21-68] years; M:F, 15:10; ethnicity not reported) for analysis (20 for post-intervention analysis). No formal power calculation was described for this study. The study was conducted in Canada. Ethical approval and informed consent was reported. The study did not restrict inclusion to those receiving cranial irradiation (85% received cranial irradiation). Patients were randomised using a random number generator and allocation concealment was achieved through the allocation spreadsheet being viewable only to the intervention provider, confirmed by correspondence with the study authors. Blinding of participants was not possible due to the nature of the interventions.

There were three groups in this study. The intervention comprised of Goal Management Training, a behavioural intervention that combined mindfulness and strategy training, delivered in eight two-hour individual sessions by a clinical neuropsychologist. An active control group underwent a novel psycho-educational Brain Health Program that included content on brain and cognition but no cognitive strategy training, also delivered in eight two-hour individual sessions by a clinical neuropsychologist. The third group was a wait-list passive control group that received usual care but no neuropsychological intervention. In the Goal Management Training group, one participant only completed six out of eight sessions (due to new employment). In the active control group, one participant withdrew after baseline assessments without providing a reason, and another after completing seven out of eight sessions (due to increased work responsibilities). In the wait-list control group, one participant withdrew after baseline assessment with no reason provided, one declined assessment at post-training, and an

additional two declined at follow-up (all citing a lack of time). An analysis comparing study completers (n = 21) and non-completers (n = 4) showed that non-completers were younger at enrolment and had worse language abilities, slower processing speed, and higher apathy scores.

Following randomisation, 11, eight and six participants were allocated to the Goal Management Training, active control and wait-list control groups, respectively, with data on 10, six, and four available for post-intervention analyses. Cognitive function was assessed using neuropsychological testing covering the domains of executive functioning, memory, and processing speed. The study also assessed self-reported measures of cognitive symptoms, emotional functioning, coping and adjustment and everyday life function. Assessments were completed at baseline, immediately following the training and at four months. Analysis of variance, Pearson's Chi^2, Kruskal-Wallis and Mann-Whitney U statistical tests were performed. The primary outcome measure was change in the executive functioning composite score. Secondary endpoints included changes in processing speed, memory, self-reported cognitive symptoms, emotional functioning and coping/adjustment, programme adherence and patient-reported use and effects of programme contents, including functional goal attainment.

Excluded studies

For detailed information on excluded studies see the 'Characteristics of excluded studies' table.

In the original review, after screening 16 full-text articles, 10 studies were excluded in the original review (Attia 2012; Boele 2013; Chan 2003; Gehring 2009; Hulshof 2002; Jatoi 2005; Levin 2011; Meyers 1998; Schellart 2011; Shaw 2006).

For this update, 21 full-text articles were screened, and a further 19 studies were excluded:

- Seven amelioration studies investigating lidocaine (Peng 2016), Internet-based guided self-help (Boele 2018), cognitive rehabilitation (Van der Linden 2018; van der Linden 2021), home-based exercise (Gehring 2018; Gehring 2020), and home-based psychotherapy and rehabilitation (Ownsworth 2012) did not include a majority (80%) of participants who had received cranial irradiation, or did not analyse these patients separately. Two of these studies (Gehring 2018; Van der Linden 2018) also did not include cognitive impairment as an inclusion criterion, and one study (Boele 2018) did not include cognitive assessment via neuropsychological testing.
- One amelioration study investigating cognitive rehabilitation (Maschio 2015) did not include a control group.
- Three amelioration studies investigating armodafinil (Page 2015; Porter 2022) and dexamphetamine sulfate (Laigle-donadey 2018) did not include cognitive impairment in at least one domain as an inclusion criterion.
- One prevention study investigating the radioprotective effect of memantine (Wong 2016) was a sub-study of a study already included in the review (Brown 2013)
- One study investigating donepezil (Naughton 2018) did not include cognitive assessment via neuropsychology testing.
- Two amelioration studies investigating the role of metformin (Ayoub 2020) and aerobic exercise training (Cox 2020) on cognition focused on childhood cancer survivors that were largely still children at the point of recruitment into the study.
- One study evaluating the role of exercise therapy focused on postmenopausal breast cancer survivors (Campbell 2017).
- One study evaluating the role of online couple-based meditation for patients in primary or metastatic brain tumours did not formally assess cognitive outcomes (Milbury 2020).
- One amelioration study evaluating the role of virtual reality training on cognitive outcomes in brain tumour patients with cognitive dysfunction did not specify how many patients received radiotherapy (Yang 2014).
- One prevention study investigating Shenqi fuzheng (Chen 2019) was published as a randomised controlled trial although some aspects of the exclusion criteria needed clarification. At the time of publication of this systematic review update no further clarification was available from the authors. As a result, we have placed the study in the 'Studies awaiting Clarification' section.

Studies Awaiting Classification

In the original review there was one study published in conference proceedings (Shaw 2013). The updated search identified the full published article (Page 2015) which did not meet the inclusion criteria to be included in the review as it did not include cognitive impairment in at least one cognitive domain as an inclusion criterion (see 'Characteristics of excluded studies' table). In addition, as mentioned above one study (Chen 2019) was published as a randomised controlled trial although some aspects of the exclusion criteria needed clarification that was not available from the authors at the time of publication of this systematic review update.

Ongoing Studies

In the original review there was one ongoing study identified (Umphrey 2013). The full-text version of this study has now been published (Porter 2022), which was excluded because the study did not meet the criteria to be included in the review as it did not include cognitive impairment in at least one cognitive domain as an inclusion criterion (see Characteristics of excluded studies table). The updated search found one additional ongoing study, evaluating the effect of ramipril on memory loss in patients with glioblastoma receiving chemoradiation (Chan 2018).

Risk of bias in included studies

We assessed studies using the Cochrane risk of bias tool (Higgins 2011). Between the two review authors of the original (JD, KZ) and updated (MK, JD) reviews, there was agreement in the risk of bias scores following discussion. Attempts to contact authors were carried out where there was an unclear risk of bias. A summary of the risk of bias is presented in Figure 2 and Figure 3.

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

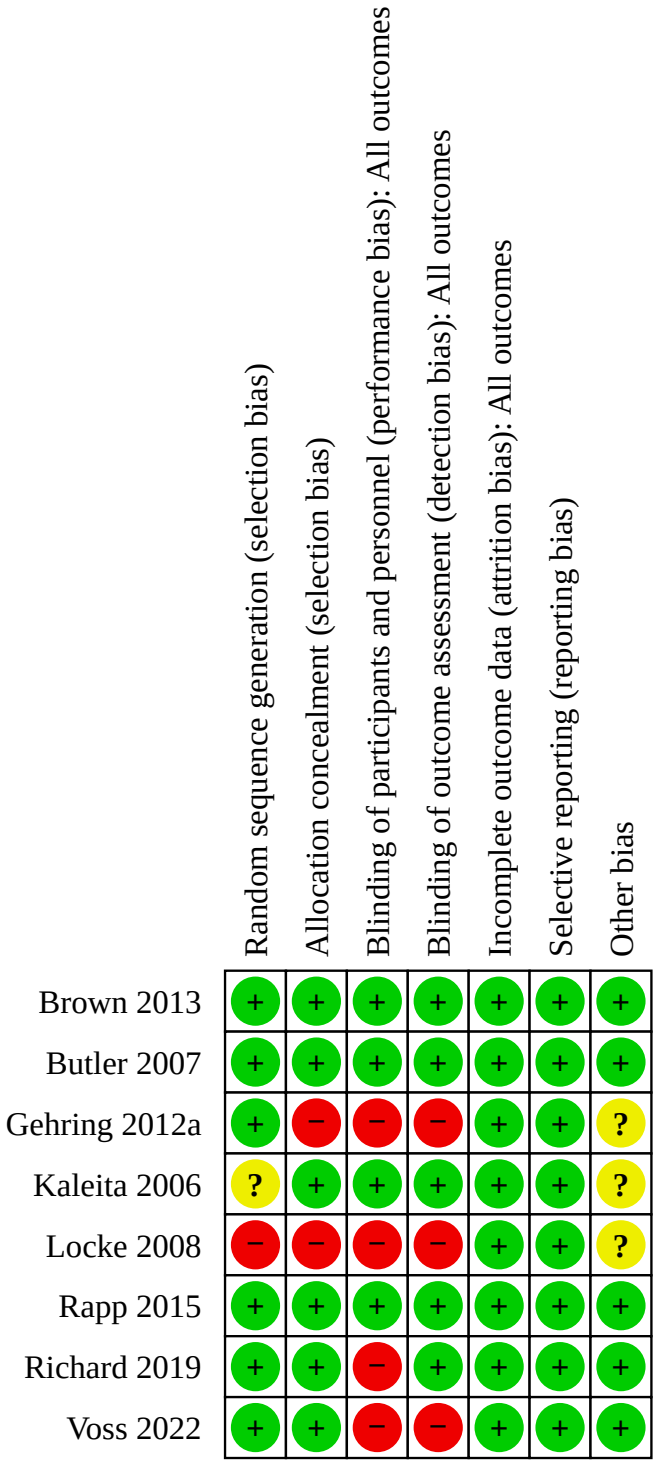
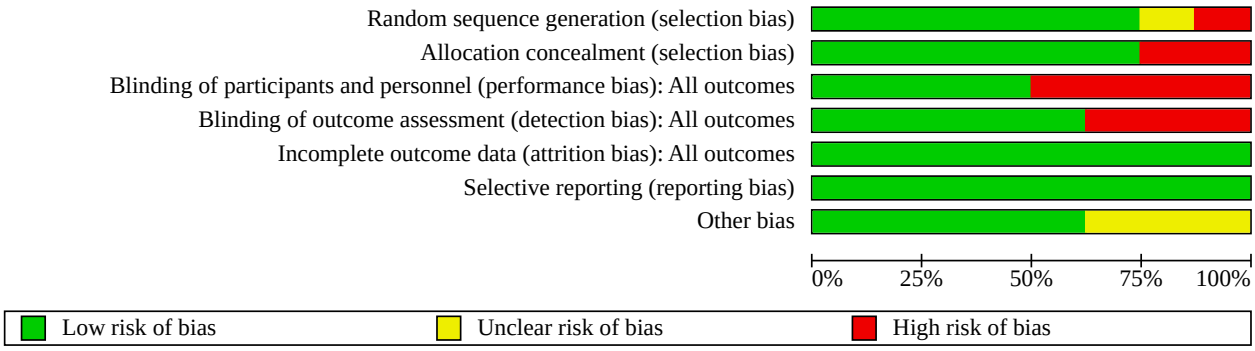


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Three of the five pharmacological studies were at a low risk of bias in relation to random sequence generation and allocation concealment as they used a stratification randomisation method and a pharmaceutical company to create identical drug containers (Brown 2013; Butler 2007; Rapp 2015). One pharmacological study was at an unclear risk of bias in relation to random sequence generation as it reported the use of a randomisation method, however the method used could not be identified (Kaleita 2006). The same study had a low risk of bias in relation to allocation concealment as blinding was used (Kaleita 2006). Two studies were at a high risk of bias regarding allocation concealment: one of these was a pharmacological study that used an open-label design (Gehring 2012a); the other was a non-pharmacological study that reported the use of a randomisation method but this was abandoned due to low accrual, which also placed it at a high risk of bias in relation to random sequence generation (Locke 2008). The pharmacological study at a high risk of bias regarding allocation concealment was at a low risk of bias regarding random sequence generation as a computer was used for randomisation (Gehring 2012a). Two of the three non-pharmacological studies had a low risk of bias in relation to random sequence generation and allocation concealment as patients were randomised using a random number generator and allocation concealment was confirmed by correspondence with the authors (Richard 2019; Voss 2022).

Blinding

Four of the five pharmacological studies were at a low risk of bias and blinded participants and personnel to the intervention group (Brown 2013; Butler 2007; Kaleita 2006; Rapp 2015). The other pharmacological study used an open-label design (Gehring 2012a) and was at a high risk of bias. The three non-pharmacological studies (Locke 2008; Richard 2019; Voss 2022) were at a high risk of bias; blinding of participants to the intervention was not possible due to the nature of the intervention, and in two of these studies blinding of assessors was also not carried out (Locke 2008; Voss 2022).

Incomplete outcome data

The majority of studies included reasons for participant dropout, which were unlikely to be related to the outcomes and all studies were judged at a low risk of bias. Three studies performed intention-to-treat analyses (Brown 2013; Butler 2007; Rapp 2015). One study was terminated early (Butler 2007). Three studies recruited the projected number of participants (Brown 2013; Kaleita 2006; Voss 2022). However, no study was able to include the number of participants required to reach the desired statistical power due to withdrawal from participation as a result of patient death, tumour progression or withdrawal of consent. One study reported the use of a multiple imputation procedure via the Markov chain Monte Carlo method for patients still alive at the time of assessments; this included the imputation of scores for 47% of recruited participants at 24 weeks (Brown 2013). One study reported the use of an imputation method in all participants (Rapp 2015). Two studies carried out statistical comparisons between patients who withdrew consent, and those who remained in the study (Brown 2013; Butler 2007). Butler 2007 reported that patients who dropped out were significantly older and with worse performance status, but did not differ in any of the outcome measures. Brown 2013 reported that patients who could not complete cognitive assessments were more likely to have worse neurological function and a shorter survival time and had not undergone surgery or radiosurgery. In one study (Locke 2008), most patients did not return in-person for follow-up, instead electing for telephone follow-up; as the cognitive test used (RBANS) cannot be administered via telephone, most patients did not complete the RBANS at follow-up.

Selective reporting

All outcomes were reported by all included studies and therefore were all judged at a low risk of bias. It was noted that some studies did not report assessments carried out following withdrawal of the drug (Brown 2013; Butler 2007), and did not report interim assessments (Kaleita 2006; Rapp 2015).

Other potential sources of bias

An unclear risk of bias was reported for three studies. Due to a small sample size, two studies combined intervention groups of participants receiving different forms of the drug methylphenidate (Gehring 2012a) and different doses of modafinil (Kaleita 2006) when analysing results. One study did not perform statistical analyses on the cognitive data pre-/post-intervention, instead providing only descriptive data (Locke 2008).

Effects of interventions

In the original review, study interventions and comparisons were heterogenous, and were too different clinically to be able to pool the data. Following the addition of two additional studies in this updated review, the same issue still prevents pooling of data. Eight studies were identified for inclusion in the review. Due to differences in interventions and aim of interventions (prevention versus amelioration) investigated, including the use of drugs with different modes of actions and dosage schedules, and use of different non-pharmacological interventions, the results are reviewed separately in this review.

Prevention

Pharmacological Studies

The large differences in the mode of action of the drugs investigated, and the unavailability of mean changes in scores, standard deviations or P values, meant pooling of the data was inappropriate. Therefore, results of the studies are reviewed separately and the data are reviewed as reported in the study.

Memantine versus placebo

Brown 2013 compared memantine, which acts on the glutamatergic system as an N-Methyl-D-aspartate receptor antagonist, with placebo intervention in patients with brain metastases. Mean cognitive decline was reported for 280 participants at eight, 16 and 24 weeks assessments. The primary endpoint was Hopkins Verbal Learning Test-Revised (HVLT-R) at 24 weeks, but between-group (n = 149) differences in decline did not reach significance (P =0.059); this was attributed to attrition. The memantine arm had significantly longer time to cognitive decline (hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.62-0.99, P = 0.01), which was a secondary endpoint; the probability of cognitive function failure at 24 weeks was 53.8% in the memantine arm and 64.9% in the placebo arm. Median change and interquartile ranges (IQRs) were also reported for individual neuropsychological tests at 24 weeks, which are summarised in Table 1. A cognitive functioning composite score was also calculated and the median change was -0.41 (IQR) -1.30 to 0.12) in the control group and -0.03 (IQR -0.90 to 0.72) in the intervention group at 24 weeks, which was reported to be significantly different (P = 0.02). This indicated a stability of cognitive function in the intervention group and a decline in the control group. The most common adverse events were fatigue, alopecia, nausea and headache; there was no difference in the adverse events reported between groups (risk ratio (RR) 1.00; 95% CI 0.76 to 1.32). It was noted that more participants in the memantine group were receiving steroids at entry into the study than the control group (P = 0.05), which may have indicated more symptoms and mass effect from brain metastases in the memantine group and would be expected to portend worse cognitive outcome at this time point, although this difference in steroid use did not continue over time.

d-threo-methylphenidate hydrochloride (d-MPH) versus placebo

Butler 2007 evaluated d-MPH, a central nervous system (CNS) stimulant that acts as a norepinephrine-dopamine reuptake inhibitor, compared with placebo in patients with primary or metastatic brain tumours. Mean cognitive functioning, as assessed with the Mini-Mental State Examination (MMSE), in the control group ranged from 26.5 (3.39 SD) to 27.8 (6.12 SD) at the end of radiation to 25.6 (11.54 SD) at eight weeks follow-up. Mean overall cognitive functioning in the intervention group ranged from 27.2 (2.92 SD) at baseline to 26.4 (5.92 SD) at the end of radiation to 23.3 (10.46 SD) at eight weeks follow-up. This difference was not significant and the standard deviation of mean change could not be calculated as P values were not reported. No other measures of cognitive performance were used, and it is noted that the MMSE is not considered a sensitive measure of cognitive function (Meyers 2003). Fatigue was the primary outcome in this study, but was not found to be significantly different between groups at eight weeks follow-up of drug use (mean difference (MD) 3.30, 95% CI -10.37 to 16.97). Depression and quality of life were also assessed, reporting no significant difference between groups, although again P values were not provided. Four adverse events were reported in total, although they were not all reported specifically to the arm and therefore the risk ratio could not be calculated; two participants experienced nausea and vomiting, one participant experienced tachycardia (control arm) and one participant was withdrawn from the study due to an increase in liver enzymes.

Non-Pharmacological Studies

Cognitive rehabilitation versus standard care

Locke 2008 evaluated a two-week cognitive rehabilitation and problem-solving program, compared with standard care in patients with primary brain tumours. Control participants were reported as more significantly impaired on a measure of immediate memory than intervention participants at baseline (P = 0.03). Using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the mean total cognitive functioning score remained stable at 73 from baseline (SD 13.4) to post-intervention (SD 9.3) in the control groups and improved from 79 (SD 20.0) at baseline to 80 (SD 18.6) at post-intervention in the intervention group; a statistical comparison was not carried out. Mood, fatigue, quality of life and caregiver burden measures were also recorded, but again no statistical comparisons were made. The primary outcomes of the study were feasibility, strategy implementation and patient satisfaction; 7/8 of the intervention group participants were using strategies at least once per week at the eight-week follow-up and 7/8 of both the participants and the caregivers found the intervention 'very helpful'.

Calorie-restricted ketogenic diet with intermittent fasting versus standard diet

Voss 2022 evaluated the effect of a calorie-restricted ketogenic diet with intermittent fasting compared to a standard diet in patients with recurrent glioblastoma. Cognition was evaluated using the MMSE and d2 Test of Attention. Median MMSE scores were reported to not be significantly different between baseline and follow-up for both groups (median = 29 points in both groups). However, baseline evaluation with the d2 Test of Attention revealed severely impaired median cognitive function percentile corrected for age, 5% (range: <1 to 42%) in the intervention group and 16% (range: <1 to 76%) in the standard diet group. At day 6, a non-significant increase in d2 Test of Attention scores was found in both groups, with a median age-corrected attention score of 12% in the intervention group (P = 0.187) and 23.5% in the standard diet group (P = 0.103). These scores increased significantly until one-month follow-up, with median age-correct attention scores of 17% in the intervention group (P = 0.035) and 27% in the standard diet group (P = 0.049). Cognitive function was not affected by the diet. Of note, the standard diet group had a lower calorie intake than expected, 21 kcal per kg per day instead of 30 kcal per kg per day. Significant

metabolic changes were found. Adverse events were reported in an original paper focusing on the primary outcome of the trial (Voss 2020); until day 12, nine adverse events were reported (four in the intervention group and five in the standard diet group), three of which were seizures and the remainder were headaches, nausea, and possible epileptic seizures. From day 12 until one month, 11 adverse events were reported (five in the intervention group, six in the standard diet group), the majority of which were epileptic seizures (five focal epileptic seizures).

Amelioration

Pharmacological Studies

Due to the differences in control groups or differences in the drug investigated, pooling of the data was inappropriate. Therefore, results of the studies are reviewed separately.

Modafinil at two different doses

Kaleita 2006, published as a conference abstract only, compared two doses of the CNS stimulant modafinil, 200 mg/day or 400 mg/day in divided doses, in patients with primary brain tumours. A significant improvement from baseline was seen at 12 weeks across all cognitive tests; Trail Making Test A (P = 0.002) and B (P < 0.0001), Verbal Fluency (P = 0.002) and Symbol Digit Modalities-Oral (P = 0.006) and -Manual (P = 0.004). Significant differences were also found at eight weeks for all tests. Improvements in fatigue and mood were found at eight and 12 weeks. Adverse events were reported, however the distribution of adverse events between treatment arms was not reported. Thirteen participants experienced symptoms of headache, eight of insomnia, seven of dizziness, seven of dry mouth, five of depressed consciousness and four of nausea.

Methylphenidate versus modafinil

Gehring 2012a compared two CNS stimulants, in three treatment arms; sustained-release methylphenidate, immediate-release methylphenidate and modafinil in patients with primary brain tumours. The mean cognitive functioning scores comparison for each test is summarised in Analysis 4.2; Digit Span (MD 0.38; 95% CI 0.03 to 0.73), favouring methylphenidate, and Trail Making Test A (MD -2.48, 95% CI -4.82 to -0.14), favouring modafinil were the only tests to show a significant difference between groups. The two stimulant groups together demonstrated significant improvement of individual Trail Making Test B scores P = < 0.01), corrected for practice effects. Mood, fatigue, quality of life and sleep also significantly improved in both groups, but with no significant difference between groups (see Analysis 4.5; Analysis 4.6; Analysis 4.8; Analysis 4.9; Analysis 4.11). None of the participants who completed the study experienced adverse events in either treatment arm.

Donepezil versus placebo

Rapp 2015 compared donepezil, an acetylcholinesterase inhibitor, with placebo in patients with primary and metastatic brain tumours, and patients undergoing prophylactic cranial irradiation. The mean cognitive functioning score comparison for each test is reported in Analysis 5.2, based on raw data provided by the authors. The primary outcome was a calculated cognitive composite score, in which both groups were found to significantly improve after 24 weeks; there was no significant difference between groups (MD 0.03, 95% CI -0.06 to 0.13). A significant difference was found in scores of tests of long-term memory recognition (MD 0.57, 95% CI 0.07 to 1.07), long-term memory discrimination (MD 0.94, 95% CI 0.26 to 1.62), and dominant hand psychomotor functioning (MD -11.92, 95% CI -21.58 to -2.27) favouring donepezil. Furthermore, the benefits of donepezil were greater for those who were more cognitively impaired prior to study treatment. The commonest toxicity reported was fatigue (58% of those receiving donepezil and 67% receiving placebo), and the only toxicity that was significantly different between the two arms was diarrhoea (25% of those receiving donepezil and 9% receiving placebo; P = 0.005).

Non-Pharmacological Studies

Goal Management Training versus active control and wait-list control

Richard 2019 compared Goal Management Training, an active control (Brain Health Program) and a wait-list control group in patients with primary brain tumours. The comparison in group changes from baseline to immediately post-training and four-month follow-up for the cognitive performance measures is summarised in Table 2, and analyses for the cognitive performance measures (executive functioning composite, memory composite and processing speed) as well as the self-reported outcome measures are shown in Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5; Analysis 6.6. A significant intervention effect on the executive composite was observed at four months follow-up (with a time-by-group interaction F(2,16) = 3.760, P = 0.046, partial eta-squared value = 0.320), which reflected a large improvement in the Goal Management Training group (effect size = 1.08, P = 0.002, corrected effect size = 1.09) and minimal change in the Brain Health Program (effect size = 0.09, P > 0.1) and wait-control (effect size = -0.06, P > 0.1) groups. There was a statistically significant difference in the proportion of participants that scored in the impaired range on one or more tests of executive functioning between groups by follow-up (Goal Management Training: 91% at baseline to 20% at four months; Brain Health Program, 88% at baseline to 67% at four months; wait-list control, 100% throughout; chi-square value = 7.234, P = 0.027). For the memory composite, all groups improved at follow-up (main effect of time: F(1,16) = 6.435, P < 0.001, partial eta-squared = 0.524). Effect sizes were moderate to large, although within-group simple effects tests for the Brain Health Program and wait-list control groups were not significant (Goal Management Training effect size = 1.37, P > 0.002; Brain Health Program effect size = 0.74, P = 0.093; wait-list control effect size = 1.06, P > 0.1). Regarding processing speed, at follow-up the Goal Management Training group had moderate gains relative to baseline (effect size = 0.61, P = 0.015, corrected effect size = 0.68), whereas no improvement was observed in the Brain Health Program (effect size = -0.09, P > 0.1) and wait-list control (effect size = -0.30, P > 0.1) groups. Both the Goal Management Training and Brain Health Program groups reported fewer cognitive concerns immediately post-training (P = 0.049) and at 4-months follow-up (P < 0.001).

DISCUSSION

Summary of main results

The aim of this review was to evaluate the effect of any pharmacological or non-pharmacological intervention on cognitive functioning during or following cranial irradiation. In the original review, we included three randomised trials for the prevention of cognitive deficits, recruiting a total of 641 heterogeneous patients and three randomised trials for

the amelioration of cognitive deficits, recruiting a total of 199 heterogeneous patients. In this update, we included an additional randomised trial for preventing cognitive deficits that recruited 50 patients and an additional trial for ameliorating cognitive defects that randomised 25 patients.

Prevention

The two trials that compared drug versus placebo used very different drug agents, dosage schedules and time points for follow-up; a meta-analysis was therefore inappropriate.

Brown 2013 compared memantine in a large sample of 554 patients with brain metastases from 143 centres across the USA and Canada, and carried out imputation in participants who had not withdrawn from the study as a result of death. The primary outcome measure, memory as measured using the Hopkins Verbal Learning Test-Revised (HVLT-R for Delayed Recall) at 23 weeks, showed a non-significantly reduced rate of decline in the memantine group. Significant differences between groups were found in other cognitive domains.

Butler 2007 compared d-threo-methylphenidate hydrochloride (d-MPH) in a small sample of 68 patients with primary and metastatic brain tumours with a high drop-out rate; no difference was found between the intervention group and control group in the primary outcome (fatigue), or in cognitive functioning, depression and quality of life.

The one prevention trial that investigated a cognitive rehabilitation and problem-solving program, compared with standard care, had the primary aim of assessing the tolerability and feasibility of the intervention (Locke 2008). Therefore, no statistical comparisons were made of the difference between groups in cognitive functioning. Consequently, this study provides very little evidence for the prevention of cognitive deficits, but did offer a tolerable and feasible intervention for further investigation.

Voss 2022 compared calorie-restricted ketogenic diet and intermittent fasting to standard diet in 50 patients undergoing re-irradiation for glioblastoma. The study's primary endpoint measure was progression-free survival at six months (reported in a different manuscript), and cognitive functioning was evaluated as one of several secondary endpoints. The study found no significant change in the primary endpoint measure, or in median Mini-Mental State Examination (MMSE) scores in either group, at baseline and at follow-up. Attention was severely impaired at baseline but increased significantly until follow-up at one month in both groups. Cognitive function was not affected by the diet, and the standard diet group had a lower calorie intake than expected, which complicated interpretation of the results.

Amelioration

The three pharmacological trials that investigated the amelioration of cognitive deficits used different drug agents and/or control groups and different time points for follow-up; a meta-analysis was therefore inappropriate.

Gehring 2012a compared two forms of methylphenidate with modafinil, in a small sample of 24 mostly glioma patients. Inconsistent, differential effects were found in cognitive performance between groups in attention, favouring methylphenidate, and processing speed, favouring modafinil. However, when treatment groups were combined, and after corrections for practice effects, there was evidence of a beneficial effect on test performance in speed of processing and executive function requiring divided attention.

Kaleita 2006, published as a conference abstract, also combined intervention arms in a study of 30 patients with mainly gliomas and found an overall significant improvement (but without correction of practice effects) in all cognitive assessments at eight and 12 weeks, compared to baseline.

Rapp 2015 with a larger sample size (146 patients, from 24 sites, with primary or metastatic brain tumours or receiving prophylactic cranial irradiation) than either Gehring 2012a or Kaleita 2006 compared donepezil with placebo. Treatment with donepezil did not significantly improve the primary outcome measure, a cognitive composite score, but did result in modest improvements in several cognitive functions, especially among patients with greater pre-treatment impairments. However, the clinical relevance of some of these improvements, particularly in the HVLT-R, are unclear.

Only one study investigated the amelioration of cognitive deficits via a non-pharmacological intervention. Richard 2019 compared two active interventions, Goal Management Training and Brain Health Program, to a wait-list control group in a group of 25 patients with primary brain tumours from a single Canadian centre. The study found executive functions improved only in the Goal Management Training group and were maintained at four months follow-up. Processing speed also improved in the Goal Management Training and Brain Health Program groups, although this was only maintained at four months in the Goal Management Training group. All three groups improved in the memory tests, suggesting a practice effect.

Overall completeness and applicability of evidence

We included eight randomised controlled trials (RCTs) examining the efficacy of interventions for the prevention or amelioration of cognitive deficits in adults treated with cranial irradiation. Due to differences in drug agents, it was inappropriate to combine data into a meta-analysis.

The evidence identified in this review is insufficient to address the objective of this review and to make generalisations about the applicability (external validity) of the described interventions to the wider population of patients with brain tumours that have received cranial irradiation. This is due in part to the low sample sizes of several of the included studies, as well as the wide heterogeneity in study populations, interventions, study designs, outcome measures and timing of assessments. Most of the included studies were restricted by these and the following limitations, which further reduced both the internal and external validity of the evidence; it is also of note that the completeness of the evidence is hampered by the lack of randomised studies evaluating interventions such as exercise therapy, hyperbaric oxygen therapy and dietary supplements.

Several of the studies included in this review were at high risk of bias in at least one domain. Generally, the non-pharmacological studies were more likely to be at high risk of bias due to the nature of the intervention and the inability to provide a placebo condition. This negatively affected the internal validity of the included studies.

Many studies were limited by low accrual. Studies that recruited from few centres were unable to reach the necessary number of participants required for sufficient statistical power (Butler 2007; Gehring 2012a; Kaleita 2006; Locke 2008). It may also be that patients may be reluctant to take any additional medication, especially if they are not subjectively experiencing cognitive impairment at the time of enrolment.

Most studies were limited by high attrition rates. One study was able to recruit the projected participants required for 80% statistical power with the involvement of 143 centres (Brown 2013). However, 34% of participants died at 24 weeks of drug use and 47% of the remaining 280 participants missed their assessment appointment. It is important to understand the reasons for missed appointments. For example, in studies that focus on prevention rather than treatment, a lack of interest may be found in patients not experiencing cognitive impairment at that stage. Therefore, it is important to make sufficient attempts to keep patients engaged in study participation, such as by emphasising the importance of ongoing cognitive function assessment. It is also notable that, in some studies, patients withdrawing from the trial tended to be older, and/or had worse performance status/neurological function and/or had shorter survival.

Differences in the time points at which cognitive functioning is measured are also present, both in pharmacological and non-pharmacological intervention studies. One study carried out assessments at baseline, and at four weeks of modafinil or methylphenidate use (Gehring 2012a), whereas another continued to follow up patients at eight, 16, 24 and 52 weeks following initiation of the drug memantine (Brown 2013). In cognitive rehabilitation studies, patients were assessed at baseline and at the end of a two-week intervention and at three months (Locke 2008). These studies also demonstrate the variations in duration of the intervention.

Only one study mentioned specifically attempting to minimise practice effects (Gehring 2012a).

A number of assessment tools were used to evaluate cognitive function in the included studies, ranging from a battery of numerous tests (Brown 2013; Gehring 2012a; Kaleita 2006; Rapp 2015; Richard 2019), to the MMSE and d2 Test of Attention (Voss 2022), or the MMSE (Butler 2007) or RBANS (Locke 2008) alone. The use of a single cognitive outcome measure is unlikely to fully and comprehensively represent a participant's cognitive status. In addition, although neuropsychological tests provide objective evidence of cognitive performance, it is largely unclear whether any improvements in test scores translate to genuine long-term benefits in everyday life/quality of life. More extensive and longer-term study of neuropsychological performance alongside self- and caregiver-reported measures are required to elucidate further on this issue.

Failure to report all study and patient characteristics meant that limitations remained a concern. The lack of adequately presented data, or lack of reporting of mean differences and standard deviation or P values, meant that the reporting of results as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) could not be carried out in five studies (Brown 2013; Butler 2007; Kaleita 2006; Locke 2008; Voss 2022). Further correspondence to obtain these data were unsuccessful. The use and changes in use of medications associated with cognitive functioning were rarely reported. Only one study reported the use, and change in use of steroids during participation (Brown 2013), and reported that more intervention participants were receiving steroids at study entry than control participants. No studies reported the use, or change in use of anti-epileptic drugs during participation. As these drugs may also play a role in cognitive functioning (Kirkman 2022), findings may be attributable to changes in these medications during the study period. Assessment of cognitive functioning following withdrawal of the drug under study may have provided additional information relating to the efficacy of the drug. Two studies carried out post-drug withdrawal assessments (Brown 2013; Butler 2007), but these data were not reported.

Quality of the evidence

See Figure 2 and Figure 3.

Overall, this review summarises limited evidence for the effect of pharmacological and non-pharmacological interventions for the prevention or amelioration of cognitive deficits in adults treated with cranial irradiation. Two of the studies were at high risk of bias in three or more domains, with additional domains at an unclear risk of bias (Gehring 2012a; Locke 2008). Blinding was not carried out in four studies (Gehring 2012a; Locke 2008; Richard 2019; Voss 2022) and, in two studies, randomisation could not be concluded (Gehring 2012a) or was abandoned (Locke 2008). Four RCTs were at a low risk of bias across all (Brown 2013; Butler 2007; Rapp 2015) or almost all (Richard 2019) domains.

Although a formal GRADE assessment was not conducted as part of this review, it is clear from the above evaluation of the studies that the evidence identified is largely of 'low' and 'very low' certainty, indicating that any new evidence is likely to have an impact on the existing results; this reinforces the need for further high-quality studies evaluating interventions to prevent and improve cognitive dysfunction in adult patients that have received cranial irradiation.

Potential biases in the review process

We carried out extensive searches in four databases, which included published studies and conference proceedings as well as searching the reference lists of included studies. However, we may have failed to identify all eligible studies. We were somewhat successful in our attempts to obtain further information about the methodology of the studies by emailing the authors. Overall, our attempts to obtain further data on the included studies did not allow us to report all studies as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Agreements and disagreements with other studies or reviews

In the search results we found one other review reporting interventions for preventing or ameliorating cognitive deficits in adults treated with cranial irradiation (Tallet 2013), but did not find any additional studies from the review that were eligible to include in this review.

Other reviews identified were associated more generally with all brain tumour patients, all cancer patients, or more widely in all clinical conditions, who had not necessarily received cranial irradiation. For example, Gehring 2008 conducted a systematic review of interventions for cognitive deficits in patients with all types of brain tumour. Davis 2013 and Gehring

2012b conducted reviews of ongoing studies investigating pharmacological interventions to treat cancer patients with cognitive dysfunction. Rooney 2014 reviewed pharmacological interventions to treat or prevent neurocognitive decline after brain radiation. Challman 2000 reviewed the use of methylphenidate in many clinical conditions, including patients with a brain tumour. Wefel 2015 reviewed evidence relating to cognitive impairment in patients with non-CNS tumours and focused on patients with breast cancer. Coomans 2019 reviewed studies of antitumour treatment strategies that aimed to prevent or minimise cognitive deficits in brain tumour patients and incorporated all treatment modalities, including surgery and chemotherapy. Karschnia 2019 focused on the pharmacologic management of cognitive impairment induced by cancer therapy.

The studies included in these reviews did not provide additional evidence specifically for cranial irradiated patients. Similar conclusions were made, emphasising that the evidence is limited by significant methodological limitations; such as the absence of a control group, lack of statistical comparisons between groups when control groups were present (due to small sample sizes), the use of unreliable cognitive tests, and the overall need for larger trials with more statistical power. Gehring 2012b suggested the use of home assessments and/or Internet-based programmes as potential solutions to help with accrual and attrition.

AUTHORS' CONCLUSIONS

Implications for practice

One study provided supportive evidence that memantine in the early radiotherapy treatment phase may improve some of the objective neuropsychological tests of cognition. The benefit to day-to-day memory is uncertain. Adverse events were similar across groups. Memantine may therefore be a safe agent for people with brain metastases receiving whole brain radiotherapy; there is evidence supporting its favourable long-term safety profile in Alzheimer's disease (Farlow 2008) and migraine (Mistry 2021), but further long-term evidence is required to confirm this applies to patients receiving cranial irradiation. One study provided supportive evidence that donepezil in the delayed radiation/late effect phase may improve some of the objective neuropsychological tests of cognition. The benefit to day-to-day memory is uncertain. Adverse events were not reported. However, it is noted that these supportive findings for memantine and donepezil were for both study's secondary outcomes (time to cognitive failure in the memantine study and memory in the donepezil study); negative findings were found for the primary outcomes (preserved cognitive function in the memantine study and a cognitive composite score in the donepezil study), although the primary endpoint nearly reached statistical significance for memantine. Caution is required in the interpretation of these secondary outcome results in the presence of non-significant primary outcome measures.

Two studies offered some evidence for the role of central nervous system stimulants in preventing or improving cognitive deficits with few adverse events; these studies were limited by a small sample size, and one by practice effects. There is currently limited evidence to suggest non-pharmacological interventions are beneficial in the prevention or amelioration of cognitive deficits in adults treated with cranial irradiation, with only one very small study suggesting a benefit of Goal Management Training, a behavioural intervention that combined mindfulness and strategy training, on executive function and processing speed. There was no effect of a nine-day calorie-restricted ketogenic diet with intermittent fasting during re-irradiation on cognitive function in patients with recurrent glioblastomas.

Implications for research

In part due to the increased survival of patients with brain tumours and the effects of cognitive dysfunction on quality of life of patients and their caregivers, interventions to address and prevent cognitive dysfunction in this population have gained increasing research interest. However, much more high-quality research is required to address this unmet need and to overcome some of the limitations of previous studies.

There are challenges in performing research in patients with primary and metastatic brain tumours. High drop-out rates are to be expected in studies examining prophylactic cranial irradiation and therapeutic cranial irradiation. This is due to progression of systemic cancer or primary brain tumours leading to death, disability or affecting quality of life resulting in study withdrawal. Further research is necessary to determine whether memantine is effective in other patient populations receiving cranial irradiation, including patients with primary brain tumours and patients with tumours elsewhere in the body receiving prophylactic cranial irradiation. Further research is required in other pharmacological agents, for example, the effects of methylphenidate and modafinil are still to be clarified. Sufficient attempts to recruit and maintain sufficient numbers of participants is essential. Appropriate control groups are necessary to rule out practice effects and determine the efficacy compared to standard care. It is also important to identify and report patient characteristics and use of other medications, such as steroid and anti-epileptic drugs, which are associated with impaired cognitive function.

Further research is needed to determine the efficacy of cognitive rehabilitation in this patient population. Other studies that have investigated cognitive rehabilitation programmes in patient groups with other types of brain tumour offer detailed descriptions of eHealth cognitive interventions that could be investigated (Gehring 2009; Gehring 2011; Hassler 2010; Zucchella 2013; van der Linden 2021).

Exercise may also be a useful treatment for counteracting impairments associated with brain tumours, including fatigue, functional decline, cognitive impairment, and depression as well as anxiety (Cormie 2015; Gehring 2020).

Lastly, non-randomised trials and observational studies reporting other non-pharmacological interventions including hyperbaric oxygen therapy and dietary supplements such as vitamin E and *Ginkgo biloba* also provide results that could be explored further using appropriate control groups, blinding, and when funding is more accessible.

Finally, the alignment of cognitive outcome assessments using the same tools would help improve the homogeneity and thus comparability of data across studies. One way to achieve this could be through greater collaboration between centres.

ACKNOWLEDGEMENTS

With thanks to Robin Grant, Co-ordinating Editor of Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group (GNOC), Gail Quinn for continued support and feedback throughout the editorial process and Joanne Platt, Information Specialist for GNOC.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

The authors and Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Team, are grateful to the following peer reviewers for their time and comments: Andrew Bryant, Helen Bulbeck, Jane Cerhan and Alasdair Rooney.

REFERENCES

References to studies included in this review

Brown 2013 *{published and unpublished data}*

Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro-oncology* 2013;**15**(10):1429-37. [DOI: 10.1093/neuonc/not114]

Butler 2007 *{published and unpublished data}*

Butler JM Jr, Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, et al. A phase III, double-blind, placebo-controlled prospective randomised clinical trial of d-threo-methylphenidate HCl in brain tumour patients receiving radiation therapy. *Internation Journal of Radiation Oncology *Biology *Physics* 2007;**69**(5):1496-501. [DOI: 10.1016/j.ijrobp.2007.05.076]

Gehring 2012a *{published and unpublished data}*

Gehring K, Patwardhan SY, Collins R, Groves MD, Etzel CJ, Meyers CA, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *Journal of Neuro-oncology* 2012;**107**(1):165-74. [DOI: 10.1007/s11060-011-0723-1]

Kaleita 2006 *{published data only (unpublished sought but not used)}*

Kaleita TA, Wellisch DK, Graham CA, Steh B, Nghiemphu, Ford JM et, al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. In: Journal of Clinical Oncology. Vol. 24. 2006:1503.

Locke 2008 *{published and unpublished data}*

Locke DEC, Cerhan JH, Wu W, Malec JF, Clark MM, Rummans TA, et al. Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumours: a pilot study. *Journal of Supportive Oncology* 2008;**6**(8):383-91.

Rapp 2015 *{published and unpublished data}*

Rapp SR, Case LD, Peiffer A, Naughton MM, Chan MD, Stieber VW, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. *Journal of Clinical Oncology* 2015;**33**(15):1653-9.

Richard 2019 *{published and unpublished data}*

Richard NM, Bernstein LJ, Mason WP, Laperriere N, Maurice C, Millar BA, et al. Cognitive rehabilitation for executive dysfunction in brain tumor patients: a pilot randomized controlled trial. *Journal of Neuro oncology* 2019;**142**(3):565-75. [DOI: 10.1007/s11060-019-03130-1]

Voss 2022 *{published and unpublished data}*

Voss M, Wenger KJ, von Mettenheim N, Bojunga J, Vetter M, Diehl B, et al. Short-term fasting in glioma patients: analysis of diet diaries and metabolic parameters of the ERGO2 trial. *European Journal of Nutrition* 2022;**61**(1):477-87. [DOI: 10.1007/s00394-021-02666-1]

References to studies excluded from this review

Attia 2012 *{published data only}*

Attia A, Rapp SR, Case LD, D'Agostino R, Lesser G, Naughton M, et al. Phase II study of *Ginkgo biloba* in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood. *Journal of Neuro-oncology* 2012;**109**:357-63. [DOI: 10.1007/s11060-012-0901-9]

Ayoub 2020 *{published data only}*

Ayoub R, Ruddy RM, Cox E, Oyefiade A, Derkach D, Laughlin S, et al. Assessment of cognitive and neural recovery in survivors of pediatric brain tumors in a pilot clinical trial using metformin. *Nature Medicine* 2020;**26**(8):1285-94. [DOI: 10.1038/s41591-020-0985-2]

Boele 2013 *{published data only}*

Boele FW, Douw L, de Groot M, Van Thuijl HF, Cleijne W, Heimans JJ, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro-oncology* 2013;**15**(10):1420-8. [DOI: 10.1093/neuonc/not102]

Boele 2018 *{published data only}*

Boele FW, Klein M, Verdonck-de Leeuw IM, Cuijpers P, Heimans JJ, Snijders TJ, et al. Internet-based guided self-help for glioma patients with depressive symptoms: a randomized controlled trial. *Journal of Neuro-oncology* 2018;**137**(1):191-203.

Campbell 2017 *{published data only}*

Campbell KL, Kam JW, Neil-Sztramko SE, Liu Ambrose T, Handy TC, Lim HJ, et al. Effect of aerobic exercise on cancer-associated cognitive impairment: A proof-of-concept RCT. *Psychooncology* 2018;**27**(1):53-60. [DOI: 10.1002/pon.4370]

Chan 2003 *{published data only}*

Chan AS, Cheung MC, Law SC, Chan JH. Phase II study of alpha-tocopherol in improving the cognitive function of patients with temporal lobe radionecrosis. *Cancer* 2004;**100**(2):398-404. [DOI: 10.1002/cncr.11885]

Cox 2020 *{published data only}*

Cox E, Bells S, Timmons BW, Laughlin S, Bouffet E, de Medeiros C, et al. A controlled clinical crossover trial of exercise training to improve cognition and neural communication in pediatric brain tumor survivors. *Clinical Neurophysiology* 2020;**131**(7):1533-47. [DOI: 10.1016/j.clinph.2020.03.027]

Gehring 2009 *{published data only}*

Gehring K, Sitskoorn MM, Gundy CM, Sikkes SA, Klein M, Postma TJ, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *Journal of Clinical Oncology* 2009;**27**(22):3712-22. [DOI: 10.1200/JCO.2008.20.5765]

Gehring 2018 *{published data only}*

Gehring K, Kloek CJ, Aaronson NK, Janssen KW, Jones LW, Sitskoorn MM, et al. Feasibility of a home-based exercise

intervention with remote guidance for patients with stable grade II and III gliomas: a pilot randomized controlled trial. *Clinical Rehabilitation* 2018;**32**(3):352-66.

Gehring 2020 *{published data only}*

Gehring K, Stuiver MM, Visser E, Kloek C, van den Bent M, Hanse M, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. *Neuro Oncology* 2020;**22**(1):103-15.

Hulshof 2002 *{published data only}*

Hulshof MCC, Stark NM, van der Kleij A, Sminia P, Smeding HM, Gonzalez DG. Hyperbaric oxygen therapy for cognitive disorders after irradiation of the brain [Hyperbare oxygenierung bei patienten mit kognitiven störungen nach hirnbestrahlung]. *Strahlentherapie und Onkologie* 2002;**178**(4):192-8. [DOI: 10.1007/s00066-002-0916-9]

Jatoi 2005 *{published data only}*

Jatoi A, Kahanic SP, Frytak S, Schaefer P, Foote RL, Sloan J, et al. Donepezil and vitamin E for preventing cognitive dysfunction in small cell lung cancer patients: preliminary results and suggestions for future study designs. *Supportive Care in Cancer* 2005;**13**:66-9. [DOI: 10.1007/s00520-004-0696-0]

Laigle-donadey 2018 *{published data only}*

Laigle-Donadey F, Ducray F, Boone M, Diallo H, Ramirez C, Chinot O, et al. A phase III double-blind placebo-controlled randomised study of dexamphetamine sulfate for fatigue in patients suffering from primary brain tumors. In: MASCC/ISOO Annual Meeting on Supportive Care in Cancer. 2018.

Levin 2011 *{published data only}*

Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *International Journal of Radiation Oncology *Biology *Physics* 2011;**79**(5):1487-95.

Maschio 2015 *{published data only}*

Maschio M, Dinapoli L, Fabi A, Giannarelli D, Cantelmi T. Cognitive rehabilitation training in patients with brain tumor-related epilepsy and cognitive deficits: a pilot study. *Journal of Neuro-oncology* 2015;**125**(2):419-26.

Meyers 1998 *{published data only}*

Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood and function of brain tumor patients. *Journal of Clinical Oncology* 1998;**16**(7):2522-7.

Milbury 2020 *{published data only}*

Milbury K, Weathers SP, Durrani S, Li Y, Whisenant M, Li J, et al. Online couple-based meditation intervention for patients with primary or metastatic brain tumors and theirpPartners: results of a pilot randomized controlled trial. *Journal of Pain Symptom Management* 2020;**59**(6):1260-7. [DOI: 10.1016/j.jpainsymman.2020.02.004]

Naughton 2018 *{published data only}*

Naughton MJ, Case LD, Peiffer A, Chan M, Stieber V, Moore D, et al. Quality of life of irradiated brain tumor survivors treated with donepezil or placebo: Results of the WFU CCOP research base protocol 91105. *Neuro-oncology Practice* 2018;**5**(2):114-21.

Ownsworth 2012 *{published data only}*

Ownsworth T, Chambers S, Stewart E, Casey L, Walker DG, Shum DHK. The making sense of brain tumour project: A homebased psychotherapy and rehabilitation program. *Asia-Pacific journal of Clinical Oncology* 2012;**8**:184-5.

Page 2015 *{published data only}*

Page BR, Shaw EG, Lu L, Bryant D, Grisell D, Lesser GJ, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro-oncology* 2015;**17**(10):1393-401.

Peng 2016 *{published data only}*

Peng Y, Zhang W, Zhou X, Ji Y, Kass IS, Han R. Lidocaine did not reduce neuropsychological-cognitive decline in patients 6 months after supratentorial tumor surgery: a randomized, controlled trial. *Journal of Neurosurgical Anesthesiology* 2016;**28**(1):6-13.

Porter 2022 *{published and unpublished data}*

* Porter AB, Liu H, Kohli S, Cerhan JL, Sloan J, McMurray RP, et al. Efficacy of treatment with armodafinil for cancer-related fatigue in patients with high-grade glioma: a phase 3 randomized clinical trial. *JAMA Oncology* 2022;**8**(2):259-67. [DOI: 10.1001/jamaoncol.2021.5948]

Schellart 2011 *{published data only}*

Schellart NA, Reits D, van der Kleij, Stalpers LJ. Hyperbaric oxygen treatment improved neurophysiologic performance in brain tumor patients after neurosurgery and radiotherapy: a preliminary report. *Cancer* 2011;**117**(15):3434-44. [DOI: 10.1002/cncr.25874]

Shaw 2006 *{published data only}*

Shaw EG, Rosdhal R, D'Agostino RB Jr, Lovato J, Naughton MJ, Robbins ME, et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. *Journal of Clinical Oncology* 2006;**24**(9):1415-20.

Van der Linden 2018 *{published data only}*

van der Linden SD, Sitskoorn MM, Rutten GM, Gehring K. Feasibility of the evidence-based cognitive telerehabilitation program Remind for patients with primary brain tumors. *Journal of Neuro-oncology* 2018;**137**(3):523-32.

van der Linden 2021 *{published data only}*

van der Linden SD, Rutten GM, Dirven L, Taphoorn MJB, Satoer DD, Dirven CMF, et al. eHealth cognitive rehabilitation for brain tumor patients: results of a randomized controlled trial. *Journal of Neuro-oncology* 2021;**154**(3):315-26. [DOI: 10.1007/s11060-021-03828-1]

Wong 2016 *{published data only}*

Wong P, Leppert IR, Roberge D, Boudam K, Brown PD, Muanza T, et al. A pilot study using dynamic contrast enhanced-MRI as a

response biomarker of the radioprotective effect of memantine in patients receiving whole brain radiotherapy. *Oncotarget* 2016;**7**(32):50986–96.

Yang 2014 *{published data only}*

Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. *Annals of Rehabilitation Medicine* 2014;**38**(6):726-33. [DOI: 10.5535/arm.2014.38.6.726]

References to studies awaiting assessment

Chen 2019 *{published data only (unpublished sought but not used)}*

Chen LJ, Zhang RG, Yu DD, Wu G, Dong XR. Shenqi Fuzhengi Injection ameliorates radiation-induced brainiInjury. *Current Medical Science* 2019;**39**(6):965-71. [DOI: https://doi.org/10.1007/s11596-019-2129-9]

References to ongoing studies

Chan 2018 *{published data only}*

Chan MD. Testing ramipril to prevent memory loss in People with glioblastoma. ClinicalTrials.gov 2018. [NCT03475186]

Additional references

Abrey 1998

Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *Journal of Clinical Oncology* 1998;**16**(3):859-63.

Anscher 1991

Anscher MS, Swift PS, Gaspar LE, Marks LB. Radiation injury of the brain and spinal cord. In: Wilkins RH, Rengachary SS, editors(s). Neurosurgery. New York: McGraw-Hill, 1996:1921-36.

Benedict 1998

Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-revised: normative data and analysis of inter-form and test-retest reliability. *Clinical Neuropsychologist* 1998;**12**(1):43-55.

Benton 1989

Benton AL, Hamsher KS. Multilingual Aphasia Examination. Iowa City, IA, AJA Associates 1989.

Brown 2020

Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, e al, for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with Brain Metastases: phase III trial NRG Oncology CC001. *Journal of Clinical Oncology* 2020;**38**(10):1019-29.

Challman 2000

Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clinic Proceedings* 2000;**75**(7):711-21.

Chang 2009

Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncology* 2009;**10**(11):1037-44. [DOI: 10.1016/S1470-2045(09)70263-3]

Cicerone 2011

Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Archives of Physical Medicine and Rehabilitation* 2011;**92**(4):519-30.

Cochran 2012

Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. *Journal of Neurosurgery* 2012;**116**(5):978-83. [DOI: 10.3171/2012.2.JNS111353]

Coomans 2019

Coomans MB, van der Linden SD, Gehring K, Taphoorn MB. Treatment of cognitive deficits in brain tumour patients: current status and future directions. *Current Opinion in Oncology* 2019;**31**(6):540-7.

Cormie 2015

Cormie P, Nowak AK, Chambers SK, Galvão DA, Newton RU. The potential role of exercise in neuro-oncology. *Frontiers of Oncology* 2015;**5**:85. [DOI: 10.3389/fonc.2015.00085]

Correa 2004

Correa DD, DeAngelis LM, Shi W, Thaler H, Glass A, Abrey LE. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology* 2004;**62**(4):548-55. [PMID: 14981169]

Correa 2007

Correa DD, DeAngelis LM, Shi W, Thaler HT, Lin M, Abrey LE. Cognitive functions in low-grade gliomas: disease and treatment effects. *Journal of Neurooncology* 2007;**81**(2):175-84. [DOI: 10.1007/s11060-006-9212-3]

Crossen 1994

Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *Journal of Clinical Oncology* 1994;**12**(3):627-42.

Cull 1996

Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. What do cancer patients mean when they complain of concentration and memory problems? *British Journal of Cancer* 1996;**74**(10):1674-9.

Davis 2013

David J, Ahlberg FM, Berk M, Ashley DM, Khasraw M. Emerging pharmacotherapy for cancer patients with cognitive dysfunction. *BMC Neurology* 2013;**13**(1):153.

DeAngelis 1989

DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989;**39**(6):789. [DOI: 10.1212/WNL.39.6.789]

Deeks 2001

Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001;**323**(7305):157-62. [DOI: 10.1136/bmj.323.7305.157]

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Dietrich 2008

Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *Oncologist* 2008;**13**(12):1285-95. [DOI: 10.1634/thoncologist.2008-0130]

Duff 2012

Duff K, Callister C, Dennett K, Tometich D. Practice effects: a unique cognitive variable.. *Clinical Neuropsychology* 2012;**26**(7):1117-27.

Farlow 2008

Farlow MR, Graham SM, Alva G. Memantine for the treatment of Alzheimer's disease: tolerability and safety data from clinical trials. *Drug Safety* 2008;**31**(7):577-85.

Fink 2012

Fink J, Born D, Chamberlain MC. Radiation necrosis: relevance with respect to treatment of primary and secondary brain tumors. *Current Neurology and Neuroscience Reports* 2012;**12**(3):276-85. [DOI: 10.1007/s11910-012-0258-7]

Folstein 1975

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;**12**(3):189-98.

Gage 2019

Gage FH. Adult neurogenesis in mammals. *Science* 2019;**364**(6443):827-8.

Gehring 2008

Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJ. Interventions for cognitive deficits in adults with brain tumours. *Lancet Neurology* 2008;**7**(6):548-60.

Gehring 2011

Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoorn MM. Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. *Journal of International Neuropsychological Society* 2011;**17**(2):256-66.

Gehring 2012b

Gehring K, Roukema JA, Sitskoorn MM. Review of recent studies on interventions for cognitive deficits in patients with cancer. *Expert Review of Anticancer Therapy* 2012;**12**(2):255-69. [DOI: 10.1586/era.11.202]

Gehring 2015

Gehring K, Taphoorn MJ, Sitskoorn MM, Aaronson NK. Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neurooncology Practice* 2015;**2**(1):20-31.

Gill 2004

Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *QJM: an International Journal of Medicine* 2004;**97**(7):385-95. [DOI: 10.1093/qjmed/hch074]

Gilroy 2000

Gilroy J. Basic Neurology. 3rd edition. New York: McGraw-Hill Health Professions Division, 2000.

Gligoroska 2012

Gligoroska JP, Manchevska S. The effect of physical activity on cognition - physiological mechanisms. *Materia Socio Medica* 2012;**24**(3):198-202. [PMID: PMC363396]

Gondi 2013

Gondi V, Paulus R, Bruner DW, Meyers CA, Gore EM, Wolfson A, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of radiation therapy oncology group randomized trials 0212 and 0214. *International Journal of Radiation Oncology* Biology* Physics* 2013;**86**(4):656-64. [DOI: 10.1016/j.ijrobp.2013.02.033]

Gondi 2014

Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *Journal of Clinical Oncology* 2014;**32**(34):3810-6.

Gonzales 2007

Gonzales J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacizumab on radiation necrosis of the brain. *International Journal of Radiation Oncology* Biology* Physics* 2007;**67**(2):323-6. [DOI: 10.1016/j.ijrobp.2006.10.010]

Haldbo-Classen 2020

Haldbo-Classen L, Amidi A, Lukacova S, Wu LM, Oettingen GV, Lassen-Ramshad Y, et al. Cognitive impairment following radiation to hippocampus and other brain structures in adults with primary brain tumours. *Radiotherapy and Oncology* 2020;**148**:1-7. [DOI: 10.1016/j.radonc.2020.03.023]

Hassler 2010

Hassler MR, Elandt K, Preusser M, Lehrner J, Binder P, Dieckmann K, et al. Neurocognitive training in patients with high-grade glioma: a pilot study. *Journal of Neuro-Oncology* 2010;**97**(1):109-15.

Higgins 2011

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

Karschnia 2019

Karschnia P, Parsons MW, Dietrich J. Pharmacologic management of cognitive impairment induced by cancer therapy. *Lancet Oncology* 2019;**20**(2):e92-102.

Kim 2018

Kim KS, Wee CW, Seok JY, Hong JW, Chung JB, Eom KY, et al. Hippocampus-sparing radiotherapy using volumetric modulated arc therapy (VMAT) to the primary brain tumor: the result of dosimetric study and neurocognitive function assessment. *Radiation Oncology* 2018;**13**(1):29.

Kirkman 2022

Kirkman MA, Hunn BH, Thomas MS, Tolmie AK. Influences on cognitive outcomes in adult patients with gliomas: a systematic review. *Frontiers in Oncology* 2022;**12**:943600.

Klein 2002

Klein M, Heimans JJ, van der Ploeg HM, Grit J, Muller M, Postma TJ, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet* 2002;**360**(9343):1361-8.

Lee 2002

Lee AW, Kwong DL, Leung SF, Tung SY, Sze WM, Sham JST, et al. Factors affecting risk of symptomatic temporal lobe necrosis: significance of fractional dose and treatment time. *International Journal of Radiation Oncology* Biology* Physics* 2002;**53**(1):75-85. [DOI: 10.1016/S0360-3016(02)02711-6]

Lehrer 2022

Lehrer EJ, Jones BM, Dickstein DR, Green S, Germano IM, Palmer JD, et al. The Cognitive Effects of Radiotherapy for Brain Metastases. *Frontiers in Oncology* 2022;**12**:893264.

Lidstone 2003

Lidstone V, Butters E, Seed PT, Sinnott C, Beynon T, Richards M. Symptoms and concerns amongst cancer outpatients: identifying the need for specialist palliative care. *Palliative Medicine* 2003;**17**(7):588-95.

Lyubimova 2004

Lyubimova N, Hopewell JW. Experimental evidence to support the hypothesis that damage to vascular endothelium plays the primary role in the development of late radiation-induced CNS injury. *British Journal of Radiology* 2004;**77**(918):488-92. [PMID: 15151969]

Makale 2017

Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours.. *Nature Reviews in Neurorology* 2017;**13**(1):52-64.

Malec 2003

Malec JF, Kragness M, Evans RW, Finlay KL, Kent A, Lezak M. Further psychometric evaluation and revision of the Mayo-Portland Adaptability Inventory in a national sample. *Journal of Head Trauma Rehabilitation* 2003;**18**(6):479-92.

Meyers 2000

Meyers CA, Hess KR, Yung WA, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *Journal of Clinical Oncology* 2000;**18**(3):646.

Meyers 2003

Meyers CA, Wefel JS. The use of the Mini-Mental State Examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *Journal of Clinical Oncology* 2003;**21**(19):3557-8.

Miotto 2013

Miotto EC, Savage CR, Evans JJ, Wilson BA, Martin MG, Balardin JB, et al. Semantic strategy training increases memory performance and brain activity in patients with prefrontal cortex lesions. *Clincal Neurology and Neurosurgery* 2013;**115**(3):309-16.

Mistry 2021

Mistry VM, Morizio PL, Pepin MJ, Bryan WE, Brown JN. Role of memantine in the prophylactic treatment of episodic migraine: a systematic review. *Headache* 2021;**61**(8):1207-13.

Mitchell 2010

Mitchell AJ, Kemp S, Benito-León J, Reuber M. The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatrica* 2010;**22**(1):2-13. [DOI: 10.1111/j.1601-5215.2009.00439.x]

Monje 2007

Monje ML, Vogel H, Masek M, Ligon KL, Fisher PG, Palmer TD. Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies. *Annals of Neurology* 2007;**62**(5):515-20. [DOI: 10.1002/ana.21214]

Mora 2013

Mora F. Successful brain aging: plasticity, environmental enrichment, and lifestyle. *Dialogues in Clinical Neuroscience* 2013;**15**(1):45-52. [PMID: PMC3622468]

Mukand 2001

Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *American Journal of Physical Medicine & Rehabilitation* 2001;**80**(5):346-50.

Mulhern 2004

Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncology* 2004;**5**(7):399-408.

Palmer 2002

Palmer SL, Reddick WE, Glass JO, Gajjar A, Goloubeva O, Mulhern RK. Decline in corpus callosum volume among pediatric patients with medulloblastoma: longitudinal

MR imaging study. *American Journal of Neuroradiology* 2002;**23**(7):1088-94. [PMID: 12169462]

Pazzaglia 2020

Pazzaglia S, Briganti G, Mancuso M, Saran A. Neurocognitive decline following radiotherapy: mechanisms and therapeutic implications. *Cancers (Basel)* 2020;**12**(1):146.

Perez 2022

Perez WD, Perez-Torres CJ. Neurocognitive and radiological changes after cranial radiation therapy in humans and rodents: a systematic review. International Journal of Radiation Biology 2022 [Epub ahead of print]. [DOI: 10.1080/09553002.2022.2074167]

Postma 2002

Postma TJ, Klein M, Verstappen CC, Bromberg JE, Swennen M, Langendijk JA, et al. Radiotherapy-induced cerebral abnormalities in patients with low-grade glioma. *Neurology* 2002;**59**(1):121-3. [DOI: 10.1212/wnl.59.1.121]

Randolph 1998

Randolph C. Repeatable battery for the assessment of neuropsychological status (RBANS). Psychological Corporation, San Antonio 1998.

Rapp 2013

Rapp SR, Case D, Peiffer A, Naughton MJ, Stieber VW, Bayer GK, et al. Phase III randomized, double-blind, placebo-controlled trial of donepezil in irradiated brain tumor survivors. In: Journal of Clinical Oncology. Vol. 31. 2013:2006.

Reddick 2006

Reddick WE, Shan ZY, Glass JO, Helton S, Xiong X, Wu S, et al. Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. *Cancer* 2006;**106**(4):941-9. [PMID: 16411228]

Reitan 1992

Reitan RM. Trail making test manual for administration and scoring. Reitan Neuropsychology Laboratory, Tucson 1989.

RevMan 2020 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Robinson 2006

Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. *Drugs* 2006;**66**(11):1515-34. [PMID: 16906789]

Rooney 2014

Rooney JW, Laack NN. Pharmacological interventions to treat or prevent neurocognitive decline after brain radiation. *CNS Oncology* 2013;**2**(6):531-41.

Shaw 2013

Shaw EG, Case D, Bryant D, Grisell D, Lesser G, Monitto DC, et al. Phase II double-blind placebo-controlled study of armodafinil for brain radiation induced fatigue. In: Journal of Clinical Oncology. Vol. 13. 2013:9505.

Sheline 1980

Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *International Journal of Radiation Oncology* Biology* Physics* 1980;**6**(9):1215-28.

Smith 2003

Smith JV, Luo Y. Studies on molecular mechanisms of *Ginkgo biloba* extract. *Applied Microbiology and Biotechnology* 2004;**64**(4):465-72. [DOI: 10.1007/s00253-003-1527-9]

Steinberg 2011

Steinberg M, Lyketsos CG. Pharmacological therapies in Alzheimer's disease. In: Abou-Saleh MT, Katona C, Kumar A, editors(s). Principles and Practice of Geriatric Psychiatry. 3rd edition. Oxford: John Wiley & Sons, 2010. [DOI: 10.1002/9780470669600.ch52]

Sultana 2020

Sultana N, Sun C, Katsube T, Wang B. Biomarkers of brain damage induced by radiotherapy. *Dose Response* 2020;**18**(3):1559325820938279.

Surma-aho 2001

Surma-aho O, Niemelä M, Vilkki J, Kouri M, Brander A, Salonen O, et al. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. *Neurology* 2001;**56**(10):1285-1290. [DOI: 10.1212/wnl.56.10.1285]

Szerlip 2011

Szerlip N, Rutter C, Ram N, Yovino S, Kwok Y, Maggio W, et al. Factors impacting volumetric white matter changes following whole brain radiation therapy. *Journal of Neuro-oncology* 2011;**103**(1):111-9. [PMID: 20725847]

Tallet 2013

Tallet A, Dhermain F, Taillia H, Ricard D, Mornex F, Métellus P. Cognition and radiation therapy for brain metastases: a new paradigm to define [Cognition et radiothérapie dans les métastases cérébrales: un nouveau paradigme à définir]. *Bulletin du Cancer* 2013;**100**(1):63-9. [DOI: 10.1684/bdc.2012.1682]

Taphoorn 2003

Taphoorn MJ. Neurocognitive sequelae in the treatment of low-grade gliomas. *Seminars in Oncology* 2003;**30**(6):45-8. [PMID: 14765385]

Taphoorn 2004

Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurology* 2004;**3**(3):159-68.

Torcuator 2009

Torcuator R, Zuniga R, Mohan YS, Rock J, Doyle T, Anderson J et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. *Journal of Neuro-oncology* 2009;**94**(1):63-8.

Umphrey 2013

Umphrey AB. Armodafinil in reducing cancer-related fatigue in patients with high grade glioma.. ClinicalTrials.gov 2013. [NCT01781468]

van Kessel 2021

van Kessel E, Huenges Wajer IM, Ruis C, Seute T, Fonville S, De Vos FYF, et al. Cognitive impairments are independently associated with shorter survival in diffuse glioma patients. *Journal of Neurology* 2021;**268**(4):1434-42.

Vigliani 1996

Vigliani MC, Sichez N, Poisson M, Delatrre JY. A prospective study of cognitive functions following conventional radiotherapy for supratentorial gliomas in young adults: 4-year results. *International Journal of Radiation Oncology* Biology* Physics* 1996;**35**(3):527-33.

Volkow 2002

Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ. Mechanism of action of methylphenidate: insights from PET imaging studies. *Journal of Attention Disorders* 2002;**6**:S31-43.

Voss 2020

Voss M, Wagner M, von Mettenheim N, Harter PN, Wenger KJ, Franz K, et al. ERGO2: A rospective, randomized trial of calorie-restricted ketogenic diet and Fasting in addition to reirradiation for malignant glioma. *International Journal of Radiation Oncology, Biology, Physics* 2020;**108**(4):987–95. [DOI: 10.1016/j.ijrobp.2020.06.021]

Wang 2012

Wang Y, Pan L, Sheng X, Mao Y, Yao Y, Wany E et al. Reversal of cerebral radiation necrosis with bevacizumab treatment in 17 Chinese patients. *European Journal of Medical Research* 2012;**17**(1):25. [DOI: 10.1186/2047-783X-17-25]

Wechsler 1981

Wechsler. Wechsler Adult Intelligence Scale-Revised. Psychological Corporation, San Antonio 1981.

Wefel 2011

Wefel JS, Vardy J, Ahles T, Schagen SB. International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncology* 2011;**12**(7):703-8. [DOI: 10.1016/S1470-2045(10)70294-1]

Wefel 2015

Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults.. *CA: a Cancer Journal for Clinicians* 2015;**65**(2):123-38.

Welzel 2008

Welzel G, Fleckenstein K, Schaefer J, Hermann B, Kraus-Tiefenbacher U, Mai SK, et al. Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *International Journal of Radiation Oncology* Biology* Physics* 2008;**72**(5):1311-8. [DOI: 10.1016/j.ijrobp.2008.03.009]

Wujanto 2021

Wujanto C, Vellayappan B, Chang EL, Chao ST, Sahgal A, Lo SS. Radiotherapy to the brain: what are the consequences of this age-old treatment? *Ann Palliative Medicine* 2021;**10**(1):936-52.

Xue 2022

Xue S, Zeng H, Yan S, Wang Q, Jia X. Prophylactic cranial irradiation for extensive-stage small-cell lung cancer: A controversial area. *Frontiers in Oncology* 2022;**12**:772282.

Zhou 2022

Zhou Y, Su Y, Li S, Kennedy BC, Zhang DY, Bond AM, et al. Molecular landscapes of human hippocampal immature neurons across lifespan. *Nature* 2022;**607**(7919):527-33.

Zucchella 2013

Zucchella C, Capone A, Codella V, De Nunzio AM, Vecchione C, Sandrini G, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *Journal of Neuro-Oncology* 2013;**114**(1):93-100.

References to other published versions of this review

Day 2014a

Day J, Zienius K, Taphoorn M, Li J, Gehring K, Grosshans D, Grant R, Brown P. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No: CD011335. [DOI: 10.1002/14651858.CD011335]

Day 2014b

Day J, Zienius K, Gehring K, Grosshans D, Taphoorn M, Grant R, Li J, Brown PD. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No: CD011335. [DOI: 10.1002/14651858.CD011335.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brown 2013

Study characteristics

Brown 2013 *(Continued)*

Methods	Randomised controlled trial, parallel arm, double-blind, stratification by recursive partitioning analysis class and prior surgical therapy.
Participants	**Inclusion criteria:** adult patients; pathologically proven diagnosis of solid malignancy within 5 years of registration; brain metastases visible on contrast-enhanced MRI (or a contrast-enhanced CT for patients unable to have an MRI) with stable systemic disease 3 months prior to study entry; receiving 37.5 Gy of WBRT via 15 fractions of 2.5 Gy; KPS ≥ 70; serum creatinine ≤ 3 mg/dL, creatinine clearance ≥ 30 mL/min, total bilirubin ≤ 2.5 mg/dL, blood urea nitrogen (BUN) 20 mg/dL; MMSE score > 18; negative serum pregnancy test. **Exclusion criteria:** memantine allergy, current alcohol or drug abuse, chronic use of benzodiazepines, severe active comorbidity. **No. randomised:** memantine: 278; placebo: 276. **Follow-up:** 8, 16, 24 and 52 weeks. **Setting:** 143 centres in the USA and Canada
Interventions	Treatment arm schedule: Week 1: 5 mg oral memantine taken in the morning Week 2: 10 mg oral memantine taken in divided dosage (5 mg morning, 5 mg night) Week 3: 15 mg oral memantine taken in divided dosage (10 mg morning, 5 mg night) Week 4-24: 20 mg oral memantine taken in divided dosage (10 mg morning, 10 mg night) Control Arm: Matched placebo The dosage was lowered to 5 mg twice daily, as week 2, if creatinine clearance decreased to 30 mL/min, and was continued at this dosage if creatine clearance fell below 5 mL/min following a weekly recheck.
Outcomes	Cognitive function (HVLT-R, COWA, TMT)
Notes	Efficacy reported via median change and interquartile ranges.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The Zelen treatment allocation scheme was used to stratify patients according to according to recursive partitioning analysis (RPA) class and prior surgical therapy. Within each stratum, patients were randomised in a 1:1 ratio to placebo or memantine.” Quote:"A computer at RTOG headquarters randomly generated the sequences for the randomization" (obtained via correspondence).
Allocation concealment (selection bias)	Low risk	Quote:"The placebo was actually provided by the company (Forest Pharma) and it was impossible to tell which was placebo and which was active drug." (obtained via correspondence).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding carried out.
Blinding of outcome assessment (detection bias)	Low risk	Blinding carried out.

Brown 2013 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote:"All eligible patients randomised to the study were included (intent-to-treat analysis)...The multiple imputation procedure employing the Markov chain Monte Carlo method was also used to determine values for all remaining living patients missing assessments."
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Butler 2007

Study characteristics	
Methods	Randomised controlled trial, parallel arm, double-blind, stratification by tumour type, treatment and KPS.
Participants	**Inclusion criteria:** aged 18 years or over; histologically-confirmed metastatic or primary brain tumour; KPS ≥ 70; life expectancy ≥ 3months; haemoglobin ≥ 10.0 g/dL, white blood cell count ≥ 1500 per mL of blood, platelets ≥ 75,000 per mL of blood, planned partial or WBRT at a total dose of ≥ 25 Gy via ≥ 10 fractions of 180-300 c Gy. **Exclusion criteria:** serious medical or psychiatric illness that would prevent informed consent; completion of protocol therapy or QoL questionnaires; history of hypersensitivity to d-MPH; history of steroid psychosis; history of/currently taking medication for ADD, anxiety disorder, schizophrenia or substance abuse; currently taking antidepressants; family history or active Tourette's Syndrome; history or active glaucoma; history of RT; undergoing craniospinal axis irradiation; hypertension or other CV disease requiring antihypertensives or other CV medications; pregnant of breast-feeding. **No. randomised:** d-MPH: 34; placebo: 34. **Follow-up:** end of RT and at 4, 8 and 12 weeks. **Setting:** four centres in the United States.
Interventions	Treatment arm schedule: Day 1: 10 mg oral d-MPH taken in divided doses (5 mg before breakfast, 5 mg before 6 pm) Day 5-7 to Day 10: 20 mg oral d-MPH taken in divided doses (10 mg before breakfast, 10 mg before 6pm) Day 10-14 to Week 8: 30 mg to oral d-MPH taken in divided doses (15 mg before breakfast, 15 mg before 6pm) Control Arm: Matched placebo
Outcomes	Cognitive function (MMSE) Fatigue (FACIT-Fatigue sub-scale) QoL (FACT, FACT-Br, FACIT-Fatigue) Depression (CESDS)
Notes	Study funded by pharmaceutical company and closed prematurely due to withdrawal of funding and low accrual.

Butler 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote; "Patients were stratified by tumour type, treatment and KPS and randomized within strata to one of the two treatment arms with equal probability." Quote; "Randomised by computer program" (obtained via correspondence).
Allocation concealment (selection bias)	Low risk	Quote; "Used a 3rd party research pharmacy that knew which group patient was assigned to and mailed drug or placebo in containers that were labelled to include instructions for use." (obtained via correspondence).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding carried out.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding carried out.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote; "We did do intent to treat analysis. The dropouts were due to disease progression either in the brain or systemically ... not due to toxicity of intervention" (obtained via correspondence).
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Gehring 2012a

Study characteristics	
Methods	Randomised controlled trial, three arms, open-label, stratification by tumour location.
Participants	**Inclusion criteria:** age ≥ 18; KPS ≥ 70; primary brain tumour; subjective complaint of cognitive decline or fatigue; being considered for stimulant therapy by their neuro-oncologist; the ability to speak and understand English or Spanish. **Exclusion criteria:** current use of psychostimulants, monoamine oxidase inhibitors, anticoagulants, drugs similar to erythropoietin, or illicit drugs; history of hypersensitivity reaction to methylphenidate or modafinil; history of uncontrolled seizures, cardiac or pulmonary disease, or hypertension (systolic > 140 mm Hg, diastolic > 90 mm Hg, or not on a stable dose of anti-hypertensive medication for the past month; severe headaches; current glaucoma, narcolepsy, Tourette's syndrome, major psychiatric diagnosis, alcohol or drug abuse; current use of herbals/supplements for fatigue relief, e.g. *Ginkgo biloba*, ginseng, St John's Wort, dehydroepiandrosterone; unstable dose of antidepressants; comorbidities or medications that in the treating physician's opinion could potentially interfere with safe administration of MPH or MOD. **No. randomised:** methylphenidate: 24; modafinil: 10. **Follow-up:** 4 weeks. **Setting:** one cancer centre in the USA.

Gehring 2012a *(Continued)*

Interventions	Arm I: 10 mg of oral methylphenidate (immediate release) taken in divided doses for 4 weeks Arm II: 18 mg or oral methylphenidate (sustained release) taken in the morning for 4 weeks Arm III: 200 mg of oral modafinil taken in the morning for 4 weeks.
Outcomes	Cognitive function (WAIS-III Digit span and Digit symbol, TMT, HVLT-R, grooved pegboard, MAE COWA). Fatigue (BFI, POMS-Fat, POMS-Vig sub-scales) Sleep disturbance (BSDS) Mood (POMS, BDI-II, STAI) QoL (FACT general and brain modules, FIM)
Notes	Arm I and II combined for statistical analysis. Second drug used as control arm, rather than placebo. Groups also compared with normative data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote; "Patients were stratified by tumour location (i.e., right verses left hemisphere) and randomly assigned to one of three conditions." "a computer performed the randomization" (obtained via correspondence).
Allocation concealment (selection bias)	High risk	An open-label design was used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	An open-label design was used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	An open-label design was used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced in numbers across treatment groups, and reasons for missing outcome data similar between treatment groups and unlikely to be related to outcomes measured.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Possible recruitment bias: Quote; "PBT patients were considered eligible for participation if… being considered for stimulant therapy by their neuro-oncologist."

Kaleita 2006

Study characteristics	
Methods	Randomised controlled trial, parallel arm, double-blind.

Kaleita 2006 *(Continued)*

Participants	**Inclusion criteria:** aged 21-65, primary brain tumour, receiving treatment in the UCLA Neuro-Oncology Program, prior neurosurgical resection, radiotherapy, and/or cytotoxic or cytostatic chemotherapy, mild to severe fatigue and/or attention/memory impairment, as measured by the Clinical Global Impression of Severity Scale, able to speak English, capable of completing self-rating scales and one-on-one psychometric tests, at least 30 days since prior stimulants (e.g., amphetamines or methylphenidate), negative pregnancy test and use of contraception if fertile, concurrent conventional chemotherapy (e.g., carboplatin, lomustine, temozolomide), glucocorticoids (e.g. dexamethasone) and tamoxifen allowed. **Exclusion criteria:** significant hepatic disease, significant renal disease, severe cognitive impairment, other terminal illness, emergency patient, institutional resident, prisoner or parolee, UCLA students or staff, pregnant or nursing, concurrent irinotecan, concurrent participation in UCLA experimental chemotherapy trials, prior modafinil, concurrent experimental anticancer medication, concurrent tricyclic antidepressants and/or monoamine oxidase inhibitors. **No. randomised:** 30 (each arm not reported). **Follow-up:** 1, 3, 4, 8 and 12 weeks. **Setting:** one centre in the USA.
Interventions	Arm I: 200 mg/day modafinil in divided doses for 3 weeks Arm II: 400 mg/day modafinil in divided doses for 3 weeks Both arms then completed a 1-week wash out period, followed up 200 mg/day modafinil for 3 days, followed by a titrated dose for 8 weeks.
Outcomes	Cognitive function (TMT, SDM, verbal fluency test) Fatigue (Fatigue severity scale, Visual analogue fatigue scale, modified fatigue impact scale) Mood (HDS)
Notes	All participants required to have mild or severe fatigue.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Use of a randomisation method reported but not described.
Allocation concealment (selection bias)	Low risk	Blinding carried out.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding carried out.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding carried out.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Projected accrual successful.

Kaleita 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	All participants required to have mild or severe fatigue.

Locke 2008

Study characteristics	
Methods	Randomised controlled trial, parallel arm, unblinded.
Participants	**Inclusion criteria:** 18 years of age or older; mild-to-moderate cognitive impairment based on a combination of quantitative neuropsychological test data from the clinical assessment and the clinical judgement of the evaluation neuropsychologist; prognosis of at least 6 months of life; ability to attend sessions at our medical centre for 2 weeks; designated caregiver available to attend all sessions; receiving radiation therapy. **No. randomised:** cognitive rehabilitation program: 7; standard care: 12. **Follow-up:** post-intervention and 3 months. **Setting:** one radiation oncology clinic in the USA.
Interventions	Treatment arm schedule: 1. Six 50-minute sessions of cognitive rehabilitation carried out over 2 weeks, involving the learning and use of a calender as a compensatory aid. 2. Six 50-minute sessions of problem-solving carried out over 2 weeks, involving education of a model of stress and learning positive problem-solving management techniques. Control arm: standard care.
Outcomes	Cognitive function (RBANS) QoL (CQOLC, LASA) Mood (POMS) Fatigue (BFI) Functional capacity (FACT-BR, MPAI-4)
Notes	No cognitive function statistical comparisons were made between groups.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote; "Patients were randomized by our randomization center at the time of their enrollment. The randomization center is an entirely separate group of personnel from those recruiting and enrolling patients for the study" (obtained via correspondence). However, Quote; "Due to low accrual and anticipation of the ending of the enrolment period, the last three patient/caregiver dyads were not randomized and were enrolled directly into the intervention group."

Locke 2008 *(Continued)*

Allocation concealment (selection bias)	High risk	Quote; "Randomization was not pre-scheduled. That is, they were randomized patient by patient as they enrolled so I could not foresee their group because it had not been determined yet." (obtained via correspondence). However, "Due to low accrual and anticipation of the ending of the enrolment period, the last three patient/caregiver dyads were not randomized and were enrolled directly into the intervention group."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the intervention, blinding of patients to the treatment or control group was not possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is unclear who carried out the assessments, and whether they were blinded, but it is likely that is was the neuropsychologist, master's level behavioural therapist or master's level psychology study personnel that had been involved in delivering the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar reasons between groups for missing data. Quote; "Most patients did not return at that time for in-person follow-up…so most patients did not complete the RBANS at follow-up."
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	No cognitive function statistical comparisons were made between groups.

Rapp 2015

Study characteristics	
Methods	Randomised controlled trial, parallel arm, double-blind, stratification according to whole-brain vs partial-brain irradiation type and by study site.
Participants	**Inclusion criteria:** adults ≥ 18 years; primary or metastatic brain tumour; completed a course of fractionated partial or whole brain irradiation of at least 30 Gy ≥ 6 months prior to enrolment; no imaging evidence of disease progression within 6 months prior to enrolment; life expectancy > 6 months; ECOG score ≥ 2; **Exclusion criteria:** currently taking cognition enhancing medications; planned treatment for the next 6 months; pregnant. **No. randomised:** donepezil: 99; placebo: 99. **Follow-up:** 24 weeks **Setting:** two academic medical centres, 21 Community Clinical Oncology Programs (CCOPs), 3 Cancer Trial Support Unit sites (USA).
Interventions	Treatment arm schedule: Week 1-6: 5 mg oral donepezil Week 7-24: 10 mg oral donepezil if tolerated. Control arm: Matched oral placebo
Outcomes	Cognitive functioning (HVLT-R, COWA, Digit Span, mROCF, TMT, grooved pegboard)

Rapp 2015 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was generated using nQuery Advisor"... Quote; "Patients were stratified by accruing site (academic centers vs CCOP sites) and type of radiation (whole vs partial) and assigned within strata to receive donepezil or a placebo with equal probability using variably sized permuted block randomization." (obtained via correspondence).
Allocation concealment (selection bias)	Low risk	Quote; "Drug and placebo were over encapsulated and distributed to the study sites by Biologics Inc., Raleigh, NC" (obtained via correspondence).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding carried out.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding carried out.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis carried out.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Richard 2019

Study characteristics

Methods	Randomised controlled trial, three arms, unblinded
Participants	**Inclusion criteria:** diagnosis of a primary brain tumour; ≥ 3 months post-radiation or surgery (where applicable); persistent cognitive dysfunction (≤ 1 *SD* below normative mean on standardised performance-based or self-report measures of executive functioning); age ≥ 18 years; English fluency; no prior history of neurological, psychiatric, or other medical condition suspected to influence cognition. **Exclusion criteria:** not specified in the manuscript. **No. randomised:** Goal Management Training: 11; Brain Health Program: 8; Wait-list: 6. **Follow-up:** immediately post-training and 4 months later. **Setting:** single centre in Canada.
Interventions	Arm I: Goal Management Training (minfulnesss practice and strategy training) Arm II: Brain Health Workshop (supportive psychoeducation) Arm III: Wait-list control

Richard 2019 *(Continued)*

Outcomes	Cognitive function tests (TMT parts A and B, TEA, SART, BADS Zoo Map Test, Hotel test, HVLT-R) Patient-reported outcome measures (BRIEF-A, FrSBe, PANAS, HADS, General Self-Efficacy Scale, IIRS) Everyday life functional measures (Goal attainment scaling, semi-structured interview)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote; "Patients were randomized using a random number generator" (obtained by correspondence).
Allocation concealment (selection bias)	Low risk	Quote; "Group assignment was maintained in a spreadsheet...the group assignment spreadsheet was viewable only by the intervention provider" (obtained by correspondence).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote; "All testing (pre, post, follow-up) was done by a research assistant who was blind to each participant's study group" (obtained by correspondence).
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant excluded, with reason provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Voss 2022

Study characteristics

Methods	Randomised controlled trial, parallel arm, open-label
Participants	**Inclusion criteria:** recurrence of a histologically confirmed glioblastoma, gliosarcoma or malignant progression of a lower grade glioma on MRI; age above 18 years; Karnofsky performance score >60%; prior radiation therapy of the tumour at least 6 months before inclusion; prior therapy with temozolomide; multidisciplinary tumor board recom- mendation for reirradiation; and adequate haematologic, hepatic, renal, and coagulatory function. **Exclusion criteria:** bowel obstruction and malnutrition, cachexia, insulin-dependent diabetes or other medical conditions that might increase the risk of the dietary intervention or impair the ability to adhere to the diet. **No. randomised:** ketogenic diet and intermittent fasting: 25; standard diet: 25. **Follow-up:** day 6, day 12 and 1 month after radiation therapy.

Voss 2022 *(Continued)*

	Setting: three centres in Germany.
Interventions	Ketogenic diet and intermittent fasting group: two calorically restricted ketogenic diet intervals flanking 3 days of fasting. Calorie restriction to 21-23 kcal/kg/d was intended and carbohydrate intake was limited to 50 g/d. Patients fasted on days 4-6 with unlimited intake of fluid. Standard diet group: standard diet according to the recommendations of the German Society of Nutrition without calorie restriction. A calorie intake of approximately 30 kcal/kg/d was expected.
Outcomes	Functional outcome (KPS) Cognitive outcome (MMSE) Attention (d2 test of attention) Quality of life (EORTC Quality of Life Questionnaire) Body weight Blood samples (urea, uric acid, sodium, potassium, insulin, insulin-like growth factor 1, leptin)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using quote; "computer generated numbers" (obtained by correspondence).
Allocation concealment (selection bias)	Low risk	The clinicians quote; "did not know the group assignment of the patient in advance" (obtained by correspondence).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote; "The study nurses performing the cognitive assessment were not blinded to the patient's treatment" (obtained by correspondence).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Details provided and balance of withdrawal between groups.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None.

Scales

BADS: behavioral assessment of the dysexecutive syndrome;**BDI-II Beck's:** Depression Inventory-III; **BFI:** Brief Fatigue Inventory;**BRIEF-A:** Behavior Rating Inventory of Executive Function-Adult Version; **BSDS:** Brief Sleep Disturbance Scale; **CESD:S** Center for Epidemiological Studies Depression Scale; **COWA:** Controlled Oral Word Association Test; **CQOLC:** Caregiver Quality of Life Index-Cancer; **ESS:** Epworth Sleepiness Scale; **HDS:** Hamilton Depression Scale; **FACIT:***-Fatigue sub-scale* The Functional Assessment of Chronic Illness Therapy - Fatigue sub-scale; **FACT:** Functional Assessment of Cancer Therapy; FACT-Br: Functional Assessment of Cancer Therapy - Brain; *FIM* Functional Independence Measure; *FrSBe* Frontal Systems Behavior Scale; **HADS:** Hospital Anxiety and Depression Scale; **HVLT***-R*

Hopkin's Verbal Learning Test-Revised; **IIRS:** Illness Intrusiveness Rating Scale; **KPS:** Karnofsky Performance Score; **LASA:** Linear Analogue Self-Assessment; **MMSE** Mini-Mental State Examination; **MoCA** Montreal Cognitive Assessment;**MPAI-4:** Mayo-Portland Adaptability Inventory-4; **PANAS:** Positive and Negative Affect Schedule; **POMS:** Profile of Mood States; **POMS-Fat:** POMS-Fatigue sub-sale; *P***OMS-Vig:** POMS-Vigilance sub-scale; **RBANS:** Repeatable Battery of Assessment of Neuropsychological Status; **SART:** sustained attention to response task;**STAI:** State-Trait Anxiety Inventory; *T***EA:** test of everyday attention; **TMT:** Trail making test; **WAIS-III:** Digit Span and Digit Symbol Wechsler Adult Intelligence Scale III Digit Span and Digit Symbol sub-tests;***ZSAS:*** Zung Self-Rating Anxiety Scale; ***ZSDS:*** Zung Self-Rating Depression Scale.

Other

AD:D attention deficit disorder; **CT:** computed tomography; **CV:** cardiovascular; **EORTC:** European Organisation for Research and Treatment of Cancer;**MRI:** magnetic resonance imaging; **RT:** radiotherapy;**SD:** stamdard deviation; **WBRT:** whole brain radiotherapy.

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

Study	Reason for exclusion
Attia 2012	Not a controlled trial.
Ayoub 2020	Wrong patient population.
Boele 2013	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately.
Boele 2018	Did not include formal cognitive assessment.
Campbell 2017	Wrong patient population.
Chan 2003	Patients not randomised.
Cox 2020	Wrong patient population.
Gehring 2009	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately.
Gehring 2018	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately. Cognitive impairment in at least one domain was not an inclusion criteria. Did not include formal cognitive assessment.
Gehring 2020	Study included >20% non-irradiation patients and did not analyse separately.
Hulshof 2002	Patients not randomised.
Jatoi 2005	1 participant completed the study.
Laigle-donadey 2018	Cognitive impairment in at least one domain not an inclusion criteria.
Levin 2011	The primary outcome not cognitive functioning or other quality of life measure.
Maschio 2015	Not a controlled trial.
Meyers 1998	Not a controlled trial.
Milbury 2020	Wrong outcomes.
Naughton 2018	Did not include formal cognitive assessment.
Ownsworth 2012	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately.

Study	Reason for exclusion
Page 2015	Cognitive impairment in at least one domain not an inclusion criteria.
Peng 2016	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately.
Porter 2022	Cognitive impairment in at least one domain not an inclusion criteria.
Schellart 2011	Not a controlled trial.
Shaw 2006	Not a controlled trial.
Van der Linden 2018	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately. Cognitive impairment in at least one domain was not an inclusion criterion.
van der Linden 2021	Study included > 20% non-irradiation patients and did not analyse cranial irradiation patients separately.
Wong 2016	Subgroup of included study.
Yang 2014	Wrong patient population.

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

Chen 2019

Methods	Randomised controlled trial, parallel arm, unblinded
Participants	**Inclusion criteria:** aged between 18 and 80 years; KPS ≥ 70; MRI or CT demonstrating brain metastases from histologically proven lung cancer; life expectancy ≥ 6 months; radiation dose of whole brain radiation ≥ 30 Gy; being well-informed about the study and having good compliance with the treatment. **Exclusion criteria:** KPS <70; being poorly informed about radiation; half-way termination of radiation with total dose < 30 Gy; follow-up time <6 months or being lost to follow up; suffering from severe cerebrovascular diseases or psychiatric symptoms; having received cranial radiation. **No. randomised:** shenqi fuzheng: 48; control: 52. **Follow-up:** 3, 6, 9, and 12 months after radiotherapy. **Setting:** single centre in China.
Interventions	Treatment arm: radiotherapy in combination with intravenous shenqi fuzheng (250 mL daily for 4 weeks). Control arm: radiotherapy alone.
Outcomes	Cognitive function (MoCA, MMSE) Anxiety (ZSAS) Depression (ZSDS) Blood tests (serum inflammatory cytokines TGF-β1, TNF-α, IL-10)

Chen 2019 *(Continued)*

Notes	No statistical analyses.

CT: computed tomography**; MMSE**: Mini-Mental State Examination;**MoCA** Montreal Cognitive Assessment; **MRI:** magnetic resonance imaging; **RT:** radiotherapy; **ZSAS**: Zung Self-Rating Anxiety Scale; **ZSDS**: Zung Self-Rating Depression Scale.

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

Chan 2018

Study name	Testing ramipril to prevent memory loss in People with glioblastoma
Methods	Interventional single-arm pilot study.
Participants	Patients aged 18 years or older with glioblastoma receiving partial brain radiation and concurrent and adjuvant temozolamide Inclusion Criteria • Histologically proven diagnosis of glioblastoma or gliosarcoma (World Health Organization [WHO] grade IV) obtained at the time of a partial or gross total resection of the tumour. Patients who undergo a stereotactic needle biopsy alone are not eligible • The tumour must have a supratentorial component. • History/physical examination within 14 days prior to enrolment • The patient must have recovered from the effects of surgery, postoperative infection, and other complications before enrolment • Patient planning to receive brain RT, and concurrent and adjuvant temozolomide chemotherapy for six weeks as per standard of care therapy. Use of the Optune® (also known as Tumor Treating Fields or TTFields) device is allowed at provider discretion, but must begin after the Month 1 Post RT (10 week [wk]) Neurocognitive-PRO assessment • Study drug (Ramipril) must be given > 21 days and ≤ 35 days after surgery. • All available brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging reports from surgery to study completion must be submitted. This includes any postoperative or pre-radiation scan reports • Eastern Cooperative Oncology Group (ECOG) 0, 1 or 2 • Absolute neutrophil count (ANC) >= 1,500 cells/mm^3 (obtained within 14 days prior to enrolment) • Platelets >= 100,000 cells/mm^3 (obtained within 14 days prior to enrolment) • Haemoglobin >= 10.0 g/dL. (Note: The use of transfusion or other intervention to achieve haemoglobin [Hgb] >= 10.0 g/dL is acceptable) (obtained within 14 days prior to enrolment) • Blood urea nitrogen (BUN) =< 30 mg/dL within 14 days prior to enrolment • Creatinine =< 1.7 mg/dL within 14 days prior to enrolment • Total bilirubin =< 2.0 mg/dL within 14 days prior to enrolment • Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) =< 3 x normal range within 14 days prior to enrolment • Patient must provide study specific informed consent prior to study entry • Baseline potassium level <5.0. High potassium values that are thought to be a result of sample haemolysis may be repeated to determine an accurate potassium level and to determine potential study eligibility. Likewise high potassium values thought to be a result of potassium supplementation may be repeated at an appropriate time (5 half-lives after supplement discontinuation) to determine potential study eligibility Patient must be able to complete neurocognitive tests in the English language • Women of childbearing potential and male participants must practice adequate contraception • For females of child-bearing potential, negative serum or urine pregnancy test within 14 days of enrolment

Chan 2018 *(Continued)*

- Local site must be follow the standard GBM radiation treatment dosimetry plan
- For patients who will be treated with the Optune® device in addition to standard of care radiation plus concurrent and adjuvant temozolomide, the following inclusion criteria also apply:
- Patients must have only a supratentorial glioblastoma
- The treating physician must be a qualified provider having successfully completed the training course provided by Novocure, the device manufacturer
- Patients with prior malignancies if all treatment for that malignancy was completed at least 2 years before registration and the patient has no evidence of disease

Exclusion Criteria

- Prior allergic reaction or intolerance to angiotensin-converting-enzyme (ACE) inhibitor
- Hypotension (< 110 mg Hg systolic) at the time of enrolment
- Renal insufficiency with creatinine clearance of < 40 mL/min (at time of enrolment)
- Solitary kidney or known renal artery stenosis
- Current ACE inhibitor or angiotensin receptor blocker use. Patients can come off ACE inhibitors or angiotensin receptor blockers for 1 week to be eligible for this study
- Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 2 years. (For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible)
- Recurrent or multifocal malignant gliomas
- Metastases detected below the tentorium or beyond the cranial vault
- Prior chemotherapy or radiosensitisers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide. Prior use of Gliadel wafers or any other intratumoural or intracavitary treatment are not permitted
- Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields
- Severe active co-morbidity, defined as follows:
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrolment
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalizations or precluding study therapy at the time of enrolment
- Known HIV positivity or acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity
- Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy
- Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic
- Patients treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study
- Patients planning to receive therapeutic antitumour agents (excluding use of the Tumor Treating Fields (TTFields or Optune®) device after the Month 1 Post RT (10 wk) Neurocognitive-PRO assessment.) in addition to standard radiation and concurrent and adjuvant temozolomide are not eligible to participate in this study
- Patients with impaired decision-making capacity; this exclusion is necessary because such patients may not be able to adequately give informed consent
- Pregnant or lactating women, due to possible adverse effect on the developing fetus or infant due to study drug
- For patients who will be treated with the Optune® device in addition to standard of care radiation plus concurrent and adjuvant temozolomide, the following exclusion criteria also apply:
- Optune® is not permitted in patients who have an active implanted medical device, skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic

Chan 2018 *(Continued)*	devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmatic shunts • Optune® is not permitted in patients who are known to be sensitive to conductive hydrogels. Examples of conductive hydrogels are gels used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes
Interventions	Ramipril will be titrated to the highest tolerable dose during chemoradiation (2.5-5 mg). Once this dose is determined, the patient will continue at this dose for 4 months after the completion of chemoradiation.
Outcomes	Change from baseline neurocognitive function at 10 weeks - Hopkins Verbal Learning Test-Revised, Trail Making Test Part A and B, and Controlled Oral Word Association Test Efficacy of ramipril on neurocognitive function at baseline - Shipley Institute of Living Scale-Version 2 Vocabulary Retention rate at 10 weeks (percentage of patients who took 75% of the ramipril doses and completed the neurocognitive battery of tests)
Starting date	2018
Contact information	Study locations: 421 listed. Contact: Karen Craver, MT, MHA. 336-716-0891. NCORP@wakehealth.edu Principal investigator: Michael D Chan, MD. Wake Forest University Health Sciences.
Notes	ClinicalTrials.gov Identifier: NCT03475186 Recruitment status: Recruiting as of 7 May 2022.

ADDITIONAL TABLES

Table 1. Summary of findings: Memantine versus placebo

Cognitive functioning measure **(standardised scores)**	Memantine		Placebo		P
	N	Median change after 24 weeks (IQR)	*N*	Median change after 24 weeks (IQR)	
Short-term verbal memory	77	-0.23 (-1.16 to 0.70)	90	-0.415 (-1.86 to 0.46)	0.21
Long-term verbal memory (recall)	76	0 (-1.67 to 0.59)	90	-0.90 (-2.22 to 0.55)	0.06
Long-term verbal memory (recognition)	76	0 (-1.12 to 1.43)	90	-0.72 (-2.73 to 0.71)	0.01*
Verbal Fluency	78	-0.10 (-0.62 to 0.53)	90	-0.16 (-0.83 to 0.61)	0.31
Trail Making Test A	76	0.08 (-1.01 to 1.82)	92	-0.37 (-2.08 to 0.50)	0.02*

Table 1. Summary of findings: Memantine versus placebo *(Continued)*

Trail Making Test B	74	-0.45 (-2.37 to 1.04)	90	-0.49 (-2.60 to 0.62)	0.30
Cognitive composite score	73	-0.03 (-0.90 to 0.72)	90	-0.41 (-1.30 to 0.12)	0.02*

* $P < 0.05$
IQR: interquartile range

Table 2. Summary of findings: Goal Management Training versus Brain Health Program versus wait-listed control

Cognitive performance measure	Goal Management Training		Brain Health Program		Wait-listed control		P	Goal Management Training		Brain Health Program		Wait-listed control		P
	N	Domain composite score change post-training compared to baseline (SD)	*N*	Domain composite score change post-training compared to baseline (SD)	*N*	Domain composite score change post-training compared to baseline (SD)		*N*	Domain composite score change at 4-month follow-up compared to baseline (SD)	*N*	Domain composite score change at 4-month follow-up compared to baseline (SD)	*N*	Domain composite score change at 4-month follow-up compared to baseline (SD)	
Executive composite	10	0.33 (0.54)	6	0.08 (0.43)	4	-0.44 (0.45)	0.077	10	0.69 (0.51)	6	0.13 (0.50)	3	-0.07 (0.44)	0.046
Memory composite	10	0.40 (0.84)	6	0.11 (0.91)	4	0.43 (0.76)	0.778	10	1.08 (0.82)	6	0.86 (1.01)	3	0.84 (0.52)	0.842
Processing speed	10	0.44 (0.55)	6	0.47 (0.43)	4	-0.65 (1.53)	0.071	10	0.54 (0.57)	6	-0.14 (0.94)	3	-0.18 (1.03)	0.179

SD: standard deviation
P values refer to time-by-group interaction (intervention) effects on change compared to baseline, using analysis of variance

WHAT'S NEW

Date	Event	Description
9 May 2022	New citation required and conclusions have changed	Review updated with two additional studies included.
9 May 2022	New search has been performed	Review updated.

HISTORY

Protocol first published: Issue 10, 2014
Review first published: Issue 12, 2014

Date	Event	Description
20 April 2015	Amended	Minor editorial amendments to text.

CONTRIBUTIONS OF AUTHORS

Develop and run the search strategy	MK, JD, KZ, KG
Obtain copies of trials	MK, JD, KZ
Select which trials to include	MK, JD, KZ, KG
Extract data from trials (2 people)	MK, JD, KZ
Enter data into RevMan	MK, JD, KZ
Carry out the analyses	MK, JD, KZ
Interpret the analyses	All authors
Draft the final review	All authors
Update the review	All authors

DECLARATIONS OF INTEREST

Matthew A. Kirkman: nothing to declare

Julia Day: nothing to declare

Karolis Zienius: nothing to declare

Martin Taphoorn: nothing to declare

Jing Li: nothing to declare

Karin Gehring: nothing to declare

David Grosshans: nothing to declare

Paul Brown: nothing to declare

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

External sources

- National Institue of Health Research (NIHR), UK

  Infrastructure funding to GNOC

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods section of this review are based on a standard template established by the Cochrane Neuro-oncology Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Brain Neoplasms; Cognition; *Cognitive Dysfunction [etiology] [prevention & control]; Cranial Irradiation [adverse effects]; *Dementia; Donepezil; Fatigue [etiology] [prevention & control]; Memantine; *Methylphenidate [therapeutic use]; Modafinil [therapeutic use]; Quality of Life

MeSH check words

Adult; Humans