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Interventions to help support caregivers of people with a brain or spinal cord tumour (Review)

Boele FW, Rooney AG, Bulbeck H, Sherwood P

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[Intervention Review]

Interventions to help support caregivers of people with a brain or spinal cord tumour

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ABSTRACT

Background

The diagnosis and treatment of a brain or spinal cord tumour can have a huge impact on the lives of patients and their families with family caregiving often resulting in considerable burden and distress. Meeting the support needs of family caregivers is critical to maintain their emotional and physical health. Although support for caregivers is becoming more widely available, large-scale implementation is hindered by a lack of high-quality evidence for its effectiveness in the neuro-oncology caregiver population.

Objectives

To assess the effectiveness of supportive interventions at improving the well-being of caregivers of people with a brain or spinal cord tumour. To assess the effects of supportive interventions for caregivers in improving the physical and emotional well-being of people with a brain or spinal cord tumour and to evaluate the health economic benefits of supportive interventions for caregivers.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7), MEDLINE via Ovid, and Embase via Ovid. We also handsearched relevant published conference abstracts (previous five years), publications in the two main journals in the field (previous year), searched for ongoing trials via ClinicalTrials.gov, and contacted research groups in the field. The initial search was in March 2017 with an update in August 2018 (handsearches completed in January 2019).

Selection criteria

We included all randomised controlled trials (RCTs) where caregivers of neuro-oncology patients constituted more than 20% of the sample and which evaluated changes in caregiver well-being following any supportive intervention.

Data collection and analysis

Two review authors independently selected studies and carried out risk of bias assessments. We aimed to extract data on the outcomes of psychological distress, burden, mastery, quality of patient–caregiver relationship, quality of life, and physical functioning.

Main results

In total, the search identified 2102 records, of which we reviewed 144 in full text. We included eight studies. Four interventions focused on patient–caregiver dyads and four were aimed specifically at the caregiver. Heterogeneity of populations and methodologies precluded meta-analysis. Risk of bias varied, and all studies included only small numbers of neuro-oncology caregivers (13 to 56 participants). There

was some evidence for positive effects of caregiver support on psychological distress, mastery, and quality of life (low to very low certainty of evidence). No studies reported significant effects on caregiver burden or quality of patient–caregiver relationship (low to very low certainty of evidence). None of the studies assessed caregiver physical functioning. For secondary outcomes (patient emotional or physical well-being; health economic effects), we found very little to no evidence for the effectiveness of caregiver support. We identified five ongoing trials.

Authors' conclusions

The eight small-scale studies included employed different methodologies across different populations, with low certainty of evidence overall. It is not currently possible to draw reliable conclusions regarding the effectiveness of supportive interventions aimed at improving neuro-oncology caregiver well-being. More high-quality research is needed on support for family caregivers of people diagnosed, and living, with a brain or spinal cord tumour.

PLAIN LANGUAGE SUMMARY

Interventions to help support caregivers of people with a brain or spinal cord tumour

The issue

Family caregivers (e.g. spouses, family members or close friends) often provide physical and emotional support to peoples with a brain or spinal tumour (cancer). However, family caregiving is linked to considerable burden and distress. Therefore, it is important to meet the support needs of family caregivers so their emotional and physical health is maintained. This is expected to help the caregiver, the patient, and the family unit.

The aim of the review

To assess the effectiveness of supportive interventions at improving the well-being of caregivers of people with a brain or spinal cord tumour. To assess the effects of supportive interventions for caregivers in improving the physical and emotional well-being of patients with a brain or spinal cord tumour and to evaluate the health economic benefits of supportive interventions for caregivers.

Study characteristics

We included eight clinical studies. Four studies reported on interventions for patient–caregiver relationship and four studies were aimed specifically at improving caregiver well-being. We found five ongoing studies.

What were the main findings?

The interventions tested were diverse in nature (e.g. cognitive behavioural therapy (talking therapy); psychoeducation (providing education and information to people seeking or receiving mental health services); coping skills training; self-management; social network intervention); and delivery (e.g. face-to-face; web-based), and all studies were relatively small (included between 13 and 56 neuro-oncology caregivers). We found some evidence for positive effects of caregiver support on psychological distress, feelings of mastery (i.e. the feeling of being in control of the caregiving situation), and quality of life.

Reliability of the evidence

None of the studies reported effects on caregiver burden or quality of patient–caregiver relationship. None of the studies measured caregiver physical well-being. Overall, the certainty of the evidence was low to very low, which means the true effect of caregiver support may be substantially different.

Conclusions

Our findings suggest it is not currently possible to draw definitive conclusions about the effectiveness of supportive interventions to improve neuro-oncology caregiver well-being. More high-quality research is needed on support for family caregivers of patients diagnosed, and living, with a brain or spinal cord tumour.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interventions to help support caregivers of people with a brain or spinal cord tumour

Interventions to help support caregivers of people with a brain or spinal cord tumour

Patient or population: caregiver well-being
Setting: any
Intervention: supportive interventions
Comparison: any control condition

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Caregiver psychological distress assessed with: DASS-21; Fear of Recurrence Questionnaire – Family Member; CES-D; POMS; STAI; HADS Follow-up: range 1 days to 8 months	4 studies found improvements after the intervention (early palliative care; interactive-educational programme; electronic social network intervention; self-management programme); 1 found no significant effects (e-mental health); 1 only reported descriptives (cognitive rehabilitation and problem-solving).	(6 RCTs)	⊕⊕⊖⊖ **Low**[a,b,c,d,e]
Caregiver burden assessed with: MBCB Scale; Zarit Caregiver Burden Scale Follow-up: range 6 weeks to 3 months	2 studies found no statistically significant differences in burden scales between the intervention and control groups (early vs delayed palliative care; electronic social network intervention).	(2 RCTs)	⊕⊕⊖⊖ **Low**[e]
Caregiver mastery assessed with: Caregiver Mastery Scale; General Self-Efficacy Scale; Utrecht Coping List Follow-up: range 6 months to 8 months	1 study found improvements in mastery after the intervention (psychoeducation and cognitive behavioural therapy) compared to care-as-usual, corrected for changes in patient functioning. 1 study found no improvements in self-efficacy or coping strategies (self-management programme).	(2 RCTs)	⊕⊖⊖⊖ **Very low**[d,e,f,g]
Quality of patient–caregiver relationship assessed with: McMaster Family Assessment Device	1 study found no statistically significant differences in family functioning between the intervention and control groups (e-mental health vs waiting list).	(1 RCT)	⊕⊖⊖⊖ **Very low**[e,h]
Caregiver quality of life assessed with: SF-36; QoL – Family Caregiver Tool; CQOLC; LASA Follow-up: range 30 days to 8 months	2 studies found improvements in QoL over time in the intervention group (psychosocial intervention; self-management programme) compared to the control group; 1 study found stable QoL in the intervention group vs decline in the control group (no longer statistically significant after controlling for patient functioning); 2 studies found no statistically significant improvements after the intervention (e-mental health; early palliative care); 1 only reported descriptives (cognitive rehabilitation and problem-solving).	(6 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c,e,g,i]
Caregiver physical functioning – not measured	None of the included studies assessed caregiver physical functioning.	—	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CQOLC: Caregiver QoL Index – Cancer; **CES-D:** Center for Epidemiological Studies Depression Scale; **CI:** confidence interval; **DASS-21:** Depression, Anxiety and Stress Scales; **HADS:** Hospital Anxiety and Depression Scale; **LASA:** Linear Analogue Self-Assessment; **MBCB:** Montgomery-Borgatta Caregiver Burden; **POMS:** Profile of Mood States; **RCT:** randomised controlled trial; **SF-36:** 36-item Short Form; **STAI:** State-Trait Anxiety Inventory.

GRADE Working Group grades of evidence
High certainty : we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty : we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty : we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Different populations (e.g. mixed cancer caregiver samples, paediatric or adult (or both) caregiver samples).
[b]Different interventions.
[c]One quasi-RCT included.
[d]Outcomes measure similar constructs but do not completely overlap.
[e]Small number of neuro-oncology caregivers.
[f]Only long-term effects reported (six to eight months post baseline).
[g]High attrition, analysed using last observation carried forward in one study.
[h]Only included parents of children with brain tumours.
[i]One study with inadequate sequence generation and allocation concealment.

BACKGROUND

Description of the condition

The diagnosis and treatment of a brain or spinal cord tumour can have a huge impact on the lives of patients and their families. Approximately 28 per 100,000 adults aged 20 years and over are affected by central nervous system tumours, with the majority of tumours (approximately 66%) being non-malignant (Ostrom 2014). In children and young adults under 19 years of age, central nervous system tumours are the most common tumour, with an annual age-adjusted incidence rate of 5.4 per 100,000 (Ostrom 2014).

The treatment and expected outcome depend heavily on the tumour type, molecular markers, tumour grade, and location. Treatment generally consists of surgical intervention, radiotherapy, chemotherapy, or a combination of treatment methods. In making treatment decisions, benefit from treatment is weighed against the expected quality of life (QoL) and symptom burden of patients.

Depending upon the tumour location and treatment adverse effects, patients can experience neurological symptoms such as weakness, sensory loss, and motor dysfunction, or visual-perceptual deficits and problems with speech and language (Mukand 2001). Cognitive deficits such as problems with memory and concentration occur in most patients, and epilepsy is also common (Armstrong 2016a; Durand 2015; van Loon 2015). Moreover, fatigue, depression, and changes in personality and behaviour are frequently reported throughout the course of the disease (Armstrong 2016b; Cavers 2012; Rooney 2011). These symptoms can influence the degree to which patients can participate in vocational and social activities and can prevent independence and affect QoL (Aaronson 2011; Klein 2001; Macartney 2014).

Patients commonly come to rely on their family caregivers (e.g. spouses, family members, or close friends) for both physical and emotional support. Consequently, many family caregivers experience considerable burden and distress, and consistently report feeling ill-prepared for their caregiving role (Choi 2012; Sterckx 2013). Therefore, interventions to support caregivers are expected to help the caregiver, the patient, and the family unit.

Various studies have explored the needs of family caregivers in neuro-oncology, and showed a desire for clear information and communication with healthcare professionals, concerning managing patients' symptoms, treatment, and available resources; health service needs and care co-ordination; and the need for psychological and social supportive care options (Moore 2012; Sterckx 2013).

Description of the intervention

Individual caregivers' needs can vary greatly depending on the patient's time point in treatment, the caregiver's social support system, expectations and experienced burden (i.e. the stress experienced as a result of the home care situation) (Ownsworth 2015a). Therefore, any intervention programme aimed at improving the well-being of family caregivers in neuro-oncology was considered for this review. Here, the term 'well-being' encompassed all aspects of QoL, psychological distress, coping, and mastery (i.e. the feeling of being in control of the caregiving situation).

The interventions under investigation included, but were not limited to, programmes aimed at supporting family caregivers through:

- improving information provision (e.g. what to expect from their role as a family caregiver; teaching caregivers what the treatment options are; and educating them on supportive care options);
- caregiver skills training (e.g. how to recognise (changes in) patients' symptoms; how to manage symptoms or improve patients' everyday functioning); and
- psychosocial support (e.g. psychosocial interventions to help caregivers cope better; therapeutic interventions to promote a healthy relationship between the patient and caregiver; bereavement support after the patient has died).

Following the National Institute for Health and Care Excellence (NICE) recommended model of psychological assessment and support (NICE 2004), interventions could be any from level 1 (information and general support given by any health and social care professional – or self-help) to level 4 (specialist psychological or psychiatric interventions delivered by mental health professionals). We did not expect effectiveness of interventions to vary within different subgroups of caregivers (e.g. grade of tumour and age of patient). The interventions were not expected to pose a risk to caregivers; however, length or complexity of intervention programmes may have increased caregiver burden and could have caused caregivers to feel overwhelmed instead of supported.

How the intervention might work

Supportive interventions for family caregivers in neuro-oncology may help in various ways.

Improving information provision and caregiver skills training can help prepare family members and friends for their caregiving role and activities. When caregivers learn more about the disease and its symptoms, they feel more confident in distinguishing between which (changes in) symptoms could be normal or expected and which may require medical follow-up. Through this mechanism, patient outcomes may be improved as better symptom management is initiated sooner and new tumour activity may be detected earlier in the disease trajectory, allowing treatment to commence. Moreover, symptoms may be recognised and treated before becoming more serious and requiring inpatient treatment, thus potentially reducing healthcare costs. Finally, increasing caregivers' confidence in dealing with the care situation can substantially improve their feelings of mastery. This may have a positive effect on their overall well-being, their QoL, and the quality of care they deliver in the home situation.

Psychosocial support can provide caregivers with the tools to improve coping strategies to deal with the psychological burden of being a caregiver to a person who has been diagnosed with a brain or spinal cord tumour. Many patients and caregivers struggle with maintaining a healthy relationship, particularly after changes in the patient's personality and behaviour, and psychological support to caregivers or patient–caregiver dyads can help couples work through these issues together. It is known that patients who go through divorce or separation are more likely to be hospitalised and less likely to complete treatment, become involved in clinical trials, or die at home (Glantz 2009). Therefore, promoting healthy

patient–caregiver relationships may have a positive effect on long-term patient outcomes. This can help decrease caregivers' levels of distress and burden. As many caregivers will provide care for a longer period of time, up to many years on end, decreasing distress and burden may prove beneficial as the physical consequences of long-term high levels of stress may be prevented. Finally, maintaining good physical as well as emotional health in caregivers will allow them to continue their caregiving tasks, which will benefit patients as well.

Why it is important to do this review

Meeting the needs of family caregivers in neuro-oncology, by decreasing their distress and burden and improving their sense of mastery, is imperative in order to maintain their emotional and physical health. Protecting caregivers' QoL can enable them to continue their caregiving activities to maintain the best possible level of patients' well-being. Indeed, caregiver support is listed as a top research priority in neuro-oncology in the UK through the James Lind Alliance Priority Setting Partnership (Grant 2015). Furthermore, the UK National Health Service (NHS) has made several commitments to caregivers, including supporting caregivers' mental health and well-being alongside physical needs (NHS England 2014).

Information and support for caregivers of patients with brain and spinal cord tumours is becoming more widely available and caregiver programmes are becoming more common in clinical practice in some centres. Specialised nurses who may also provide caregiver support corresponding with level 1 of the NICE model of psychological support (NICE 2004), are in many countries part of the treatment team. However, large-scale implementation of caregiver support may be hindered by the lack of high-quality evidence for the effects of caregiver interventions in populations of brain and spinal tumour patients. Indeed, one report from Macmillan Cancer Support revealed that more than half of family caregivers in oncology did not receive support at present (Macmillan/You Gov 2016). This systematic review will provide an overview of caregiver interventions for those taking care of patients with a brain or spinal tumour, assessed in randomised controlled trials (RCTs). It will also provide a brief economic summary of the health economic benefits where these have been measured. It is expected that this will be useful to make recommendations for policy and practice.

OBJECTIVES

To assess the effectiveness of supportive interventions at improving the well-being of caregivers of people with a brain or spinal cord tumour. To assess the effects of supportive interventions for caregivers in improving the physical and emotional well-being of patients with a brain or spinal cord tumour and to evaluate the health economic benefits of supportive interventions for caregivers.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs. We included trials that used quasi-randomised methods if there was sufficient evidence that the treatment and control groups were similar at baseline. If this was unclear, we contacted trial authors to request clarification.

Types of participants

Studies with adult caregivers (aged 18 years or older) for people with a brain or spinal cord tumour. The people for which they provide care could have been of any age, with any type of malignant or non-malignant, primary or secondary brain or spinal cord tumour, at any time during the disease trajectory.

Types of interventions

Any type of intervention whose primary aim was to improve caregiver well-being. We included trials that evaluated the effectiveness of individual- and group-based interventions for caregivers or for patient–caregiver dyads as long as they reported caregiver outcomes. We placed no restrictions on: the setting (e.g. hospital, clinic, psychologist office, at home, or elsewhere); the facilitator of the intervention (e.g. a healthcare professional (including nurse specialists), social worker, or (guided) self-help); or the method of delivery of the intervention (e.g. delivered face-to-face, online, written, or by telephone). Thus, interventions could reflect any level of psychological support from the NICE model (NICE 2004). Any control condition was acceptable (e.g. wait list control groups, attention-only control groups, and information-only control groups). We contacted trial authors if it was unclear whether a trial met our inclusion criteria.

Types of outcome measures

For all primary outcomes, we accepted recognised caregiver questionnaires or instruments measuring mood, caregiver burden, mastery, marital adjustment, QoL, and physical functioning. Where measured, we assessed the effect on patient emotional and physical well-being patient questionnaires under Secondary outcomes. Acceptable outcomes are listed below.

Primary outcomes

Outcomes related to caregiver emotional or physical well-being

- Psychological distress (depression and anxiety) (e.g. Hospital Anxiety and Depression Scale (HADS; Crawford 2001), Center for Epidemiological Studies Depression Scale (CES-D; Radloff 1977)).
- Caregiver burden (e.g. Caregiver Reaction Assessment (CRA; Given 1992)).
- Caregiver mastery (e.g. Mastery Scale (Pearlin 1978)).
- Quality of patient–caregiver relationship (e.g. Locke-Wallace Short Marital Adjustment Test for spousal relationships (Jiang 2013)).
- Quality of life (QoL), either caregiver specific (e.g. Caregiver QoL index-cancer (CQOLC; Weitzner 1999), Caregiver Oncology QoL Questionnaire (CarGOQoL; Minaya 2012), or generic, e.g. Short Form Health Survey (SF-36; McHorney 1993), EuroQol (EQ-5D Brooks 1996)).
- Physical functioning (e.g. number of chronic conditions present, physical measures of stress levels (e.g. cytokines), physical subscales of QoL questionnaires).

Secondary outcomes

Outcomes related to patient emotional or physical well-being

- Psychological distress (depression and anxiety) (e.g. HADS (Crawford 2001), CES-D (Radloff 1977)).

- QoL (e.g. European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30; Aaronson 1993); Functional Assessment of Cancer Therapy (FACT; Weitzner 1995), 36-item Short Form Health Survey (SF-36; McHorney 1993)).
- Symptom management, number or severity (or both) of symptoms (e.g. measured with MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT; Armstrong 2006), EORTC Brain Cancer Module (EORTC QLQ-BN20; Taphoorn 2010)).
- Number of visits to the emergency department (e.g. as detailed in medical records).
- Number and length of hospitalisations (e.g. as detailed in medical records).

Outcomes related to the health economic effects

- Caregiver or patient (or both) employment status (e.g. self-reported).
- Productivity loss at work of caregiver or patient (or both) (e.g. self-reported).
- Caregiver healthcare utilisation for acute or chronic (or both) conditions (e.g. self-reported or as detailed in caregiver's medical records).

We included trials with different outcomes to those mentioned above, when they measured the same construct.

Search methods for identification of studies

There were no restrictions based on type of publication, year of publication, or language. We considered both published and unpublished RCTs.

Electronic searches

We searched the following databases on 24 August 2018:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7), in the Cochrane Library, using the search strategy in Appendix 1;
- MEDLINE via Ovid (1946 to August week 3 2018), using the search strategy in Appendix 2;
- Embase via Ovid (1980 to 2018 week 34), using the search strategy in Appendix 3.

We also searched ClinicalTrials.gov (clinicaltrials.gov/).

Searching other resources

We handsearched the references of identified studies for studies that were not identified through the electronic search.

We searched conference abstracts and proceedings from 2013 to 2018 through the American Society of Clinical Oncology (ASCO; www.asco.org/ASCO/Meetings), the Society for Neuro-Oncology (SNO; supplements of *Neuro-Oncology*; academic.oup.com/neuro-oncology), and the International Psycho-Oncology Society (IPOS; special issues of *Psycho-oncology*).

We handsearched the two main journals in the field of neuro-oncology, *Neuro-oncology* and *Journal of Neuro-oncology*, for publications from 2017 that were not identified through the electronic search.

We contacted the authors of publications known to focus on improving the well-being of caregivers of patients with a brain or spinal cord tumour, to enquire about unpublished or ongoing trials. These additional searches were completed on 20 July 2017 (for the initial search) and 23 January 2019 (for the updated search).

Data collection and analysis

Full details on planned data collection and analysis are available in the published protocol (Boele 2017a).

Selection of studies

Two review authors (FB and AR) selected studies for inclusion. After removing duplicates, the two review authors independently screened all titles and abstracts. We excluded studies that did not meet the inclusion criteria while storing these discarded studies in a file as potentially relevant. We retrieved full-text reports and subjected the eligible studies to further assessment. We documented reasons for exclusion and resolved disagreements between review authors by discussion. If the published report contained too little information to assess the trial, one review author (FB) contacted the study authors to request further details.

Data extraction and management

Two review authors (FB and AR) examined each selected report and extracted data using a data collection form based on Cochrane Consumers and Communication's Group data extraction template (Cochrane CCG 2016). This data collection form included participant characteristics (e.g. age, sex, group size, patients' tumour type, grade, disease stage, etc.) and information about the supportive intervention (e.g. method, duration, delivery, provider); the time points at which the outcomes were assessed; whether outcomes were self-reported or other; whether the tool was validated; how missing data were handled; statistical methods used; and whether these were appropriate. The form also included details on the results (continuous outcomes: mean difference (MD) and standard error (SE), number of participants; dichotomous outcome data: e.g. number of caregivers who showed an improvement in terms of emotional or physical well-being as a proportion of the total number treated; and other results e.g. MD, odds ratio, risk difference, confidence intervals (CI), P values), and information on adherence and attrition (Chandler 2013).

Assessment of risk of bias in included studies

The two review authors responsible for the selection of studies and data extraction assessed the risk of bias in accordance with the Cochrane tool for assessing risk of bias (Higgins 2011a). This included several domains: random sequence generation; allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The risk of bias was categorised as high, low, or unclear. 'High risk' was selected if there was a non-random component (random sequence generation); if participants or investigators enrolling participants could possibly foresee assignment which could introduce selection bias (allocation concealment); if participants and personnel were not completely blinded and the outcome was likely to be affected by lack of blinding (blinding of participants and personnel); if there was no blinding of outcome assessment and outcome measurement was likely to be influenced (blinding of outcome assessment); if the reason for missing data was likely related to true outcome

with either imbalance in numbers or reasons for missing data across groups, if the results for missing outcomes likely induced clinically relevant bias, if participants in 'as treated' analysis did not receive the intervention as planned, or if simple imputation was inappropriately applied (incomplete outcome data); if not all prespecified outcomes were reported or outcomes were reported using measurements, analysis methods or subsets of the data that were not prespecified (selective reporting). The risk of bias in the included studies was discussed between review authors.

Measures of treatment effect

For dichotomous outcome data, we aimed to abstract the number of caregivers who showed an improvement in terms of emotional or physical well-being as a proportion of the total number treated. We aimed to calculate and present risk ratios (RRs) with 95% CIs.

For continuous outcome data from studies using the same instrument, we aimed to estimate MDs between treatment groups. Where different instruments were used, we aimed to calculate the standardised mean difference (SMD) by dividing the MD in postintervention scores between the intervention and control groups by the standard deviation (SD) of the outcome among participants. We aimed to present both the MD and SMD with 95% CIs for individual outcomes in individual studies. If these data were unavailable, we contacted study authors to request additional information, and if still unavailable, we presented the reported significance levels instead.

Unit of analysis issues

Different levels of randomisation (e.g. at the level of participants or groups) were taken into account. When there were long-term follow-up assessments available within trials, we aimed to analyse outcomes for two different follow-up categories: short term (i.e. zero to three months); or medium to long term (i.e. four months and more). If studies with multiple intervention groups were identified, we aimed to make pair-wise comparisons between all possible pairs of intervention groups. We aimed to make efforts not to double-count participants in the analysis.

Dealing with missing data

We contacted the corresponding authors of the trials in writing to request missing data. We evaluated the reporting of important numerical data such as the number of screened and randomised participants, and whether intention-to-treat or per-protocol analyses were done. Missing data were not imputed (Higgins 2011a).

Assessment of heterogeneity

We planned to assess the impact of the heterogeneity of included intervention studies with the I^2 statistic for each outcome (Higgins 2011b). Substantial heterogeneity would be defined as I^2 greater than 50% and forest plots were to be visually inspected for heterogeneity. In the case of meta-analysis being possible, we planned to use a random-effects model as a certain degree of heterogeneity was expected.

Assessment of reporting biases

We planned to draw funnel plots of treatment effect versus precision with the data from all studies (Higgins 2011b), if at least 10 studies were identified. The funnel plots were to be visually inspected to assess whether there was selective reporting of outcomes.

Data synthesis

If trials included different outcomes, we aimed to pool outcomes that measured the same construct, or systematically report on outcomes that did not measure the same construct.

We aimed to perform a meta-analysis if we found two or more RCTs with a low risk of bias in which study population, intervention, and outcome measures were comparable. With meta-analysis not possible, two review authors (FB and HB) synthesised the findings of the included studies in Summary of findings for the main comparison, and rated the overall certainty of the evidence according to the GRADE levels of evidence (Higgins 2011a; Ryan 2016).

Subgroup analysis and investigation of heterogeneity

If sufficient studies were identified (i.e. at least two for each subgroup), we had planned to perform subgroup analyses for the study design (RCT or quasi-RCT), the type of intervention, the type of control group, timing (e.g. shortly after the patient's diagnosis, during initial antitumour treatment, following initial treatment, in the palliative phase or during the bereavement phase), and patient tumour type.

Sensitivity analysis

If sufficient data were available, we planned to perform a sensitivity analysis to assess the robustness of results (e.g. excluding studies with high risk of bias).

RESULTS

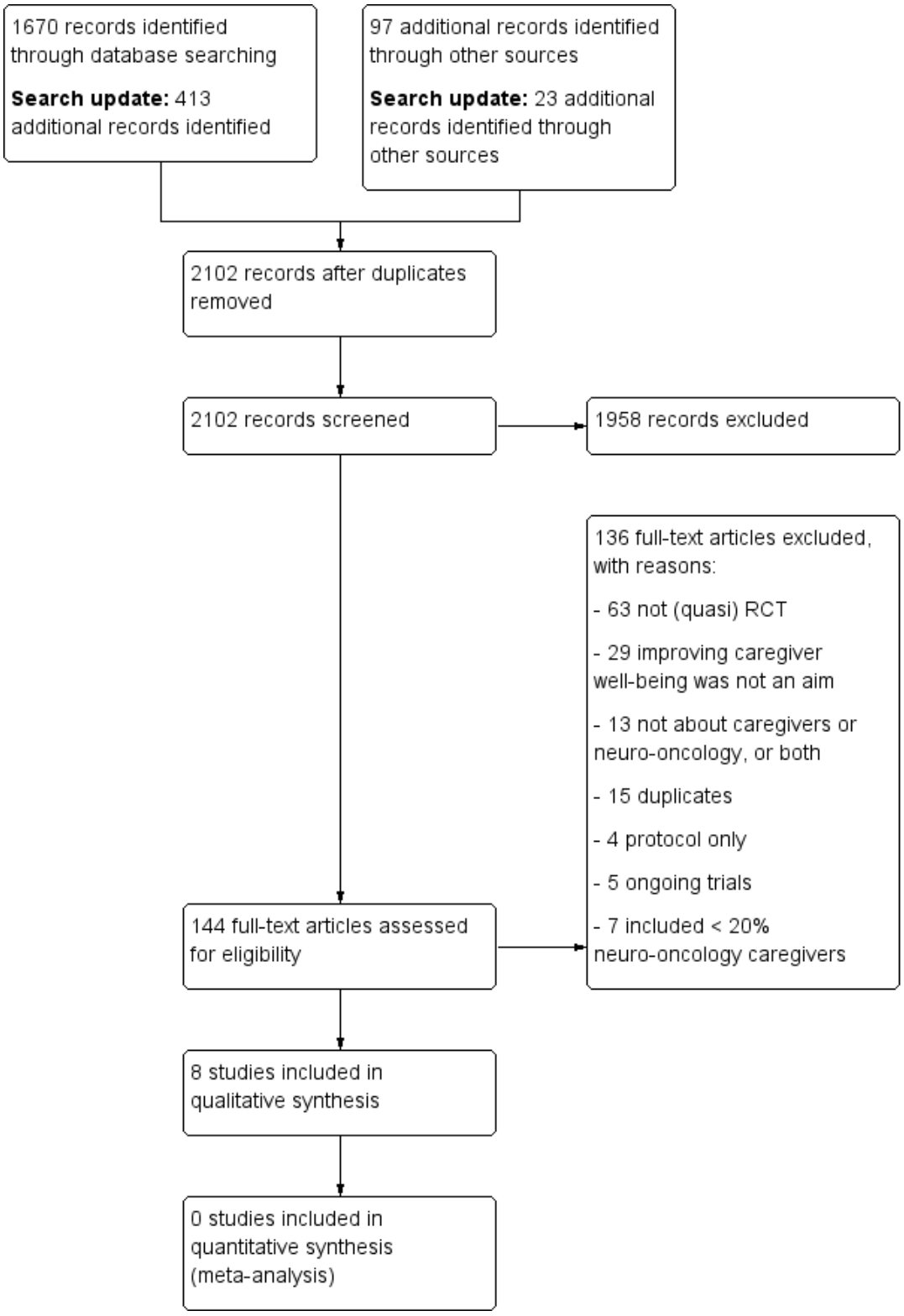
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies tables.

Results of the search

A flowchart of our search is shown in Figure 1. The initial search yielded 1670 records, supplemented by 413 records found in electronic database searches and handsearching conference abstracts and proceedings from 2013 to 2018, as well as publications in *Neuro-oncology* and *Journal of Neuro-oncology* from 2017. After removing duplicates, 1666 records remained. Upon screening of titles and abstracts, results were narrowed down to 122 records. Of these, 117 were excluded: 50 records were not (quasi) RCTs; 27 studies did not aim to improve caregiver well-being; 13 were not focused on caregivers or (or both) neuro-oncology; 15 were duplicates; four were published protocols only. Thirteen studies were potentially eligible and we requested additional information from the authors. Four publications included less than 20% of neuro-oncology caregivers in their samples (Cernvall 2015; Hudson 2015; Kissane 2016; Mooney 2015), making it debatable whether the outcomes would be generalisable to the neuro-oncology caregiver population. There were four ongoing trials (Halkett 2015; Langbecker 2016; Ownsworth 2015b; Roberge 2016).

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



The search update yielded a further 413 references. Publications and conference abstracts were also screened at this time. In total, the search update produced 436 records. Of these, 22 were reviewed in detail, and 19 were excluded: 13 records were not (quasi) RCT; two did not aim to improve caregiver well-being, and three included less than 20% neuro-oncology caregivers, or an unclear percentage (Epstein 2017; Holm 2016; Lawsin 2017). There was one ongoing trial (NCT03454295). Three additional trials were thus included after the search update.

Eight publications were included in the review.

Included studies

See Characteristics of included studies tables.

Design and setting

Seven studies were RCTs (Andela 2017; Boele 2013; Dionne-Odom 2015; Klosky 2007a; Reblin 2018; Safarabadi-Farahani 2016; Wakefield 2016), another was quasi randomised as the last three participants were allocated to the intervention group automatically (Locke 2008). In four publications, randomisation took place at the level of the family or patient–caregiver dyad (Andela 2017; Dionne-Odom 2015; Klosky 2007a; Locke 2008). In one study, both parents could participate and were then assigned to the same condition, but in different groups (Wakefield 2016). In three studies, caregivers were randomised at the individual level by themselves (Boele 2013; Reblin 2018; Safarabadi-Farahani 2016). Four trials took place in the US (Dionne-Odom 2015; Klosky 2007a; Locke 2008; Reblin 2018), one in Australia (Wakefield 2016), two in the Netherlands (Andela 2017; Boele 2013), and one in Iran (Safarabadi-Farahani 2016).

Participant demographics

The total sample sizes for the included studies ranged from 19 (Locke 2008) to 122 (Dionne-Odom 2015) randomised participants. However, not all eight studies exclusively focused on neuro-oncology caregiver populations. We included studies only if more than 20% of caregivers in the sample were taking care of a patient with a primary or secondary brain or spinal cord tumour. As a result, the sample size for the subset of participants of interest to this review were smaller, ranging from 13 (29% of the sample; Wakefield 2016) to 56 (100% of the sample; Boele 2013) neuro-oncology family caregivers. Participant demographics were only available for the total samples of the included studies. Two studies did not report on caregiver demographics (Klosky 2007a; Locke 2008). Participants' mean age ranged from 42 years (Wakefield 2016) to 61 years (Dionne-Odom 2015). In all studies except one (Andela 2017 (44%)), the majority of caregivers were female (ranging from 64% of the total sample in Boele 2013 to 95% in Safarabadi-Farahani 2016). Of note, three studies focused on family caregivers of children diagnosed with cancer (Klosky 2007a; Safarabadi-Farahani 2016; Wakefield 2016); the other five studies only included those taking care of an adult (Andela 2017; Boele 2013; Dionne-Odom 2015; Locke 2008; Reblin 2018). Only one study included a significant proportion of caregivers taking care of a patient with secondary brain tumours (brain metastases; Dionne-Odom 2015).

Intervention characteristics

Four of the interventions focused on patient–caregiver dyads (Andela 2017; Dionne-Odom 2015; Klosky 2007a; Locke 2008), four aimed to improve specifically caregiver well-being and did not involve the patient directly (Boele 2013; Reblin 2018; Safarabadi-Farahani 2016; Wakefield 2016).

Caregiver-focused interventions

The intervention tested by Boele 2013 was based on the principles of cognitive behavioural therapy (CBT) and psychoeducation. Once every two weeks, for a total of six sessions, a psychologist would meet with the caregiver. During the first session, the caregiver and psychologist reviewed the issues and needs of the caregiver. During the second session, an introduction of the intervention and rationale behind CBT was given. A selection of topics was available for the other four sessions: 1. contact with the patient; 2. the direct environment (contact with family, friends, and other); 3. epilepsy; 4. changes in behaviour, character, and cognition; 5. time for yourself; 6. children (what and how to tell them); and 7. practical and emotional care in the end of life phase. The participants in the control group received care as usual.

Reblin 2018 tested a web-based intervention called eSNAP, which aimed to help caregivers visualise their existing social network resources. Users were able to list people and groups who could help within six categories of support: 1. hands on; 2. informational; 3. communication; 4. financial; 5. emotional; and 6. self-care. A visualisation of the support network was created based on caregivers' input and printed in PDF. The intervention was completed within one session (taking approximately 10 to 15 minutes), while waiting for the patient's hospital appointment, and the visualisation report could be revisited by caregivers if they wished. Participants in the control group received care as usual.

The Brief Psychological Intervention (BPI) tested by Safarabadi-Farahani 2016 employed problem-solving skills training and psychoeducation. In five sessions lasting between 60 and 90 minutes, a trained social worker covered the following aims: 1. engage and motivate caregivers to participate and develop open communication with the social worker; 2. develop an optimistic attitude, maintaining hope and focus on achievable short-term goals; 3. provide information about treatments and medication, and living with uncertainty; 4. help caregivers cope with stress and teach stress-reducing techniques, coping strategies, and promote healthy lifestyle behaviours; and 5. education of self-care strategies. Sessions were followed up with a telephone call (five in total). The control group participants received care as usual, including counselling and financial support.

The Cascade programme tested by Wakefield 2016 was based on the Uncertainty in Illness model and Family-Systems-Illness model. The three-week programme consisted of weekly 120-minute online sessions delivered by a psychologist through WebEx. After each session, caregivers would get homework assignments to practice. The programme intended to target intra- and interpersonal psychological processes that are important to adaptation in the context of illness (e.g. acceptance of uncertainty). CBT strategies were used to target these core mechanisms of change. The topic areas were not specified in the publication. Control group participants could participate in the Cascade programme after a six-month waiting list period.

Patient–caregiver dyadic interventions

Andela 2017 tested the 'Patient and Partner Education Programme for Pituitary disease' (PEPP-pituitary). This was based on a standardised self-management programme originally developed for Parkinson's disease, and supplemented with information for fatigue, cognitive complaints, and problems with sexuality. It addressed psychological and social issues related to the disease and used techniques from CBT such as cognitive restructuring, situational behavioural analysis, social skills training, and relaxation training. The eight-week programme consisted of 90-minute sessions guided by a psychologist or medical social worker. Patients and caregivers participated in separate groups of five to seven participants. The sessions were titled: 1. information; 2. self-monitoring; 3. health promotion; 4. stress management; 5.

management of anxiety and depression/caregivers' challenge; 6. social competence; 7. social support; and 8. evaluation. Control group participants could take part in a single (optional) information meeting in week four or five and were given the option to take part in the PEPP-pituitary programme after the last assessment.

Dionne-Odom 2015 tested a dyadic intervention in the ENABLE III (Educate, Nurture, Advise, Before Life Ends III) trial. Based on their earlier ENABLE II palliative care intervention and exploratory interviews with family caregivers, caregivers were more closely involved in the new trial. The COPE framework (Creativity, Optimism, Planning, Expert Information) was applied in developing this coping skills intervention. In three weekly structured educational sessions, two different palliative care nurses supported both caregiver and patient. For caregivers, the first session covered the role of the caregiver, a definition of palliative and supportive care, and an introduction of problem-solving using the COPE framework. The second session covered caregiver self-care and effective partnering in patient care. The final session addressed building a support network, decision making and support, and advance care planning. At least once a month, the nurse would follow-up with telephone calls until patient death or study end. If the patient died during the study, a bereavement call was made. After a waiting list period of three months, participants in the control group could take part in the programme as well.

The programme tested by Klosky 2007a was based on CBT principles. During radiotherapy simulation, families randomised to the intervention group received a CBT-based programme including exposure to an interactive-educational ActiMates Barney, an educational video in the clinic room including filmed modelling, and passive distraction via Barney-narrated stories delivered during the simulation procedure. Families randomised to the control group received a similar intervention with exposure to a non-interactive children's character, an age-appropriate cartoon video picked by the child, and stories delivered via cassette tape during simulation.

Locke 2008 tested a dyadic intervention based on cognitive rehabilitation and problem-solving. In six sessions in a two-week period, a psychologist or behavioural therapist taught dyads to use a calendar that had a specific format as an external aid to compensate for cognitive symptoms. A model of stress was taught as well as specific positive problem-solving techniques for its management. Potential disease-related problems were covered (e.g. adverse effects, psychological distress, family issues, and sexual issues).

Primary and secondary outcomes

Caregiver-focused interventions

Boele 2013 assessed the primary outcomes of caregiver mastery (Caregiver Mastery Scale) and QoL (SF-36 Mental Component Summary) at baseline, two, four, six, and eight months' follow-up. Caregivers also completed questionnaires on patient functioning (QoL (SF-36); Medical Outcome Study (MOS) Subjective Cognitive Functioning scale; EORTC brain cancer module). Health economic effects were not assessed.

In Reblin 2018, the primary outcome was feasibility. They also assessed caregiver burden (Zarit Caregiver Burden Scale) and distress (HADS) at baseline, three weeks, and six weeks' follow-up. Caregiver completion of the intervention and satisfaction was also assessed. No patient well-being or health economic outcomes were included.

Safarabadi-Farahani 2016 assessed caregiver QoL (Caregiver QoL Index – Cancer, Persian version) at baseline, postintervention, and 30 days' follow-up. This questionnaire measured four scale scores: mental/emotional burden, lifestyle disruption, positive adaptation, and financial concerns, as well as an overall QoL score. Outcomes related to patient well-being or health economic effects were not included.

Wakefield 2016 were primarily interested in assessing feasibility (response and attrition rates, participant preference for intervention and questionnaire length; therapist's clinical impressions and technical difficulties) and acceptability (California Psychotherapy Alliance Scale-Group short version; Youth Satisfaction Questionnaire). Caregiver QoL (QoL – Family Caregiver Tool), psychological functioning (Depression Anxiety Stress Scale (DASS) Short Form), and family functioning (McMaster Family Assessment Device) were also assessed. Caregivers completed questions at baseline, two weeks, and six months. Outcomes related to patient well-being or health economic effects were not included.

Patient–caregiver dyadic interventions

Andela 2017 did not specify their primary/secondary outcomes. Caregiver measures included mood (Visual Analogue Scale – Mood), self-efficacy (General Self-efficacy Scale), illness perceptions (Brief Illness Perception Questionnaire), coping strategies (Utrecht Coping List), QoL (SF-36), fatigue (Multidimentional Fatigue Inventory), and anxiety and depression (HADS). Assessments took place at baseline, eight weeks, and six months. Patient outcomes included all of the above, plus bother and need for support (Leiden Bother and Needs Questionnaire), participation and autonomy (Impact on Participation and Autonomy), QoL (EQ-5D in addition to the SF-36), disease-specific QoL (AcroQol and CushingQol). Health economic effects were not measured.

Dionne-Odom 2015 did not specify which were their primary/secondary outcomes. Caregiver QoL (Caregiver QOL Index – Cancer), depression (CES-D), and caregiver burden (Montgomery-Borgatta Caregiver Burden) were reported in the main outcomes publication. Complicated grief (Prigerson Inventory of Complicated Grief – Short Form; Dionne-Odom 2016) and personality (Neo-3 Personality Inventory) were also assessed (confirmed via correspondence). Measurements took place at baseline and every six weeks until week 24, then every three months until patient death or student completion. Patient outcomes were reported in another publication (Bakitas 2015), and included: QoL (Functional Assessment of Chronic Illness Therapy – Palliative Care and Treatment Outcome Index), symptom impact (QoL at End of Life symptom impact sub scale), mood (CES-D), one year and overall survival, resource use and location of death (patient-reported hospital and intensive care unit (ICU) days, emergency department visits; from medical record review or proxy reports: decedents' data for period between last assessment and death, chemotherapy use in the last 14 days, location of death).

In Klosky 2007a, caregivers rated their anxiety (State-Trait Anxiety Inventory (STAI)) and completed a study-specific efficacy questionnaire. Assessments took place before and after the intervention, which was on the same day. Child outcomes were

reported elsewhere (Klosky 2004; Klosky 2007b; Tyc 2002): a behavioural observational checklist (modified from Observation Scale of Behavioral Distress) as completed by trained clinical observers; heart rate; sedation; state and trait anxiety (STAI) as completed by parents; and radiotherapy questionnaire to rate parents' expectations of their child's distress during radiotherapy. Health economic effects were not assessed.

The Locke 2008 study's primary outcomes were patients' compensation techniques (Compensation Techniques Questionnaire), patient and caregiver feedback (study- specific poststudy feedback questionnaire), and patient QoL and functional capacity (Functional Assessment of Cancer Therapy – Brain, Mayo-Portland Adaptability Inventory – 4). Secondary outcomes were patient cognitive functioning (Repeatable Battery for the Assessment of Neuropsychological Status), overall patient and caregiver QoL (Linear Analogue Self-Assessment scale), caregiver QoL (Caregiver QoL Index – Cancer), patient and caregiver mood (Profiles of Mood States (POMS)), and patient fatigue (Brief Fatigue Inventory). Health economic effects were not assessed. Assessments were done at baseline, postintervention, and three months' follow-up.

Statistical analysis

Caregiver-focused interventions

Boele 2013 analysed only the long-term effects (eight months' follow-up). Missing data (42.9%) were handled with the last observation carried forward method, missing data from within completed questionnaires were not imputed. All participants were included in analysis following the intention-to-treat principle. Delta scores for change in caregiver mastery and mental functioning were calculated and entered into a multivariate linear regression model together with patient's QoL, cognitive functioning, and neurological functioning.

Reblin 2018 used mixed models to analyse differences in distress, burden, and social support between the intervention group and control group at three and six weeks' follow-up, corrected for baseline scores. Attrition at three weeks was 7.5% (three participants dropped out in the intervention group; confirmed via correspondence), and was 20% at six weeks' follow-up. Missing data from within completed questionnaires were not imputed (confirmed via correspondence).

Safarabadi-Farahani 2016 checked for baseline differences in sociodemographic variables and QoL scores using Chi^2 and t-tests. Repeated measures analysis of variance was done to compare QoL scores at postintervention and 30 days' follow-up between the intervention and control group. This was not corrected for baseline scores. Questionnaires were checked by the research team directly after completion, resulting in no missing data (confirmed via correspondence).

Wakefield 2016 was a pilot study and not powered to evaluate the efficacy of the intervention. Preliminary analyses using a two (group: intervention versus waiting list) by three (time point: baseline versus postintervention versus follow-up) mixed analysis of variance were performed following the intention-to-treat principle. Caregivers who did not complete all three assessments were excluded from the psychosocial outcomes analysis. It is not clear how the authors handled missing data.

Patient–caregiver dyadic interventions

Andela 2017 compared mood ratings at pre- and postintervention with paired sample t-tests. Linear mixed models with random participant effect and fixed time and group effects were used to assess the effects of the intervention at eight weeks' and six months' follow-up, taking into account missing data (35% in caregivers). Post hoc analyses (linear mixed models) were performed with data from participants who attended at least six out of eight sessions (52% of caregivers). P values of 0.05 were considered statistically significant, but Bonferroni corrections were also applied ($P < 0.005$).

Dionne-Odom 2015 performed two longitudinal, intention-to-treat analyses. First, between-group differences in change from baseline to three months were examined for caregiver QoL, depressed mood, and burden. In the second analysis, data from caregivers of whom the patient had died were examined in a terminal-decline model with all data from the last 36 weeks of the patient's life. The exact statistical methods used are not specified further. The report stated that patterns of missing data were analysed and the authors referred us to another publication for further information (Bakitas 2015). Here, it is stated that maximum likelihood estimates were used to handle missing outcome data; however, it was unclear if the statistical methods applied would have been the same.

Klosky 2007a did not include a statistical methods paragraph; however, the main outcomes seem to be analysed using t-tests with a one-sided $P < 0.05$ as level of statistical significance. In email correspondence, the authors stated that the statistical methods should be included in the other publications on the same trial (Klosky 2004; Klosky 2007b; Tyc 2002).

The pilot study by Locke 2008 was primarily aimed at assessing the feasibility of the intervention. Recruitment rates, use of taught strategies, and patient satisfaction were analysed using descriptive statistics. Patient QoL and functional capacity were analysed using Wilcoxon signed rank tests (scores from the same group at different time points) and Wilcoxon rank sum tests (scores from different groups at the same time point). All other outcomes including caregiver outcomes were only displayed with descriptive statistics.

Excluded studies

See Characteristics of excluded studies table. Three studies were identified that met the inclusion criteria, but did not include a large enough proportion of family caregivers of patients diagnosed with a primary or secondary brain tumour. For the purpose of this review, the cut-off was set at 20% of the sample. Four further studies would potentially qualify but authors did not provide us with the number of family caregivers of brain tumour patients.

A 10-week online guided self-help programme based on CBT was tested in a Swedish population of parents of children on cancer treatment (Cernvall 2015; Cernvall 2017). The study showed promise in reducing post-traumatic stress symptoms in parents. Parents of children with brain tumours made up 15% of the sample.

The VOICE (Values and Options in Cancer Care) trial aimed to improve communication between people with advanced cancer, caregivers, and oncologists (Epstein 2017). Significant improvements in doctor–patient communication were found. The authors explained the study is likely to have included caregivers of

patients with primary or secondary brain tumours. However, it was unfeasible for the local team to retrieve exact numbers.

Holm 2016 tested a psychoeducational group intervention in family caregivers of patients in specialised palliative home care in Sweden. Preparedness for caregiving improved in 55% of participants randomised to the intervention (Holm 2017). We contacted the authors to enquire about the numbers of caregivers of patients with a brain or spinal cord tumour, but received no reply.

In an effort to prepare caregivers for the role of supporting patients with advanced cancer receiving home-based palliative care, a three-arm RCT was initiated comparing a one-to-one psychoeducational intervention with one or two visits, and a care as usual control group (Hudson 2013; Hudson 2015). There were no reductions in unmet needs or improvements in positive aspects of caregiving, but the intervention improved caregivers' level of preparedness and competence. Caregivers of patients with brain tumours were included, but only made up 1% of the sample (confirmed via correspondence).

A family therapy programme was trialled in people with advanced cancer and their family caregivers, which was continued into bereavement (Kissane 2016). Compared with standard care, the programme reduced the severity of complicated grief and the development of prolonged grief disorder. The authors confirmed via correspondence that only few, if any, caregivers of patients with a brain or spinal cord tumour were included (no exact percentage provided).

In Australia, the 'Rekindle' programme was tested in a phase II feasibility study (Lawsin 2017). This online programme aimed to provide psychosexual support to cancer patients and their partners. The study was found feasible, with varying levels of participant engagement with the programme. We contacted the authors to enquire about the numbers of caregivers of patients with a brain or spinal cord tumour, but we received no reply.

Finally, an abstract presented at the 2015 IPOS conference focused on an RCT of an automated remote symptom monitoring intervention versus care as usual for family caregivers providing home hospice care (Mooney 2015). Family caregivers reported their own issues as well as patients' symptoms and received automated tailored coaching. Moderate/high symptoms would generate an alert to a hospice nurse. Symptom severity decreased and anxiety and mood improved after the intervention. Family caregivers of patients with primary or secondary brain tumours made up 9% of the sample (confirmed via correspondence).

Ongoing studies

We identified five potentially relevant ongoing studies (Halkett 2015; Langbecker 2016; NCT03454295; Ownsworth 2015b; Roberge 2016; Characteristics of ongoing studies table).

Risk of bias in included studies

The Cochrane risk of bias score was determined for each trial and summarised 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.

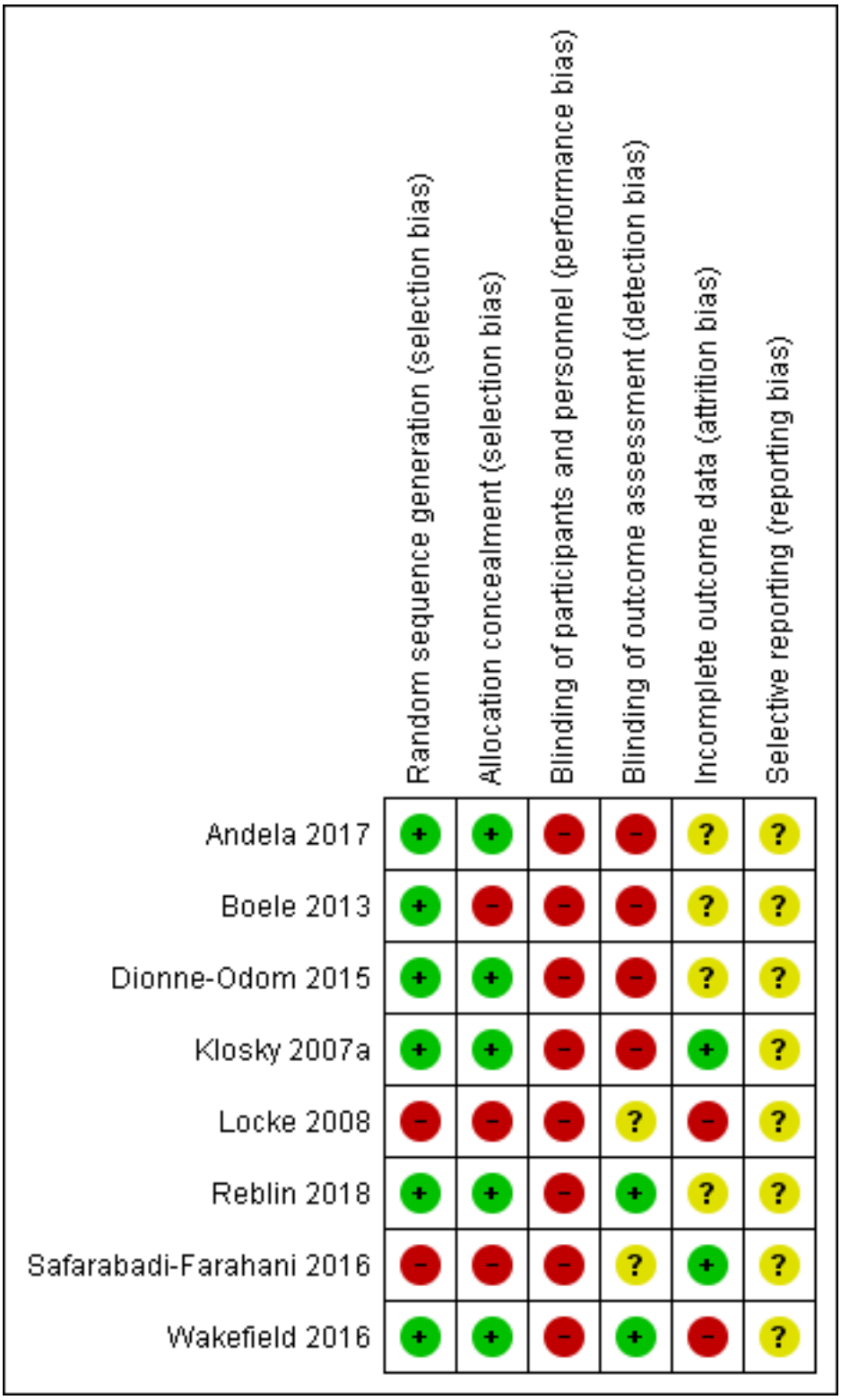
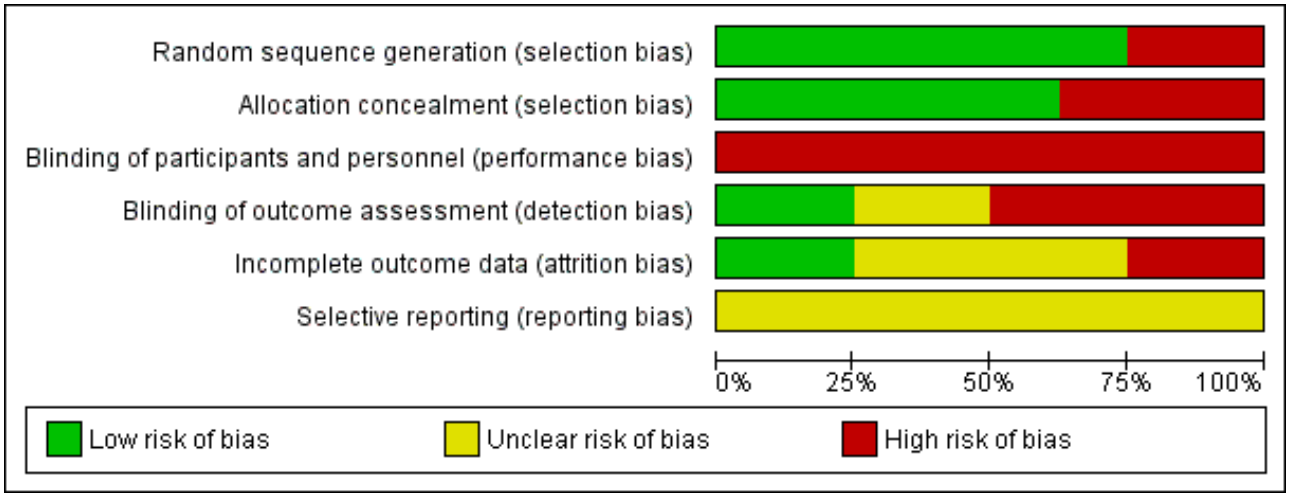


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Most studies described a random component in the sequence generation process. The Locke 2008 publication did not specify the randomisation technique used and was quasi-randomised, which introduced bias (high risk of bias). In the Safarabadi-Farahani 2016 study, a team member would number participants (0 to 65) and alternate allocation to the intervention or control group (confirmed via correspondence), leading to an increased risk of bias (high risk of bias). Selection bias may have also been introduced in Boele 2013, as tickets drawn from a concealed box were not numbered (high risk of bias).

Blinding

Blinding of participants and research personnel was generally not possible due to the nature of the interventions (high risk of bias). The person performing the statistical analysis was only blinded in the Wakefield 2016 and Reblin 2018 studies (low risk of bias). It was unclear whether the statisticians were blinded in the Locke 2008 and Safarabadi-Farahani 2016 studies (unclear risk of bias). This may have introduced performance and detection bias.

Incomplete outcome data

The Klosky 2007a study did not have any attrition, with the pre- and postintervention assessments taking place on the same day (confirmed via correspondence) (low risk of bias). In Safarabadi-Farahani 2016, only 4.6% of the sample dropped out in total, all due to patient death. For all other respondents, data were complete (confirmed via correspondence) (low risk of bias). The other studies report attrition ranging between 17% and 52%. The Boele 2013 study had the highest levels of attrition which were handled using the last observation carried forward method. They reported reasons for dropout (unclear risk of bias). In Andela 2017, 48% of caregivers did not complete all intervention sessions and there were 35% missing data in the caregiver group (confirmed via correspondence), which were handled through linear mixed modelling (unclear risk of bias). The Dionne-Odom 2015 reported about 32% of caregivers did not complete all follow-up assessments. There were no significant associations between attrition and caregiver characteristics or outcome, with maximum likelihood methods used to estimate missing outcome data (unclear risk of bias). In Locke 2008, 33% of participants did not complete the intervention, with a 26% dropout at postintervention increasing to 32% at three months. It was not reported how missing data were handled (high risk of bias). In Reblin 2018, 20% of participants did not complete the six-week follow-up assessment, with no information provided on reasons for dropout. No imputation was done within completed questionnaires (less than 10% of data was missing), hence missingness was only per person (confirmed via correspondence) (unclear risk of bias). In Wakefield 2016, there was 17% attrition at six months in the intervention group and 27% attrition in the control group. They did not report reasons for dropout and included only complete cases in their evaluation of psychosocial outcomes (high risk of bias).

Selective reporting

Wakefield 2016 was linked to a published protocol (Wakefield 2015). However, this protocol referred to the follow-up study, not the pilot. None of the other studies had published protocols available, leading to an unclear risk of reporting bias. In Boele 2013, caregiver burden data were collected but not used as many participants failed to complete the questionnaire in the intended way (unclear risk of bias). In the Dionne-Odom 2015 study, personality was assessed but not reported on (unclear risk of bias). The remaining studies were also at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Interventions to help support caregivers of people with a brain or spinal cord tumour

The heterogeneity of populations and methodologies used in the included studies hindered pooling of data and, therefore, meta-analysis was not carried out. See Summary of findings for the main comparison.

Primary outcomes

Caregiver psychological distress

We found low-certainty evidence that supportive interventions were more effective than any control condition. Across six studies, 163 neuro-oncology caregivers were included. Psychological distress was measured with six outcomes (DASS-21, the Fear of Recurrence Questionnaire – Family Member, CES-D, HADS, POMS, or STAI). Three trials reported improvements after the intervention (Dionne-Odom 2015: early versus delayed palliative care; CES-D between-group difference changed from baseline: mean –3.4 (SE 1.5); P = 0.02; *d* = –0.32; Klosky 2007a: interactive-educational programme; STAI State change score mean –19.6 (SD 3.3) intervention versus mean –14.5 (SD 2.7) control; Trait change score mean –13.5 (SD 2.9) intervention versus mean –6.9 (SD 2.6) control; Andela 2017: self-management programme; HADS Anxiety group by time interaction from baseline to six months (MD score –2.65), HADS depression group by time interaction from baseline to eight weeks and baseline to six months (MD: eight weeks: –2.60; six months: –3.47), HADS total score group by time interaction from baseline to eight weeks and baseline to six months (MD: eight weeks: –4.54; six months: –6.51; P < 0.05). Andela 2017 also compared mood (Visual Analogue Scale – Mood) before and after each session and reported caregivers' mood improved significantly after the last three sessions (mean: session six: from 73.00 (SD 6.95) to 77.17 (SD 6.46); P = 0.005; session seven: from 75.08 (SD 7.32) to 78.15 (SD 7.03); P = 0.025; session eight: from 73.08 (SD 6.09) to 77.54 (SD 7.66); P = 0.030).

Three feasibility/pilot trials also measured distress. In Reblin 2018, (electronic social network intervention) depression decreased after the intervention (mean: HADS depression scale: 9.795 with intervention versus 11.822 with control; F = 3.432; P = 0.072). There were no effects for anxiety. One trial found no significant effects (Wakefield 2016: e-mental health intervention; DASS-21; Fear of Recurrence Questionnaire – Family Member). The other trial only reported descriptives (Locke 2008; cognitive rehabilitation and problem solving), with POMS mean scores being the same postintervention in both groups. At three months, scores in control group were higher (mean 74 (SD 23.9) with control versus 73 (SD 16.1) with intervention).

Caregiver burden

There was low-certainty evidence that supportive interventions were not more effective than control conditions. One study that included a heterogeneous sample of 27 neuro-oncology caregivers (advanced cancer only; including those taking care of people with brain metastases) reported caregiver burden outcomes (Dionne-Odom 2015). There was no statistically significant difference between the groups for any of the Montgomery-Borgatta Caregiver Burden subscales (objective, demand, stress burden). A pilot study of electronic social network mapping found no differences over time in caregiver burden (Zarit Caregiver Burden Scale) between the intervention and control groups (Reblin 2018).

Caregiver mastery

Very low-certainty evidence found that psychological support was more effective than care as usual. In one study among 56 caregivers, mastery (Caregiver Mastery Scale) improved in the intervention group compared with the control group (ΔR^2 = 0.055, P = 0.021), corrected for the confounding factors of changes in patient's communication deficits (EORTC QLQ BN-20), cognitive functioning (MOS). and physical functioning (SF-36 Physical Component Summary) (Boele 2013). Self-efficacy and coping skills, concepts closely linked to mastery, did not improve in a self-management programme compared to controls (Andela 2017).

Quality of patient–caregiver relationship

Very low-certainty evidence found that a supportive e-mental health intervention was not more effective than a waiting list control condition (Wakefield 2016). This feasibility study, which included 13 parents of patients with a childhood brain tumour, showed no statistically significant difference on the McMaster Family Assessment Device family communication, problem-solving, and general functioning subscales.

Caregiver quality of life

We found very low-certainty evidence that supportive interventions were more effective than control conditions. Across six studies which included 157 neuro-oncology caregivers in total, two trials found improvements after intervention (Andela 2017: self-management programme; SF-36 Vitality sub scale group by time interaction from baseline to eight weeks and baseline to six months (MD: eight weeks: 14.03; six months: 15.45; P = 0.026); Safarabadi-Farahani 2016: psychosocial intervention; mean CQOLC total, mental/emotional burden, lifestyle disruption, positive adaptation sub scale scores higher than control group mean scores over time; all P < 0.001). One trial found stable QoL (SF-36 Mental Component Summary) in the intervention versus the control group (psychological support; Boele 2013), which was no longer statistically significant after controlling for changes in patient functioning. A trial and a pilot trial found no evidence for improvements in QoL after the intervention (Dionne-Odom 2015 using CQOLC; Wakefield 2016 using QoL – Family Caregiver Tool); one pilot trial only reported descriptive results (Locke 2008), with CQOLC scores appearing to improve slightly in both the intervention group (mean: from 95 (SD 20.1) at baseline to 98 (SD 19.5) postintervention) and control group (mean: from 93 (SD 174) at baseline to 102 (SD 11.7) postintervention).

Caregiver physical functioning

None of the included studies evaluated caregiver physical functioning.

Secondary outcomes

Patient emotional or physical well-being

Psychological distress (depression and anxiety)

There was no support for the effectiveness of caregiver support on reducing patient psychological distress. Three trials did not show statistically significant differences (Andela 2017: HADS; Dionne-Odom 2015 (Bakitas 2015): CES-D; Klosky 2007a: OBD). Andela 2017 did report improved mood (Visual Analogue Scale – Mood) after all intervention sessions except the first (before range: 65.27 to 70.76; after range: 73.11 to 77.93; all changes P < 0.0015). Klosky 2007a collected further data on STAI scores but did not report descriptive statistics or between-group changes. One trial only reported descriptive results, with POMS scores appearing to improve slightly in the intervention group (mean: baseline: 65 (SD 24.6); two weeks' follow-up: 72 (SD 7.0); three months' follow-up: 76 (SD 11.3)) and declining slightly in the control group (mean:

baseline: 81 (SD 2.3); two weeks' follow-up: 76 (SD 9.4); three months' follow-up: 79 (SD 8.7)) (Locke 2008).

Quality of life

There was little information for the effectiveness of caregiver support on improving patient QoL. Three studies found no statistically significant differences between the intervention and control groups for overall QoL (Andela 2017: EQ-5D, SF-36, CushingQol, AcroQol; Dionne-Odom 2015: FACIT-Pal; Locke 2008: FACT-BR), although Locke 2008 reported better scores after the intervention on the physical well-being sub scale (MD 3.25 95% CI 0.07 to 6.43; P = 0.04). Furthermore, Locke 2008 reported descriptive results on LASA scores, which appear to be comparable between the intervention and control groups over time. One trial collected further data on proxy-measured patient QoL, but did not report descriptive statistics or between-group changes (Boele 2013: SF-36).

Symptom management, number or severity (or both) of symptoms

No support was found for the effectiveness of caregiver support on patient symptom management. Two studies did not find statistically significant differences between the intervention and control groups (Dionne-Odom 2015: QoL at End of Life (QUAL-E) Symptom Impact sub scale; Locke 2008: Mayo-Portland Adaptability Inventory (MPAI-4)). Two studies assessed patient fatigue. Andela 2017 (Multidimentional Fatigue Inventory-20) reported no statistically significant differences. Locke 2008 (Brief Fatigue Inventory) reporting descriptive results indicating a slight improvement in the intervention group over time (mean: baseline: 4.4 (SD 2.5); two weeks' follow-up: 4.2 (SD 2.7); three months' follow-up: 3.2 (SD 2.8)), whereas scores seemed to improve for the control group at postintervention (mean: baseline: 2.6 (SD 3.0); two weeks' follow-up: 1.8 (SD 1.7)), and then deteriorate again at three months' follow-up (mean: 3.0 (SD 3.5)). Locke 2008 also assessed neuropsychological functioning (Repeatable Battery for the Assessment of Neuropsychological Status); however, results were not presented due to a lack of sufficient follow-up data. One trial further collected data on proxy-reported patient symptom burden (Boele 2013: EORTC QLQ-BN20 and MOS Cognitive Functioning scale), but did not report descriptive statistics or between-group changes.

Number of visits to the emergency department

There was no support for the effectiveness of caregiver support on the number of patient visits to the emergency department. Only one trial assessed this outcome (Dionne-Odom 2015). There was no significant difference between the early and delayed palliative care groups; however, the rate of resource use appeared to be lower in the early palliative care group (0.14, 95% CI 0.09 to 0.2) than in the delayed group (0.19, 95% CI 0.14 to 0.26).

Number and length of hospitalisations

There was no support for the effectiveness of caregiver support on the number and length of patient hospitalisations. Only one trial assessed this outcome and found no significant difference between the groups (Dionne-Odom 2015). However, hospital visits and ICU stays were less frequent in the early (rate of hospital days: 0.95, 95% CI 0.61 to 1.46; rate of ICU days: 0.1, 95% CI 0.04 to 0.24) versus delayed palliative care group (rate of hospital days: 1.3, 95% CI 0.91 to 1.86; rate of ICU days: 0.15, 95% CI 0.07 to 0.3).

Other relevant patient well-being outcomes

The self-management programme investigated by Andela 2017 found group by time interactions in patient self-efficacy with improvements in the control group (GSE MD: at eight weeks: 1.35; at six months: 1.74; both P < 0.05). Results for bother and need for support (various scales of the Leiden Bother and Needs Questionnaire for patients with pituitary disease (LBNQ-Pituitary)) were variable, showing some improvement at eight weeks after intervention, yet heightened scores indicating more bother at six months. Differences from baseline to six months were not statistically significant. There were no differences for illness perceptions (Brief Illness Perception Questionnaire (BIPQ)), coping (Utrecht's Coping List (UCL)), or participation and autonomy (Impact of Participation and Autonomy Questionnaire (IPA)). The early versus delayed palliative care intervention trialled by Dionne-Odom 2015 (Bakitas 2015) showed a 15% difference at one-year survival (63% early group versus 48% delayed group; P = 0.038). There was no statistically significant difference in overall median survival between the groups. The use of chemotherapy in the last 14 days of life was not statistically different between the groups. About 54% of people in the early group and 47% of people in the delayed group died at home.

Outcomes related to the health economic effects

None of the included studies reported outcomes related to health economic effects (e.g. caregiver or patient (or both) employment status; productivity loss at work; caregiver healthcare utilisation for acute or chronic (or both) conditions).

DISCUSSION

The aim of this review was to assess the effectiveness of supportive interventions at improving neuro-oncology caregiver well-being. The review included eight published studies.

Summary of main results

Overall, evidence was sparse. There was some evidence for positive effects of caregiver support on psychological distress, mastery, and QoL (low- to very low-certainty evidence). No studies reported significant effects on caregiver burden or quality of patient–caregiver relationship (low- to very low-certainty evidence). None of the studies assessed caregiver physical functioning. For secondary outcomes (patient emotional or physical well-being; health economic effects), we found very little to no evidence for the effectiveness of caregiver support interventions.

Overall completeness and applicability of evidence

None of the studies measured all of the primary outcomes in this review, and even fewer provided data on our secondary outcomes. Of note, none of the studies assessed caregiver physical functioning or health economics outcomes. The scarcity of data available was a major hindrance in assessing the effectiveness of caregiver support.

This review included trials from the US, Australia, the Netherlands, and Iran. The perspectives of non-Western countries was under-represented, which may be highly relevant as differences in cultural values including family obligations and social support networks could influence the family caregiving experience (Knight 2010).

We purposefully kept inclusion criteria broad, allowing any type of supportive intervention, any control group, tested in any

population which included at least 20% adult family caregivers who took care of a patient (of any age) with a primary or secondary brain or spinal cord tumour. As a result, there was significant heterogeneity in populations and interventions. Populations ranged from parental caregivers of childhood cancer survivors (three studies), to caregivers of patients with advanced cancer including brain metastases (one study), to caregivers of patients with pituitary disease (one study), to caregivers of adult patients with primary brain tumours (three studies); indicating a degree of heterogeneity in the caregiver–patient relationship, as well as patient disease and prognosis. None of the studies included caregivers of patients with spinal cord tumours. Four studies tested dyadic interventions which also involved the patient; four were focused solely on caregivers. A broad range of interventions was included: face-to-face support based on the principles of CBT, problem-solving skills training, psychoeducation or cognitive rehabilitation, or both; early access to palliative care which included coping skills training; and web-based programmes with or without guidance from a psychologist. Exposure to the intervention ranged from a single session taking 10 to 15 minutes to multiple sessions across three months, with one programme providing monthly follow-up telephone calls into the bereavement phase. Although beneficial for external validity, this heterogeneity precluded pooling of data and meta-analysis.

Quality of the evidence

We included seven RCTs and one quasi-RCT, which limited the overall potential selection bias. Together, these studies included 250 neuro-oncology caregivers (range within studies: 13 to 56). This highlights the main weakness of the state of the evidence – trials that are likely underpowered to measure the effectiveness of caregiver support in neuro-oncology introduce potential type II errors and make it difficult to draw conclusions on efficacy. Authors described three out of eight studies as 'pilot' or 'feasibility' studies, and in two cases it remained unclear whether these led on to larger-scale studies. The Wakefield 2016 study led on to a full RCT (Wakefield 2015). Due to the nature of supportive interventions, participant blinding is often not possible or desirable; however, more efforts could have been made to ensure that the person carrying out statistical analyses is naive to group allocation – which was only done in two out of eight studies. Participant attrition and lack of reported reasons may have introduced further (attrition) bias. Lack of published protocols led to unclear risk of reporting bias across all included studies.

Outcome measures assessed were not consistent between studies, with six out of eight studies measuring psychological distress and QoL, but only two studies assessed caregiver burden and mastery, and only one study assessed quality of patient–caregiver relationship. Where possible to assess this, study results seemed consistent with either no evidence of effect found, or a positive effect on caregiver well-being found. The GRADE certainty of evidence overall was low to very low, with the main reasons for downgrading being the small sample of neuro-oncology caregivers; and the heterogeneity of interventions and populations studied.

Potential biases in the review process

We have searched three databases, handsearched relevant conference abstracts since 2013, and articles published since 2017 in the two main journals in the field. We searched for ongoing trials and contacted known experts in the field. Despite this rigorous review process, it may still be possible that we did not identify all eligible trials, in particular when the protocol or results were published after our updated search date (August 2018). Therefore, regular updates of this review are needed.

Agreements and disagreements with other studies or reviews

In general, this Cochrane Review highlighted a scarcity of RCTs investigating support for family caregivers in neuro-oncology. This lack of literature mirrors the findings of other systematic (Langbecker 2015; Madsen 2011; Piil 2016; Russell 2014; Sterckx 2013), and non-systematic (Boele 2017b; Sherwood 2016), reviews that include neuro-oncology caregiver studies, all concluding that more research is required on caregivers' unmet needs and the effectiveness of specific programmes to support neuro-oncology caregivers.

There is some additional literature on non-controlled efforts to improve neuro-oncology caregivers' well-being. Programmes include nurse-led interventions, support groups, caregiver workshops, psycho-education, patient navigation or care co-ordination, use of a telephone hotline or brain tumour website, and a dyadic yoga programme (Boele 2017b; Langbecker 2015; Milbury 2018; Sherwood 2016). These generally show encouraging results such as good uptake percentages and qualitative evidence of increased family autonomy; however, these still need to be evaluated in a randomised controlled setting.

There has been similar research of other family caregiver populations. In caregivers of people with terminal illness, one Cochrane systematic review concluded that support may help reduce caregivers' psychological distress (Candy 2011). Another Cochrane systematic review on non-pharmacological interventions for caregivers of people with stroke concluded that too few high-quality RCTs had been published to determine effectiveness (Legg 2011). In cancer caregivers, one systematic review reporting on 49 intervention studies (not all RCTs) concluded that 65% of the interventions led to positive and significant improvements in caregiver or patient well-being (Applebaum 2013). A state of the science review supported this and stressed the need for guidelines to advocate changes in clinical practice (Northouse 2012).

The samples of studies included in our Cochrane Review consisted of very few caregivers of patients with brain metastases and none of the studies included caregivers of patients with spinal cord tumours. Two systematic reviews similarly reported that very little is known about the burden and support needs of patients with brain metastases and their family caregivers (Magbool 2017; Saria 2017). We are not aware of any systematic reviews which have included support needs or interventions for caregivers of patients with spinal cord tumours. In adults, most systematic reviews focus on family caregivers of patients with a high-grade primary malignant brain tumour (Piil 2016; Russell 2014; Sterckx 2013), which seems reflected in the samples of the studies included in this review.

This pattern is generally mirrored in the series of guidelines published by the European Association for Neuro-Oncology (EANO). For example, the guidelines on meningiomas (Goldbrunner 2016), ependymal tumours (Ruda 2017), and brain metastases (Soffietti 2017) did not mention caregiver support, whereas the guidelines for adults with astrocytic or oligodendrial tumours (Weller 2017) briefly acknowledged the importance of supporting

family caregivers. The palliative care guidelines refer to caregiver needs throughout (Pace 2017).

Of note, although it is commonly emphasised that support should not end after the patient has deceased (Petruzzi 2015; Piil 2019), only one of the included studies in this Cochrane Review continued to provide some support after the death of the patient (Dionne-Odom 2015).

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide the evidence required to demonstrate whether support for caregivers of people diagnosed with a brain or spinal cord tumour is effective. The eight trials included were of small size, included heterogeneous populations, and investigated effectiveness of a variety of different supportive interventions. The overall GRADE certainty of evidence was low to very low. Importantly, no evidence of effect does not equate to evidence of no effect. There is increased attention for supporting caregivers, and indeed, new evidence for research is emerging with five ongoing studies identified during this review. Should a family caregiver express the need for support, best practice would suggest that the relevant member of the treatment team would discuss the lack of evidence with the caregiver, document their views, and use their clinical judgement to provide recommendations for support available in their area.

Implications for research

Adequately powered randomised controlled trials are necessary to determine the effectiveness of caregiver support in neuro-oncological populations, including spinal cord tumours and secondary brain tumours. Important research questions remain.

- Is caregiver support effective in improving caregiver emotional or physical well-being (e.g. psychological distress; caregiver burden; caregiver mastery; quality of patient–caregiver relationship; quality of life (QoL); physical functioning)?
- Is caregiver support effective in improving patient emotional or physical well-being (e.g. psychological distress; QoL; symptom management; number or severity (or both) of symptoms; number of emergency department visits or hospitalisations (or both))?
- Are there health economic effects associated with caregiver support (e.g. caregiver/patient employment status; productivity loss at work; caregiver healthcare utilisation)?

To reduce potential risk of bias and improve the certainty of evidence, future studies should ideally include caregivers from non-Western countries, taking care of people with any brain or spinal cord tumour, including secondary tumours. Study protocols should be published in advance and care should be taken to apply blinding where possible (i.e. ensure the person carrying out statistical analysis is naive to group assignment). Attrition and other missing data should be adequately reported and handled. To increase the likelihood of a possible meta-analysis, reporting should follow CONSORT guidelines.

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CHARACTERISTICS OF STUDIES

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

Andela 2017

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** patients in follow-up for pituitary disease in a stable medical situation and their partners **Exclusion criteria:** aged < 18 or > 75 years, receiving intensive medical treatment, or have psychiatric illness **Number randomised:** 188 patients (174 included in analysis). Number of caregivers randomised not specified, but 63 were included in the analysis (25 intervention group, 38 control group). **Follow-up:** baseline, 8 weeks, 6 months **Setting:** 2 university medical centres in The Netherlands
Interventions	**Intervention group:** self-management programme drawing on techniques from CBT consisting of 8 weekly sessions of 90 minutes, guided by psychologists and medical social workers. Patients and caregivers participated in separate groups of 5–7 participants. Sessions were named: 1. information; 2.

Andela 2017 *(Continued)*

	self-monitoring; 3. health promotion; 4. stress management; 5. management of anxiety and depression/caregivers' challenge; 6. social competence; 7. social support; 8. evaluation. **Control group:** single (optional) information meeting in week 4 or 5
Outcomes	**Caregiver outcomes** • Mood (Visual Analogue Scale – Mood) • Self-efficacy (General Self-Efficacy scale) • Illness perceptions (Brief Illness Perception Questionnaire) • Coping strategies (the Utrecht Coping List) • QoL (SF-36) • Fatigue (Multidimensional Fatigue Inventory-20) • Anxiety and depression (Hospital Anxiety and Depression Scale) **Patient outcomes** • Mood (Visual Analogue Scale – Mood) • Self-efficacy (General Self-Efficacy scale) • Bother and need for support (Leiden Bother and Needs Questionnaire – Pituitary) • Illness perceptions (Brief Illness Perception Questionnaire) • Coping strategies (the Utrecht Coping List) • Participation and autonomy (Impact on Participation and Autonomy) • QoL (SF-36, EQ-5D) • Fatigue (Multidimensional Fatigue Inventory-20) • Anxiety and depression (Hospital Anxiety and Depression Scale) • Disease-specific QoL (AcroQol, CushingQol)
Notes	22% neuro-oncology (63 caregivers, 25 randomised to the intervention, and 38 to the control group. 14 caregivers of patients with brain tumours participated).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described in the report. Patients were randomised using a computer-generated scheme. Caregivers were assigned to the same group. Confirmed via correspondence.
Allocation concealment (selection bias)	Low risk	Not described in the report. Computer random number generator used (confirmed by authors).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described in the report. Analyses were not performed blind (confirmed via correspondence).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described in the report. Level of missing data was 35% in caregivers (confirmed via correspondence), analysed with linear mixed models. 48% of caregivers did not complete all intervention sessions.
Selective reporting (reporting bias)	Unclear risk	No published protocol. All caregiver outcomes in the manuscript were reported on.

Boele 2013

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** informal caregivers (i.e. a spouse or significant other providing at least 21 hours of care a week) of patients with a high-grade (WHO grade III or IV) glioma; aged > 18 years; providing written informed consent **Exclusion criteria:** patient life expectancy < 3 months; caregiver was unable to complete questionnaires due to insufficient mastery of the Dutch language or severe visual impairments; caregiver was unable to understand or apply the skills taught in the intervention due to physical or mental condition(s). **Number randomised:** 56: intervention group 31; control group 25 **Follow-up:** 8 months **Setting:** 3 tertiary referral centres for neuro-oncology patients in The Netherlands
Interventions	**Intervention group:** 6 × 1-hour face-to-face sessions with a psychologist, on a fortnightly basis, based on CBT and psychoeducation principles. First, the patient's symptoms and the caregiver's involvement were reviewed, and based on a prioritisation of the need for help to assist with patient symptoms, the psychologist and caregiver drew upon a predefined set of strategies. During the first session, patient and caregiver history and current functioning was documented. During the second session, an introduction of the intervention and rationale behind CBT was given. For the next 4 sessions, caregivers could make a selection of topics they wanted to discuss. Options were: 1. contact with the patient; 2. the direct environment (contact with family, friends, and others); 3. epilepsy; 4. changes in behaviour, character, and cognition; 5. time for yourself; 6. children (what and how to tell them); 7. practical and emotional care in the end of life phase. **Control group:** care as usual
Outcomes	**Caregiver outcomes** • Caregiver mastery (Caregiver Mastery Scale) • QoL (SF-36) *Outcomes not reported on* (confirmed via correspondence) • Caregiver burden (Caregiving Demands Scale) **Patient outcomes (by proxy):** • QoL (SF-36) – subjective cognitive functioning (MOS Subjective Cognitive Functioning Scale) • Disease-specific symptoms (EORTC BN20)
Notes	100% neuro-oncology (56 participants, intervention group 31; control group 25)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used concealed randomisation technique – drawing a ticket from a concealed box (confirmed by authors).
Allocation concealment (selection bias)	High risk	Tickets were not numbered (confirmed by authors).

Boele 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Analyses were not performed blind (confirmed by authors).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High dropout rates (52% in intervention group; 32% in control group at 8 months' follow-up). Analysed with last observation carried forward method.
Selective reporting (reporting bias)	Unclear risk	There was no published study protocol. All outcomes in the manuscript were reported on. Caregiver burden data were collected but deemed unreliable (confirmed by authors).

Dionne-Odom 2015

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** family caregiver ('a person who knows you well and is involved in your medical care') of a patient who: was aged > 18 years; had new diagnosis, recurrence, or progression of an advanced-stage cancer within about 30–60 days of the date the patient was informed of the diagnosis by his or her oncology clinician; and had an oncologist-determined prognosis of 6–24 months; was English speaking; was able to complete baseline questionnaires. **Exclusion criteria:** scored < 4 on the Callahan Cognitive Screen; had an untreated axis 1 psychiatric condition or an active substance-use disorder; or had uncorrectable hearing disorder or unreliable telephone service. No additional exclusion criteria for caregivers. **Number randomised:** 124 dyads (63 early intervention; 61 delayed intervention) **Follow-up:** by telephone, once every 6 weeks until 24 weeks; then every 3 months until end of study or patient death. Not all were followed up after 24 weeks. **Setting:** participants were recruited from a cancer centre (and affiliated outreach clinics) and a medical centre in the US.
Interventions	**Intervention group:** 3 structured 1-to-1 telephone sessions (with guidebook; once a week) between an advanced-practice palliative care nurse coach and a caregiver. Session 1 addressed taking on the caregiver role, defined palliative and supportive care, and introduced problem-solving using the framework of the COPE attitude. Session 2 covered caregiver self-care and effective partnering in patient symptoms assessment and management. Session 3 addressed the building of a support team, decision making, decision support, and advance care planning. Sessions lasted on average 23 minutes, and the same nurse coaches followed up with participants monthly until end of study or patient death. **Control group:** no treatment but could take part in the intervention after 3 months.
Outcomes	**Caregiver outcomes** • QoL (Caregiver QoL Scale – Cancer) • Depression (Center for Epidemiologic Study – Depression Scale) • Caregiver burden (Montgomery-Borgatta Caregiver Burden Scale) *Outcomes reported elsewhere* (Dionne-Odom 2016): • Complicated grief (Prigerson Inventory of Complicated Grief – Short Form)

Dionne-Odom 2015 *(Continued)*

	Outcomes not reported on (confirmed via correspondence): • Personality traits (NEO Personality Inventory-3) **Patient outcomes** (Bakitas 2015): • QoL (Functional Assessment of Chronic Illness Therapy – Palliative Care; Treatment Outcome Index) • Symptom impact (QoL at End of Life Symptom Impact sub scale) • Mood (Center for Epidemiologic Studies – Depression Scale) • 1-year and overall survival • Resource use and location of death (hospital and intensive care unit days, emergency department visits, period between last assessment and death, chemotherapy use in last 14 days, location of death)
Notes	Published and unpublished data. 22% neuro-oncology (124 participants, 63 to the intervention group and 61 to the control group. In total, 27 caregivers of patients with brain tumour were included (3 primary brain tumour; 24 secondary brain tumour; confirmed via correspondence). ENABLE III (Educate, Nurture, Advise, Before Life Ends III) trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described in the report. Patients were randomised 1:1 using a computer-generated scheme. Caregivers were assigned to the same group. Confirmed via correspondence.
Allocation concealment (selection bias)	Low risk	Not described in the report. Computer-generated randomisation after enrolment, confirmed by authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Analyses were not performed blind (confirmed via correspondence).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout: about 32% of caregivers did not complete all follow-up assessments; analyses revealed no significant associations between attrition and measured caregiver characteristics or outcome. Maximum likelihood methods were used to estimate missing outcome data.
Selective reporting (reporting bias)	Unclear risk	There was no published study protocol. All outcomes specified in the manuscript were reported on; 1 additional outcome (complicated grief) was reported in 2016 publication; personality was assessed but not reported on. Authors confirmed no other outcomes were collected.

Klosky 2007a

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** parents with a child aged 2–7 years diagnosed with a primary malignancy; English was primary language; no prior experience with external beam radiotherapy; who were functioning at the level in which the children could tolerate radiotherapy intervention.

Klosky 2007a *(Continued)*

	Exclusion criteria: not specified. **Number randomised:** 80 (41 intervention group, 39 control group). **Follow-up:** until the final day of radiotherapy simulation (not further specified). Communication with authors revealed that this was, in most cases, approximately a 90-minute interval between baseline and post assessment. **Setting:** radiotherapy outpatient clinic in the US.
Interventions	**Intervention group:** CBT package that included exposure to an interactive-educational ActiMates Barney, an educational video in the clinic room including filmed modelling, and passive auditory distraction via Barney-narrated stories delivered during the simulation procedure. **Modified control group:** similar intervention composed of exposure to non-interactive children's control character (similar size, colour, and shape to Barney), an age-appropriate cartoon video, and storied delivered via cassette tape during treatment.
Outcomes	**Caregiver outcomes** • Anxiety (State-Trait Anxiety Inventory) • Opinions about efficacy of radiotherapy and aspects of the experimental conditions (study specific Parent Exit questionnaire) **Patient outcomes** • Sedation (anaesthesia administered) • Behavioural distress (Observation Scale of Behavioral Distress) • Physiological arousal (heart rate) • Anxiety (State-Trait Anxiety Inventory)
Notes	Primary child outcomes were published previously (Klosky 2004; Klosky 2007b; Tyc 2002). 67% neuro-oncology (80 participants, 41 intervention, 39 control. In total, 53 caregivers of people with brain tumours were included).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described in the report. Computer random number generator used (confirmed by authors).
Allocation concealment (selection bias)	Low risk	Not described in the report. Computer random number generator used (confirmed by authors).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described in the report. The authors explained that participants were not fully aware of study goals and would, therefore, not know whether they were assigned to the intervention or modified control group. However, they were not formally blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described in the report. The authors could not remember exactly how data analysis was performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not described in the report, authors confirmed that there was no attrition and all participants completed the outcome measures.

Klosky 2007a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	There was no published study protocol. All outcomes in the manuscript were reported on; other (patient-focused) outcomes were published elsewhere.

Locke 2008

Methods	Quasi-randomised controlled trial
Participants	**Inclusion criteria:** people with newly diagnosed primary brain tumour eligible for radiotherapy and aged > 18 years; have mild-to-moderate cognitive impairment; have a prognosis of ≥ 6 months and ability to attend sessions at the medical centre for 2 weeks. All patients were required to have a designated caregiver available to attend all sessions. **Exclusion criteria:** none specified. **Number randomised:** 16 (9 intervention group, 7 control group). 3 more were not randomised but allocated to the intervention group. **Follow-up:** baseline, 2 weeks, 3 months **Setting:** tertiary medical centre in US
Interventions	**Intervention group:** received cognitive rehabilitation and problem solving. Cognitive rehabilitation: dyads were taught to use a calendar that had a specific format as an external aid to compensate for cognitive symptoms. 6 × 50-minute sessions over 2-week period. Specific goals were developed for each session. Problem solving: teaching dyads a model of stress and a specific problem-solving technique for its management. 6 × 50-minute sessions over 2-week period, delivered concurrently with the cognitive rehabilitation intervention. **Control group:** standard medical care
Outcomes	**Caregiver outcomes** • Study feedback (study-specific Post-Study Feedback Questionnaire) • QoL (Linear Analogue Self-Assessment Scale; Caregiver QoL Index-Cancer) • Distress (Profile of Mood States) **Patient outcomes:** • Compensation techniques (The Compensation Techniques Questionnaire) • Study feedback (study-specific Post-Study Feedback Questionnaire) • QoL and functional capacity (Functional Assessment of Cancer Therapy – Brain; Mayo-Portland Adaptability Inventory-4; Linear Analogue Self-Assessment Scale) • Cognitive functioning (Repeatable Battery for the Assessment of Neuropsychological Status) • Distress (Profile of Mood States) • Fatigue (Brief Fatigue Inventory)
Notes	100% neuro-oncology (16 participants, 9 intervention group, 7 control group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation not described. Last 3 participants enrolled were not randomly allocated.

Locke 2008 *(Continued)*

Allocation concealment (selection bias)	High risk	Last 3 participants enrolled were not randomly allocated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not described in the report, but blinding was likely not possible due to nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates: 26% at postintervention; increased to 32% at 3 months' follow-up. 33% did not complete the intervention. Not clear how missing data were handled, presumably not included in analysis.
Selective reporting (reporting bias)	Unclear risk	There was no published study protocol. All outcomes in the manuscript were reported on.

Reblin 2018

Methods	Randomised controlled trial (pilot)
Participants	**Inclusion criteria:** identified as the person who provided the most care for an adult diagnosed with primary malignant brain tumour; English speaking and reading; having an email address; aged >18 years **Exclusion criteria:** none specified. Authors clarified there were no specific exclusion criteria, other than not meeting inclusion criteria. **Number randomised:** 40; 30 intervention group, 10 control group **Follow-up:** baseline, 3 weeks, 6 weeks **Setting:** National Cancer Institute-designated comprehensive cancer centre in the US
Interventions	**Intervention group:** eSNAP, a web-based application which takes 10–15 minutes to help caregivers list people or groups who could help within 6 categories of support: 1. hands-on; 2. informational; 3. communication; 4. financial; 5. emotional; and 6. self-care. A network visualisation was provided to caregivers in PDF/print. **Control group:** care as usual
Outcomes	**Primary outcome** (confirmed by authors) • Feasibility (recruitment and retention rates) **Secondary outcomes:** • Caregiver burden (Zarit Caregiver Burden Scale) • Distress (Hospital Anxiety and Depression Scale) • Use of eSNAP (yes/no question of whether participants had reviewed their network visualisation; • Satisfaction (single item from 1 (not at all satisfied) to 5 (very satisfied)
Notes	100% neuro-oncology (40 participants; 30 intervention group, 10 control group
Risk of bias	

Reblin 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation not described in the report. Computer random number generator used (confirmed by authors).
Allocation concealment (selection bias)	Low risk	Not described in the report. Computer random number generator used (confirmed by authors).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described in the report. Analysis were performed blind (confirmed by authors).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	20% attrition at 6 weeks. No information provided on reasons for dropout or how missing data were handled in the report. Authors confirmed that within those who completed assessments, < 10% of data were missing and no data imputation was done.
Selective reporting (reporting bias)	Unclear risk	No published protocol

Safarabadi-Farahani 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** primary caregivers of a child with active cancer were eligible if: they were residents of Tehran; aged > 18 years; patient started treatment process; child aged < 14 years; had access to a telephone at home; and were willing to participate and provide written consent. **Exclusion criteria:** none specified **Number randomised:** 65 randomised, 3 withdrew due to patient death; 31 intervention group, 31 control group. **Follow-up:** baseline, postintervention, 30 days **Setting:** hospital and rehabilitation complex in Tehran, Iran
Interventions	**Intervention group:** the Brief Psychosocial Intervention plus usual support services. Caregivers were provided with information and support through individual counselling sessions delivered by a trained social worker in 60–90 minutes. Specified sessions goals were: 1. engage and motivate caregivers to participate and develop open communication with social worker; 2. develop optimistic attitude, help maintain hope and focus on achievable short-term goals; 3. provide information about treatments and medication, help caregivers learn to live with uncertainty; 4. help caregivers cope with stress and teach stress-relieving techniques, coping strategies, and healthy lifestyle behaviours; and 5. educate self-care strategies. After each session, caregivers received a homework assignment. Every session was followed up with a telephone call (30–45 minutes). **Control group:** usual services, including counselling and financial support
Outcomes	• QoL (Caregiver QoL Index Cancer, Persian version)

Safarabadi-Farahani 2016 *(Continued)*

Notes	48% neuro-oncology (65 participants randomised, 31 intervention group, 31 control group. In total, 31 caregivers of patients with brain tumours were included).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation not described in the report. Authors clarified that a member of the team would alternate group allocation in consecutive participants (i.e. sequence was not random).
Allocation concealment (selection bias)	High risk	Not described in the report ('centrally randomised'). Based on the author's explanations, we concluded that allocation concealment was not realistically possible.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if statistician was blinded. Authors explained that statistician was not in contact with cases, and would only see study case numbers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 study participants dropped out before the baseline assessment. No further information on attrition or how missing data were handled in the report. Authors confirmed that there was no missing data (all questionnaires were checked directly following completion) and that no further attrition took place.
Selective reporting (reporting bias)	Unclear risk	No published protocol.

Wakefield 2016

Methods	Randomised controlled trial
Participants	**Inclusion criteria:** parents of children who had finished cancer treatment were eligible if they: had a child aged ≤ 15 who had completed cancer treatment with curative intent in the past 5 years; were able to read English; were able to access the Internet in a private location. **Exclusion criteria:** parents could not participate if they: had insufficient English skills; were experiencing extreme anxiety or depression; endorsed current symptoms of psychosis or substance abuse; had a child who was on active treatment, had relapsed, or was in palliative care **Number randomised:** 56 consented and randomised (before baseline), 9 dropped out before baseline assessment. 25 intervention group; 22 control group. **Follow-up:** baseline, 2 weeks, 6 months **Setting:** children's hospital in Australia
Interventions	**Intervention group:** Cascade is a manualised programme consisting of 3 weekly 120-minute online sessions delivered by a psychologist through WebEx. Driven by the theoretical models, Cascade targets intra- and interpersonal psychological processes important to adaptation in the context of illness (e.g. acceptance of uncertainty; practical problem solving; mobilising social support resources). CBT strategies were used to target these core mechanisms of change. Topic areas were derived from a pre-

Wakefield 2016 *(Continued)*

	vious study (but not specified in paper). After each session, parents would get homework assignments to practice. **Control group:** waiting list control group, parents could participate in Cascade intervention after 6 months.
Outcomes	• Feasibility (80% completion rate would indicate feasibility; preference for length of intervention and questionnaires; clinical impressions and technical difficulties) • Acceptability (California Psychotherapy Alliance Scale-Group short version and Youth Satisfaction Questionnaire • QoL (QoL – Family Caregiver Tool) • Family functioning (McMaster Family Assessment Device)
Notes	28% neuro-oncology (47 participants; 25 intervention group, 22 control group. In total, 13 caregivers of brain tumour patients were included).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent personnel used an electronic randomiser to allocate participants to Cascade or waiting list.
Allocation concealment (selection bias)	Low risk	Independent personnel used an electronic randomiser to allocate participants to Cascade or waiting list.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible due to nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The statistician remained blinded until all analyses were completed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants with all 3 assessments completed were included in analysis of psychosocial outcomes (17% dropout at 6 months in intervention group; 27% dropout in waiting list control group). Unclear what reasons were.
Selective reporting (reporting bias)	Unclear risk	There was no published study protocol. All outcomes in the manuscript were reported on.

BPI: Brief Psychological Intervention; CBT: cognitive behavioural therapy; COPE: Creativity, Optimism, Planning, Expert Information; EORTC BN20: European Organization for Research and Treatment of Cancer Brain Cancer Module; EQ-5D: EuroQol; MOS: Medical Outcome Study; NEO: Neuroticism-Extraversion-Openness; QoL: quality of life; SF-36: 36-item Short Form; WHO: World Health Organization.

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

Study	Reason for exclusion
Cernvall 2015	< 20% of the study sample were neuro-oncology family caregivers (15%).
Epstein 2017	Unknown percentage of neuro-oncology caregivers.
Holm 2016	Unknown percentage of neuro-oncology caregivers.

Study	Reason for exclusion
Hudson 2015	< 20% of the study sample were neuro-oncology family caregivers (1%).
Kissane 2016	< 20% of the study sample were neuro-oncology family caregivers (no exact percentage).
Lawsin 2017	Unknown percentage of neuro-oncology caregivers.
Mooney 2015	< 20% of the study sample were neuro-oncology family caregivers (9%).

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

Halkett 2015

Trial name or title	Care-IS trial
Methods	Multicentre prospective phase III randomised controlled trial
Participants	Adult primary carers of a patient with high-grade glioma who 1. is currently undergoing active treatment and is within 2 months of diagnosis; and 2. is currently attending the outpatient departments of 1 of the participating sites. The caregiver should furthermore 1. aged >18 years; 2. understand and speak English; 3. have no mental, cognitive, or functional disability; 4. be willing and able to comply with study requirements; 5. have no familial, sociological, or geographical condition that might hamper compliance; 6. have no severe intercurrent medical or psychotic disease that would hinder the ability to participation in the study.
Interventions	The Care-IS intervention is guided by a nurse and will consist of: 1. a telephone needs assessment; 2. access to a tailored resource file for the caregiver based on the needs that had been identified; 3. an educational and supportive home visit from the nurse; 4. monthly telephone check-ups.
Outcomes	**Primary outcomes** • Caregiver preparedness (Preparedness for Caregiving Scale) • Caregiver distress (Distress Thermometer) **Secondary outcomes** • Anxiety and depression (Hospital Anxiety and Depression Scale) • QoL (Caregiver QoL Index – Cancer) • Caregiver competence (Carer Competence Scale) • Supportive care needs (Partner and Caregivers Supportive Care Needs Scale/Brain Tumour Specific Supportive Carer Needs for Carers Survey) • Health economic cost-consequences (checklist of services used)
Starting date	2015
Contact information	G.Halkett@curtin.edu.au
Notes	

Langbecker 2016

Trial name or title	Online psychoeducational intervention for family caregivers of high-grade primary brain tumour patients
Methods	Under development. Expected to be tested in a randomised controlled setting following pilot work (commencing 2019). Phase I: qualitative evaluation of acceptability of the intervention and make modifications Phase II: single-arm pre–post study to evaluate usability, feasibility, and acceptability
Participants	Family caregivers of people with high-grade glioma
Interventions	Online psychoeducational intervention based on social cognitive theory.
Outcomes	Not yet specified.
Starting date	2019
Contact information	d.langbecker@uq.edu.au
Notes	Confirmed as accurate 24 January 2019

NCT03454295

Trial name or title	Improving palliative care of caregivers of patients with glioblastoma
Methods	Randomised controlled trial
Participants	**Inclusion criteria** *Phase I: focus group with GBM caregivers* 1. English-speaking, due to the focus groups being managed in English and the use of certain validated questionnaires only being available in English; 2. aged > 18 years; 3. caregiver to patient with GBM who died ≥ 1 year ago. *Phase II: randomised intervention of GBM caregivers* 1. English-speaking; 2. current caregiver to a patient with GBM; 3. aged > 18 years; 4. score > 4 on the Distress Thermometer and indication that this distress is related in some way to the caregiving role per self-report. **Exclusion criteria** 1. In the judgement of the consenting professional, clinician or principal investigator, or as per medical record, severe psychopathology or cognitive impairment likely to interfere with the participation or completion of the protocol or ability to provide meaningful information; 2. another family member or caregiver to the same patient is currently enrolled in the study.
Interventions	**Intervention:** MCP-C. MCP-C is based on the principles of Viktor Frankl's Logotherapy. It is designed to help caregivers of patients with advanced cancer sustain or enhance a sense of meaning, peace, and purpose in their lives. MCP-C is structured as a 7-session (1-hour weekly or biweekly sessions) individual intervention that utilises a mixture of didactics, discussion, and experiential exercises that focus around particular themes related to meaning and cancer caregiving. **Control:** enhanced usual care. The 'enhancement' to usual care in this study involves the inclusion of screening and targeted referral components. Research study assistants conducting the screening and providing feedback and referrals will be trained in the National Comprehensive Cancer Net-

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	work guidelines for distress management and will discuss the screening results and associated recommendations with the study principal investigator.
Outcomes	**Aim 1:** determine the feasibility, acceptability, and preliminary effects of MCP-C delivered to caregivers of patients with GBM. **Aim 2:** to customise the content and format of the MCP-C to address the unique existential and psychosocial needs of caregivers of patients with GBM
Starting date	12 February 2018
Contact information	ApplebaA@mskcc.org
Notes	Confirmed as accurate 21 January 2019. Phase I is completed, phase II has thus far recruited 10 caregivers.

Ownsworth 2015b

Trial name or title	Making sense of brain tumor program
Methods	Randomised wait-list controlled trial
Participants	Aged ≥ 18 years; diagnosed with a primary brain tumour; living within a 1-hour drive of Brisbane; adequate communication skills; able to provide informed consent. Approximately 60% of the 27 participants in the intervention group and 23 participants in the wait-list control group had a family member involved in their programme.
Interventions	10 × 1-hour weekly sessions for people with brain tumours, guided by a therapist. Their family members were encouraged to be involved as well. During the first 2 sessions, participants described their diagnosis, treatment, and functional changes and set 3–5 goals to focus on. Treatment modules included psychoeducation, neuropsychological feedback, cognitive rehabilitation, psychotherapy, and couple and family support. The last session is used to reflect on the progress and making plans for maintaining and ongoing gains.
Outcomes	**Patient outcomes** • QoL (McGill QoL Questionnaire; Functional Assessment of Cancer Therapy – Brain) • Depression, anxiety, stress (Montgomery-Åsberg Depression Rating Scale; Depression Anxiety Stress Scales-21) **Caregiver outcomes** • Unknown. Will be reported in a separate manuscript.
Starting date	July 2010
Contact information	ownsworth@griffith.edu.au
Notes	Confirmed as accurate 29 January 2019. Authors have indicated it is unlikely that caregiver outcomes will be published separately.

Roberge 2016

Trial name or title	SmartCare: innovations in caregiving interventions

Roberge 2016 *(Continued)*

Methods	Randomised controlled trial
Participants	Family caregivers (i.e. the primary, non-professional, non-paid caregiver as identified by the patient) of patients (aged > 21 years; newly diagnosed with a primary malignant brain tumour) could participate if they 1. were aged > 21 years; 2. had telephone access; 3. could read and speak English; 4. were not currently the primary caregiver for anyone else other than children aged < 21 years; 5. obtained a score > 6 on the shortened CES-D; 6. were currently not receiving any type of formal counselling for depressive symptoms.
Interventions	The online SmartCare programme takes 8 weeks to complete. Every 2 weeks, participants complete a needs screening to identify issues that cause distress and are asked to select 1 or 2 issues to work on. Participants explore the issue in more detail and are encouraged to review past attempts to deal with the issue and any challenges faced. They are asked to set small, realistic goals related to the issue. Subsequently, the nurse interventionist provides telephone support to individualise strategies and teach them how to best use the programme to meet their needs. After 1 week of implementing the plan, the caregiver and nurse review if the chosen strategies worked adequately and if needed, revise the plan.
Outcomes	**Primary outcomes** • Depressive symptoms (shortened CES-D) **Secondary outcomes** • Unmet needs (Caregiver Needs Screen Questionnaire) • Caregiver mastery (Caregiver Mastery Scale) • Optimism (Life Orientation Test) • Spirituality (Functional Assessment of Chronic Illness Therapy – Spiritual Well-Being scale) • Oversight demand (Caregiver Vigilance Scale) • Social support (Interpersonal Support Evaluation List) • Occupational functioning (Work Limitations Questionnaire) • Positive aspects of caregiving (Positive Aspects of Caregiving scale)
Starting date	1 March 2014
Contact information	prs11@pitt.edu
Notes	Confirmed as accurate 28 January 2019.

CES-D: Center for Epidemiological Studies Depression Scale; GBM: glioblastoma multiforme; MCP-C: Meaning-Centered Psychotherapy for Cancer Caregivers; QoL: quality of life.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Central Nervous System Neoplasms] explode all trees
#2 ((brain or cereb* or spinal cord or CNS or central nervous system) near/5 (cancer* or carcinoma* or tumor* or tumour* or malignan* or neoplas* or lymphoma* or hemangioma*))
#3 MeSH descriptor: [Glioma] explode all trees
#4 (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma* or ependymoma* or medulloblastoma* or craniopharyngioma* or pineal or pituitary or PNET* or DNET* or schwannoma*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Caregivers] this term only
#7 MeSH descriptor: [Family] explode all trees
#8 (caregiver* or care giver* or carer*)

#9 ((family or families or spouse* or partner* or parent* or grandparent* or sibling* or relative* or friend* or husband* or wife or wives or close person* or significant other* or child or children) and (car*))
#10 #6 or #7 or #8 or #9
#11 #5 and #10

Appendix 2. MEDLINE search strategy

1 exp Central Nervous System Neoplasms/
2 ((brain or cereb* or spinal cord or CNS or central nervous system) adj5 (cancer* or carcinoma* or tumor* or tumour* or malignan* or neoplas* or lymphoma* or hemangioma*)).mp.
3 exp Glioma/
4 (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma* or ependymoma* or medulloblastoma* or craniopharyngioma* or pineal or pituitary or PNET* or DNET* or schwannoma*).mp.
5 1 or 2 or 3 or 4
6 Caregivers/
7 exp Family/
8 (caregiver* or care giver* or carer*).mp.
9 ((family or families or spouse* or partner* or parent* or grandparent* or sibling* or relative* or friend* or husband* or wife or wives or close person* or significant other* or child or children) and (car*)).mp.
10 6 or 7 or 8 or 9
11 5 and 10
12 randomized controlled trial.pt.
13 controlled clinical trial.pt.
14 randomized.ab.
15 placebo.ab.
16 clinical trials as topic.sh.
17 randomly.ab.
18 trial.ti.
19 12 or 13 or 14 or 15 or 16 or 17 or 18
20 11 and 19

Key:

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

Appendix 3. Embase search strategy

1. exp central nervous system tumor/
2. ((brain or cereb* or spinal cord or CNS or central nervous system) adj5 (cancer* or carcinoma* or tumor* or tumour* or malignan* or neoplas* or lymphoma* or hemangioma*)).mp.
3. exp glioma/
4. (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma* or ependymoma* or medulloblastoma* or craniopharyngioma* or pineal or pituitary or PNET* or DNET* or schwannoma*).mp.
5. 1 or 2 or 3 or 4
6. exp caregiver/
7. exp family/
8. (caregiver* or care giver* or carer*).mp.
9. ((family or families or spouse* or partner* or parent* or grandparent* or sibling* or relative* or friend* or husband* or wife or wives or close person* or significant other* or child or children) and car*).mp.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. crossover procedure/
13. double-blind procedure/
14. randomized controlled trial/
15. single-blind procedure/
16. random*.mp.
17. factorial*.mp.
18. (crossover* or cross over* or cross-over*).mp.
19. placebo*.mp.

20. (double* adj blind*).mp.
21. (singl* adj blind*).mp.
22. assign*.mp.
23. allocat*.mp.
24. volunteer*.mp.
25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 11 and 25

Key:

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

CONTRIBUTIONS OF AUTHORS

FB handsearched journals and conference abstracts.
FB and AGR performed study selection and data extraction independently.
FB and AGR assessed risk of bias.
FB and HB assessed GRADE certainty of evidence.
FB drafted the manuscript.
The other review authors reviewed the manuscript to improve its quality.

DECLARATIONS OF INTEREST

FB was involved in a randomised controlled trial aimed at supporting informal caregivers of people with high-grade glioma through psychoeducation and cognitive behavioural therapy.

PS and FB were involved in a trial to support family caregivers of patients diagnosed with a primary brain tumour through a nurse-guided online programme (not yet published).

HB: none.

AGR: none.

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other.

External sources

- Yorkshire Cancer Research University Academic Fellowship, UK.

  The lead reviewer is supported by a YCR University Academic Fellowship (L389FB).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- To carry out study selection, and ensure at least a degree of generalisability, we had to employ a cut-off for the percentage of neuro-oncology caregivers in the samples. FB and AR discussed this and set this cut-off at more than 20%.
- The protocol was written in the assumption that a meta-analysis might be possible. After performing the search and study selection it became apparent that this was not possible – hence some references to meta-analysis methods have been removed.
- Because of the narrative synthesis methods employed, we could not enter the extracted data into Review Manager as planned. Similarly, we could not assess whether confounding factors influenced study results, and the extent to which these were controlled for in the analysis (e.g. caregiver education, age, sex, income, socioeconomic status, caregiver use of psychotropic medication, nature of relationship with the patient, patient diagnosis, patient age, and patient sex). Therefore, we removed the following paragraph from the 'Data extraction and management' section: "*Where possible, we planned to assess the extent to which the following confounding factors may have influenced the results and the extent to which these were controlled for in the analysis: caregiver education, caregiver age, caregiver sex, caregiver income or socioeconomic status, caregiver use of psychotropic medication, nature of the relationship with the patient, patient diagnosis, patient age, patient sex. Extracted data were entered into Review Manager. Again, the two authors mentioned above discussed and any uncertainties were resolved by a third review author.*"
- There was a change in the author list: C Browne is no longer involved in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Adaptation, Psychological; *Quality of Life; Brain Neoplasms [psychology]; Caregivers [*psychology]; Family [psychology]; Friends [psychology]; Randomized Controlled Trials as Topic; Social Support; Spinal Cord Neoplasms [psychology]; Stress, Psychological [*prevention & control]; Terminal Care [*psychology]

MeSH check words

Humans