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[Intervention Review]

Pharmacological treatment of depression in patients with a primary brain tumour

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 3, 2010.

Patients with a primary brain tumour often experience depression, for which drug treatment may be prescribed. However, these patients are also at high risk of epileptic seizures, cognitive impairment and fatigue, all of which are potential side effects of antidepressants. The benefit, or harm, of pharmacological treatment of depression in brain tumour patients is unclear.

Objectives

To assess the benefits and harms of pharmacological treatment of depression in patients with a primary brain tumour.

Search methods

We updated the search to include the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 10), MEDLINE to October 2012, EMBASE to October 2012 and PsycINFO to October 2012. We searched the British Nursing Index, LILACS, PSYINDEX, the NHS National Research Register, the NHS Centre for Reviews and Dissemination's Database of Abstracts of Reviews of Effectiveness (DARE) and Web of Knowledge (covering Science Scisearch, Social Sciences Citation Index and Biological Abstracts) for the original review (to July 2009). In the original review we also handsearched *Neuro-oncology*, the *Journal of Neuro-oncology*, the *Journal of Neurology*, *Neurosurgery and Psychiatry* and the *Journal of Clinical Oncology* (July 1999 to June 2009) and wrote to all the pharmaceutical companies manufacturing antidepressants for use in the UK.

Selection criteria

We searched for all randomised controlled trials (RCTs), controlled clinical trials, cohort studies and case-control studies of any pharmacological treatment of depression in patients with a histologically diagnosed primary brain tumour.

Data collection and analysis

No studies met the inclusion criteria.

Main results

We found no eligible studies evaluating the benefits of any pharmacological treatment of depression in brain tumour patients.

Authors' conclusions

No high-quality studies have examined the value of pharmacological treatment of depression in patients with a primary brain tumour. RCTs and detailed prospective studies are required to inform the effective pharmacological treatment of this common and important complication of brain tumours. Since the last version of this review none of the new relevant studies have provided additional information to change these conclusions.

PLAIN LANGUAGE SUMMARY

Pharmacological treatment of depression in patients with a primary brain tumour

People with brain tumours may experience epilepsy, memory problems and fatigue. Depression is also common and doctors might choose to treat this with antidepressants, since antidepressants are thought to be effective in other patients. However, antidepressants could be less effective, or could cause more side effects, in patients with brain tumours.

The review authors researched whether any drugs have been proven to be effective, and whether they cause significant side effects when prescribed to treat depression in patients with brain tumours. They searched the medical journal literature to find high-quality studies comparing the effectiveness of any one drug treatment for depression in patients with a brain tumour against another treatment. Despite a thorough search, the authors could not find any studies and so cannot determine whether any drug is of any benefit. The review authors conclude that it is important to research whether drugs can treat depression safely and effectively in people with brain tumours.

BACKGROUND

Primary brain tumours

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 3, 2010) on 'Pharmacological treatment of depression in patients with a primary brain tumour'.

Primary brain tumours affect around seven in every 100,000 people per year worldwide (Parkin 2005). They can be categorised according to World Health Organization (WHO) criteria (Louis 2007) reflecting their cell of origin and degree of malignancy. The most common kind of primary brain tumour is glioma, a tumour of glial cells (Wrensch 2002). Glioma occurs slightly more frequently in men than women and is more common in the elderly (Barnholtz-Sloan 2003). Most gliomas (70% to 80%) are 'high-grade' aggressive tumours which significantly reduce patient survival. With current best treatment, roughly one-quarter of adults with the most common type of glioma (glioblastoma multiforme) will survive for two years after diagnosis (Stupp 2005).

Around 20% of gliomas are more slowly growing 'low-grade' tumours, associated with a median survival of seven years (Van den Bent 2005). Low-grade gliomas are more frequently associated with epileptic seizures (Pace 1998). A poorer outcome from low-

grade glioma is associated with older age, astrocytoma histology, tumour size > 6 cm and tumour affecting both sides of the brain at presentation (Pignatti 2002).

Meningiomas are another common kind of primary brain tumour, occurring more frequently in women and the elderly, and are often cured by surgery (Wrensch 2002). As a group, primary brain tumours differ from metastatic tumours which spread to the brain from cancer elsewhere in the body.

Depression

Depression is a clinical syndrome of sadness or loss of interest, negative beliefs (for example feelings of guilt or low self esteem) and psychomotor abnormalities (for example fatigue and psychomotor retardation) (Gelder 2000). Because some sadness, negative thoughts (for example about loss of health or death) and physical symptoms can be normal in cancer patients, the gold-standard method of diagnosing depression is a structured clinical interview conducted by a specialist in mental health (APA 2000b; First 2002). Significant depressive symptoms can also be identified in patients using rating scales (for example Zigmond 1968) which use cut-off scores to estimate the likelihood of depression and, being easier to administer, are often used as a 'proxy' diagnosis in clinical research.

The reported prevalence of depression in cancer varies depending on the study population, diagnostic method and time at which patients are assessed. Major depression has been reported in up to 27% of systemic cancer patients (Strong 2007). Those with primary brain tumours may meet diagnostic criteria at least as frequently (Litofsky 2004; Wellisch 2002). However, depression may often pass undiagnosed in patients with cancer (Greenberg 2004) and, even when identified, may be inadequately treated (Litofsky 2004; Sharpe 2004).

Antidepressants are recommended as a first-line treatment for moderate to severe depression in national guidelines (for example APA 2000; NICE 2004). The three main pharmacological classes of antidepressant are the selective serotonin re-uptake inhibitors (SSRI), the tricyclic antidepressants (TCA) and the monoamine oxidase inhibitors (MAOI). A fourth class of newer, 'second-generation' compounds is chemically diverse. Other drug classes, for example psychostimulants (Weitzner 1999) or acetylcholinesterase inhibitors (Shaw 2006) have also been proposed for use in patients with brain tumours. The many non-pharmacological treatments for depression (for example psychotherapy) are not covered in this review.

Although the precise mode of action is unknown (Moncrieff 2004), meta-analyses of randomised controlled trials (RCTs) enrolling patients without brain tumours have shown antidepressants to be effective in the depressed elderly (Mottram 2006) and in those with chronic low-level depression (Lima 2005), or severe or psychotic depression (Wijkstra 2005). Antidepressants may reduce depressive symptoms in patients with other neurological illnesses (Hackett 2008) but in the physically ill a limited response to treatment and high relapse rates are common observations (Iosifescu 2004).

Why it is important to do this study

Major depressive disorder can affect up to 20% of brain tumour patients in the first eight months after diagnosis (Rooney 2011) and can have important consequences for the affected person and their family. In glioma, depression has been associated with physical functional impairment (Rooney 2011), cognitive impairment (Armstrong 2002), reduced quality of life (Mainio 2006), higher mortality (Gathinji 2009; Litofsky 2004; Mainio 2006b), a greater frequency of medical complications (Litofsky 2004) and reduced work productivity (Feuerstein 2007). Men with glioma may have the highest risk of all cancer patients of psychiatric hospitalisation in the year following glioma diagnosis (Dalton 2009). Depression is a strong risk factor for suicide (Rihmer 2007) and epilepsy (Hesdorffer 2000) in patients without a brain tumour. If depression in brain tumour patients was effectively treated, personal or family suffering could potentially be reduced.

It is, however, possible that the side effects of antidepressants outweigh any benefit. Antidepressants may lower the seizure threshold (Montgomery 2005), impair memory (Peretti 2000) or cause fa-

tigue (Cassano 2004) and patients with primary brain tumours are already at high risk of these complications. Despite clinical uncertainty, the effectiveness and potential adverse impact of pharmacotherapy for depression in primary brain tumours has not been systematically reviewed.

OBJECTIVES

To assess the benefits and harms of pharmacological treatment of depression in patients with a primary brain tumour.

METHODS

Criteria for considering studies for this review

Types of studies

For evidence of efficacy we aimed to include:

- RCTs.

For evidence of adverse effects we also aimed to include:

- non-randomised controlled studies;
- cohort studies;
- case-control studies.

We aimed to find all published and unpublished studies, in any language.

Types of participants

Inclusion criteria

- Adults (aged 18 years and over)
- A diagnosis of depression at baseline (diagnosed by any validated method and satisfying the original trial authors that pharmacological treatment of depression was reasonable and necessary)
- A co-morbid histological diagnosis of any primary brain tumour

Exclusion criteria

- Studies recruiting only patients with metastatic (i.e. non-primary) brain tumours

Types of interventions

Any drug prescribed to treat depression compared, where relevant, with a control group receiving any other treatment. We anticipated that the most common drug class would be an antidepressant, but any category of prescription drug was eligible. Studies administering only unlicensed herbal remedies (for example St. John's wort) were excluded.

Types of outcome measures

Primary outcomes

The primary outcome was change in depression at final follow-up. We anticipated that this could be measured in several different ways:

- the mean change in depression scale score;
- the proportion of patients meeting pre-defined criteria for improvement in scale score;
- changes in the proportion of patients with a categorical diagnosis of depression ('present' or 'absent').

Where both categorical (present or absent) and continuous (scale score) depression data were presented, we aimed to analyse both.

Secondary outcomes

These were:

- quality of life;
- general emotional distress;
- length of time from diagnosis of brain tumour to death.

Although antidepressants can have many side effects, we identified those we considered most likely in brain tumour patients:

- seizure frequency (measured by patient or carer report);
- cognitive dysfunction (e.g. poor memory, measured by validated neuropsychological testing);
- fatigue (measured by a validated rating scale).

We planned to analyse secondary outcomes as continuous variables only.

Search methods for identification of studies

We ran searches for the original review in July 2009. We ran the subsequent (update) search in October 2012.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 10), MEDLINE (to October 2012), EMBASE (to October 2012) and PsycINFO (to October 2012). We had previously searched the British Nursing

Index, LILACS, PSYINDEX, the NHS National Research Register, the NHS Centre for Reviews and Dissemination's Database of Abstracts of Reviews of Effectiveness (DARE) and Web of Knowledge (covering Science Scisearch, Social Sciences Citation Index and Biological Abstracts) (to July 2009). In the original review we constructed individual search strategies for each database (see [Appendix 1](#) to [Appendix 10](#)). In the update, we amended search strategies where relevant to remove duplicate terms ([Appendix 11](#) to [Appendix 14](#)). Because we aimed to include studies other than RCTs, we conducted topic searches only.

Searching other resources

We searched (July 2009):

- Proquest Dissertations & Theses;
- System for Information on Grey Literature (SIGLE);
- conference abstracts in the handsearched journals.

We contacted:

- pharmaceutical companies manufacturing all antidepressants listed in the British National Formulary (BNF);
- International Network of Agencies for HTA (INAHTA);
- British Library Document Supply Centre (BLDSC).

We handsearched the following journals published in the years 1999 to 2009:

- *Journal of Neurology, Neurosurgery and Psychiatry*;
- *Journal of Neuro-oncology*;
- *Journal of Clinical Oncology*;
- *Neuro-oncology*.

We aimed to handsearch:

- reference lists of eligible studies;
- book chapters identified in the reference lists of eligible studies.

Data collection and analysis

Selection of studies

Two authors (RG/AR) initially filtered studies from the title and abstract. We then obtained full copies of potentially relevant studies which two authors (RG/AR) independently assessed for eligibility.

Data extraction and management

Two review authors (RG, AR) were to extract data independently from eligible studies using a form. For the categorical outcome of depression we aimed to abstract the number of depressed patients in each arm at final follow-up in order to estimate risk ratio (RR).

For continuous outcomes we aimed to abstract the mean and standard deviation (SD) of the outcome of interest in each arm at final follow-up.

We aimed to estimate from the means and SDs whether the data were skewed: if they were, we would write to authors requesting the mean and SDs of log transformed data.

For time-to-death data we aimed to abstract the hazard ratio (HR) and its variance from trial reports; if these were not presented, we would attempt either to estimate them or abstract relevant data from Kaplan-Meier survival curves. Failing this, we would estimate RR as outlined above.

Where possible, participants were to be analysed in the groups to which they were randomised, regardless of the treatment they actually received.

One review author (AR) was to enter data into RevMan 5 using the duplicate entry facility (RevMan 2012).

Assessment of risk of bias in included studies

Randomisation

We aimed to code the randomisation of participants to intervention groups as:

- adequate e.g. a computer-generated random sequence or a table of random numbers;
- quasi-randomised e.g. date of birth, clinic ID number or surname;
- unclear e.g. not reported.

Allocation concealment

We aimed to code allocation concealment from treatment providers and participants as:

- adequate e.g. where the allocation sequence could not be foretold (A);
 - unclear e.g. not reported (B);
 - inadequate e.g. the computer-generated random sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope (C);
 - not used (D).

Blinding

We aimed to code the blinding of participants, treatment providers and outcome assessors as:

- yes;
- no;
- unclear.

Loss to follow-up

We aimed to record the number of participants in each intervention arm whose outcomes were not reported at the end of the study, noting if loss to follow-up was not reported. Controlled non-randomised studies were to be similarly assessed, with analysis of whether:

- the treatment and comparison groups were comparable at baseline;
- analysis was adjusted for potential confounding factors.

If as a result of this assessment we considered it likely that a study was biased we were not to include it in the meta-analysis.

Statistical methods

When summarising the categorical depression outcome we aimed to calculate risk ratios (RR). When comparing continuous outcome data from studies using different rating scales we aimed to use the standardised mean difference (SMD); for studies using the same scale we aimed to calculate the mean difference (MD).

For time-to-death data we aimed to pool HRs using the generic inverse variance facility of RevMan 5.

We aimed to use random-effects models for all meta-analyses.

Dealing with missing data

Missing measures of uncertainty (for example confidence intervals and SDs) were to be calculated, where possible, or the study authors contacted to request their data. We did not intend to impute missing data.

Assessment of heterogeneity

We aimed to calculate statistical heterogeneity using the I^2 statistic, taking an I^2 value of $> 50\%$ as evidence of substantial heterogeneity (and a meta-analysis not being performed).

Funnel plot

We aimed to examine funnel plots corresponding to the primary outcome. If treatment effects were thought not to be sampled from a symmetric distribution (an assumption of the random-effects model) we would use a fixed-effect model to conduct further meta-analyses.

Subgroup analysis

We aimed to conduct subgroup analysis by antidepressant class, tumour histology and WHO grade of tumour.

Sensitivity analysis

We aimed to conduct sensitivity analyses by excluding studies which did not report adequate: (i) concealment of allocation or (ii) blinding of the outcome assessor.

RESULTS

Description of studies

We found no eligible studies for any of our primary or secondary outcomes.

Several studies, although interesting, were ineligible for this review. Wellisch et al conducted a RCT of a psychostimulant (methylphenidate) in patients with brain tumour, with depression as a secondary outcome (Wellisch 2006). However, it was not clear from the published conference abstract whether participation was limited to patients with depression and we were unable to contact the authors for clarification.

Morrow et al reported a RCT of an antidepressant (paroxetine) in a population of mixed cancer patients, including those with brain tumour. Although depression was measured as an outcome, the intervention was given primarily to treat fatigue and participation was not limited to depressed patients. Data for the small number of patients with brain tumours were not reported separately (Morrow 2003).

Moss et al conducted an open-label phase II trial of an antidepressant (bupropion) on fatigue in mixed cancer patients, including those with brain tumour, and measured levels of depression. However, participation was restricted to patients with high levels of fatigue, not depression (Moss 2006).

Shaw et al enrolled 35 patients with mixed brain tumour pathologies to an open-label phase II trial of an acetylcholinesterase inhibitor (donepezil) and measured depression using a rating scale. However, participation was not limited to patients with depression (Shaw 2006).

Meyers et al evaluated the effects of a psychostimulant (methylphenidate) in an open-label phase II trial of 30 patients with high-grade glioma, measuring depressive symptom severity among other outcomes. However, the authors explicitly excluded patients with major depression at study baseline (Meyers 1998).

Litofsky et al conducted a prospective cohort study of adults with high-grade glioma, examining the relationship between depression and survival in glioma. However, the authors did not systematically prescribe treatment for depression and did not limit participation to patients with depression (Litofsky 2004).

Koval'chuk conducted a prospective cohort study of 225 patients following operation for brain tumour. The authors measured depression, among other outcomes, and assessed the influence of different antidepressants on the postoperative normalisation of

mood. However, again, participation was not limited to depressed patients (Koval'chuk 2007).

Caudill et al conducted a retrospective cohort study of the frequency and toxicity of SSRI prescription among 160 glioblastoma patients presenting to a tertiary neuro-oncology service over a 10-year period. The authors reported that being prescribed SSRIs was associated with improved survival at two years post-diagnosis, after controlling for relevant confounders. Patients being prescribed a SSRI reported similar levels of toxicities as those on no SSRI. However, antidepressant prescription was uncontrolled and the study was not limited to depressed patients (Caudill 2011).

Other studies that were ineligible on methodological grounds were a small uncontrolled case series (Rabey 1985) and a single case study (Oyewumi 1981).

Risk of bias in included studies

No eligible studies were found.

Effects of interventions

No eligible studies were found.

DISCUSSION

We found no eligible randomised controlled trials (RCTs), controlled trials, cohort studies or case-control studies of the pharmacological treatment of depression in patients with primary brain tumours. Two RCTs, three phase II trials and three cohort studies examined aspects of drug treatment of symptoms in brain tumour patients. However, every trial recruited depressed and non-depressed patients alike, and every cohort study reported usual clinical care rather than systematically evaluating a specific treatment. The results do not therefore generalise easily to the question of treating depressed brain tumour patients that is the focus of this review. The lack of evidence is an important finding because depression is a common complication of brain tumour (Litofsky 2004; Wellisch 2002), with serious consequences for quality of life (Mainio 2006) and possibly survival (Gathinji 2009; Litofsky 2004; Mainio 2006b). Doctors need to know how to treat it.

Although national guidelines for the treatment of depression exist (for example APA 2000; NICE 2004), they cannot have been based on evidence specific to brain tumours because we failed to find any studies that were eligible for this review. Antidepressants appear to be effective in patients with other medical illnesses, but their effectiveness in patients with a brain tumour should not be assumed. Brain tumours are rapidly progressive, biologically active and with significant structural and functional effects upon the main organ implicated in depression. Brain tumours (and their

surgical treatment) may disrupt neuronal circuits crucial to the experience of emotion (Litofsky 2009) or else alter local levels of biochemical mediators (Mainio 2005). Antiepileptic drugs can affect the bioavailability of antidepressants (Hachad 2002) and corticosteroids have been associated with mood changes in glioma (Litofsky 2004). There are many reasons to be cautious about assuming that antidepressants are effective in brain tumour patients.

Brain cancer is also associated with epilepsy, cognitive dysfunction and fatigue (Pace 1998; Wen 2008), which are recognised side effects of antidepressants (Cassano 2004; Montgomery 2005; Peretti 2000). It is important to highlight the lack of evidence about the possible adverse effects of antidepressants in these high-risk patients. Antidepressants could also improve these outcomes, since depression has itself been associated with epilepsy (Hesdorffer 2000), impaired cognition (Stefanova 2006) and fatigue (Moss 2006).

Three excluded studies used a pharmacological agent other than an antidepressant (a psychostimulant or an acetylcholinesterase inhibitor). These drugs could help treat a wider range of symptoms than antidepressants. To date, however, no studies have primarily evaluated the benefit, or harm, of pharmacological treatment of depression in patients with a primary brain tumour. Direct study of this question requires that eligibility is restricted to patients with high levels of depression at baseline.

Potential biases in the overview process

Our search strategy was not designed to identify qualitative research studies, describing the individual's experience of having a brain tumour. Results from RCTs and other quantitative study designs provide information about the 'average' response to treatment but may not easily be applied to individual patients. Although the search strategy was thorough for antidepressants, we may have missed studies of other pharmacological agents. Searches on the foreign language databases (LILACS and PSYINDEX) were limited mainly to English language terms. English translations of abstracts are often included in these databases so it is possible, but unlikely, that we missed important relevant studies. We assumed that the lack of response from any drug companies is indeed because they have not studied this issue.

Agreement or disagreement with other reviews

Authors of other reviews of depression in brain tumours (Litofsky 2009; Pangilinan 2007; Price 2008; Weitzner 1999) note a similar lack of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review none of the new relevant studies have provided additional information to change the conclusions. There is currently no high-quality evidence as to whether pharmacological treatments for depression in patients with primary brain tumours are effective, or harmful. Best practice would suggest that doctors treating depressed brain tumour patients discuss the lack of evidence with the patient, document their views and use their clinical judgement. If drug treatment is started, close follow-up may help detect any adverse effects.

Implications for research

Detailed prospective studies and randomised controlled trials addressing the risks and benefits of antidepressants are vital. Important research questions include whether, among patients with a primary brain tumour and depression, there is any evidence that treatment:

- is effective in treating depression;
- has clinically significant effects on seizure frequency, fatigue and cognition;
- has clinically significant pharmacokinetic interactions with antiepileptic drugs or chemotherapy;
- has a clinically significant effect on survival.

When next updating this review we will widen our search terms to include psychostimulants and acetylcholinesterase inhibitors.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Caudill 2011	Treatment of depression was based on routine clinical care (not systematically controlled)
Koval'chuk 2007	Depression was not a necessary inclusion criterion
Litofsky 2004	Treatment of depression was not systematically controlled Depression was not a necessary inclusion criterion
Meyers 1998	Patients with severe depression were excluded and the study was not limited to those with milder depression
Morrow 2003	Depression was not a necessary study inclusion criterion Data for brain tumour patients were not presented separately
Moss 2006	Depression was not a necessary study inclusion criterion Data for brain tumour patients were not presented separately
Oyewumi 1981	Single case study
Rabey 1985	3 case studies; brain tumour not diagnosed at time of antidepressant prescription
Shaw 2006	Depression was not a necessary inclusion criterion
Wellisch 2006	Could not confirm whether depression was a necessary inclusion criterion

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. MEDLINE search strategy

Conducted 22 July 2009

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1950 to present (July week 2 2009)

1. exp depressive disorder/
 2. *Depressive Disorder, Major/
 3. *Dysthymic Disorder/
 4. Depression, involuntional.mp.
 5. Depress\$.ab,ti.
 6. Affective disorder\$.ab,ti.
 7. Mood disorder\$.ab,ti.
 8. 1 or 2 or 3 or 4 or 5 or 6 or 7
 9. exp Glioma/
 10. exp Brain Neoplasms/
 11. brain tumo\$.ab,ti.
 12. astrocytoma\$.ab,ti.
 13. meningioma\$.ab,ti.
 14. oligodendroglioma\$.ab,ti.
 15. glioblastoma\$.ab,ti.
 16. 9 or 10 or 11 or 12 or 13 or 14 or 15
 17. exp Antidepressive Agents/
 18. exp Serotonin Uptake Inhibitors/
 19. exp Monoamine Oxidase Inhibitors/
 20. exp Drug Therapy/
 21. Antidepress\$.ab,ti.
 22. TCA\$.ab,ti.
 23. Tricyclic\$.ab,ti.
 24. MAOI\$.ab,ti.
 25. SSRI\$.ab,ti.
 26. Antidepressive Agents, Tricyclic/
 27. Antidepressive Agents, Second Generation/
 28. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
 29. 8 and 16 and 28
 30. (animals not (humans and animals)).sh.
 31. 29 not 30
- (n = 57)

Appendix 2. EMBASE search strategy

Conducted 22 July 2009

EMBASE 1980 to 2009 Week 29

1. exp Depression/
 2. exp Mood Disorder/
 3. "Depress*".ti,ab.
 4. "Affect*".ti,ab.
 5. "Dysthym*".ti,ab.
 6. 1 or 2 or 3 or 4 or 5
 7. exp Glioma/
 8. exp Brain Tumor/
 9. Astrocytoma/
 10. Meningioma/
 11. (glioma* or brain tumo* or astrocytoma* or meningioma*).ti,ab.
 12. 7 or 8 or 9 or 10 or 11
 13. exp Antidepressant Agent/
 14. Monoamine Oxidase Inhibitor/
 15. Tricyclic Antidepressant Agent/
 16. Serotonin Uptake Inhibitor/
 17. (antidepress* or SSRI* or MAOI* or TCA* or tricyclic*).ti,ab.
 18. 13 or 14 or 15 or 16 or 17
 19. animal.sh
 20. human.sh
 21. 19 not (19 and 20)
 22. 6 and 12 and 18
 23. 22 not 21
- (n = 287)

Appendix 3. PsycINFO search strategy

Searched 22 July 2009

PsycINFO 1806 to July Week 2 2009

1. exp Endogenous Depression/
2. exp Reactive Depression/
3. exp Major Depression/
4. exp Mental Disorders/
5. exp Affective Disorders/
6. (depress\$ or mood\$ or affective\$ or dysthym\$).ab,ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Brain Neoplasms/
9. brain tumo?.mp.
10. Oligodendroglioma\$.mp.
11. Astrocytoma\$.mp.
12. Meningioma\$.mp.
13. (glioma\$ or brain tumo\$ or astrocytoma\$ or meningioma\$ or oligodendroglioma\$).ab,ti.
14. 8 or 9 or 10 or 11 or 12 or 13
15. exp Drug Therapy/
16. pharmacotherapy.mp.
17. exp Antidepressant Drugs/
18. exp Tricyclic Antidepressant Drugs/
19. exp Monoamine Oxidase Inhibitors/
20. exp Serotonin Reuptake Inhibitors/

21. (antidepress\$ or SSRI\$ or MAOI\$ or TCA\$ or tricyclic\$ or drug therap\$ or pharmacotherap\$).ab,ti.
 22. 15 or 16 or 17 or 18 or 19 or 20 or 21
 23. 7 and 14 and 22
- (n = 39)

Appendix 4. British Nursing Index search strategy

Searched 22 July 2009

British Nursing Index and Archive 1985 to July 2009

1. exp depression/
 2. exp psychiatric disorders/
 3. (depress\$ or mood\$ or affectiv\$ or dysthym\$).ti,ab.
 4. 1 or 2 or 3
 5. exp cancer/
 6. (glioma\$ or brain tumo\$ or astrocytoma\$ or meningioma\$ or oligodendroglioma\$).ti,ab.
 7. 5 or 6
 8. exp Drug Therapy/
 9. exp Psychiatroc disorders : Drug Therapy/
 10. SSRI\$.mp.
 11. MAOI\$.mp.
 12. Tricyclic.mp.
 13. (antidepress\$ or SSRI\$ or MAOI\$ or TCA\$ or drug therap\$ or pharmacotherap\$).ti,ab.
 14. 8 or 9 or 10 or 11 or 12 or 13
 15. 4 and 7 and 14
- (n = 20)

Appendix 5. CENTRAL search strategy

Searched 22 July 2009

EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2009

1. Glioma/
2. exp Brain Neoplasms/
3. Astrocytoma/
4. Meningioma/
5. glioma.ti,kw,ab.
6. brain tumo\$.ti,kw,ab.
7. astrocytoma\$.ti,kw,ab.
8. meningioma\$.ti,kw,ab.
9. oligodendroglioma\$.ti,kw,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Antidepressive Agents/
12. exp Antidepressive Agents, Second-Generation/
13. Antidepressive Agents, Tricyclic/
14. Serotonin Uptake Inhibitors/
15. Monoamine Oxidase Inhibitors/
16. Antidepress\$.ti,kw,ab.
17. SSRI\$.ti,kw,ab.
18. MAOI\$.ti,kw,ab.
19. TCA\$.ti,kw,ab.
20. drug therap\$.ti,kw,ab.
21. exp Drug Therapy/
22. pharmacotherapy.mp.

23. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
 24. exp Mental Disorder/
 25. Depression/
 26. Affective Symptoms/
 27. depress\$.ti,kw,ab.
 28. mood\$.ti,kw,ab.
 29. affectiv\$.ti,kw,ab.
 30. dysthym\$.ti,kw,ab.
 31. 24 or 25 or 26 or 27 or 28 or 29 or 30
 32. 10 and 23 and 31
- (n = 8)

Appendix 6. LILACS search strategy

Searched 22 July 2009

1. Depression OR Depressive OR Mood OR Affect
 2. Glioma OR Glioblastoma OR Meningioma OR Brain neoplasm
 3. Antidepressant OR Antidepressive OR SSRI OR MAOI OR TCA
 4. 1 and 2 and 3
- (n = 0)

Appendix 7. PSYINDEX search strategy

Searched 22 July 2009

(all search terms free text)

1. Depression OR Depressive OR Mood OR Affectiv?
 2. Gliom? OR gehirntumo? OR Krebs OR Astrocytom? Or Oligodendrogliom? OR Meningiom?
 3. Antidepress OR Serotonin OR SSRI OR MAOI OR TCA OR Pharmacotherap?
 4. 1 and 2 and 3
- (n = 1)

Appendix 8. National Research Register archive search strategy

Searched 22 July 2009

(Database was only active until 2007)

1. "Glioma"
- (n = 272)

Appendix 9. DARE search strategy

Searched 22 July 2009

Database of Abstracts of Reviews of Effectiveness 3rd Quarter 2009

1. depress\$.ab,ti.
2. affective disorder\$.ab,ti.
3. mood disorder\$.ab,ti.
4. 1 or 2 or 3
5. brain tumo\$.ab,ti.
6. astrocytoma\$.ab,ti.
7. meningioma\$.ab,ti.
8. oligodendroglioma\$.ab,ti.
9. glioblastoma\$.ab,ti.

10. 5 or 6 or 7 or 8 or 9
 11. antidepress\$.ab,ti.
 12. TCA\$.ab,ti.
 13. Tricyclic\$.ab,ti.
 14. MAOI\$.ab,ti.
 15. SSRI\$.ab,ti.
 16. 11 or 12 or 13 or 14 or 15
 17. 4 and 10 and 16
- (n = 0)

Appendix 10. Web of Knowledge search strategy

Searched 22 July 2009

www.isiknowledge.com

Topic=(depression OR depressive disorder OR major depression OR mood disorder OR depress* OR affectiv* OR dysthym* OR mood*) AND Topic=(antidepress* OR SSRI OR MAOI OR TCA) AND Topic=(brain neoplas* OR brain tumo* OR glioma OR astrocytoma OR oligodendroglioma OR meningioma)

(n = 306)

Appendix 11. MEDLINE updated search strategy

Searched to October 2012

1 exp Depressive Disorder/

2 Depression/

3 exp Mood Disorders/

4 depress*.mp.

5 ((affective or mood) adj disorder*).mp.

6 1 or 2 or 3 or 4 or 5

7 exp Brain Neoplasms/

8 exp Glioma/

9 (brain adj5 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).mp.

10 (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma*).mp.

11 7 or 8 or 9 or 10

12 drug therapy.fs.

13 exp Antidepressive Agents/

14 exp Serotonin Uptake Inhibitors/

15 exp Monoamine Oxidase Inhibitors/

16 (SSRI* or TCA* or MAOI* or tricyclic* or antidepress* or anti-depress*).mp.

17 12 or 13 or 14 or 15 or 16

18 6 and 11 and 17

(n = 45)

Appendix 12. EMBASE updated search strategy

Searched to October 2012

1 exp mood disorder/

2 depress*.mp.

3 ((affective or mood) adj disorder).mp.

4 1 or 2 or 3

5 exp brain tumor/

6 exp glioma/

7 (brain adj5 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).mp.

8 (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma*).mp.

9 5 or 6 or 7 or 8

10 dt.fs.

11 exp antidepressant agent/

12 (SSRI* or TCA* or MAOI* or tricyclic* or antidepress* or anti-depress*).mp.

13 10 or 11 or 12

14 4 and 9 and 13

(n = 536)

Appendix 13. PsycINFO updated search strategy

Searched October 2012

1 exp affective disorders/

2 depress*.mp.

3 ((affective or mood) adj disorder*).mp.

4 1 or 2 or 3

5 brain neoplasms/

6 glioma/

7 (brain adj5 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).mp.

8 (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma*).mp.

9 5 or 6 or 7 or 8

10 exp drug therapy/

11 exp antidepressant drugs/

12 exp Serotonin Reuptake Inhibitors/

13 exp Monoamine Oxidase Inhibitors/

14 (SSRI* or TCA* or MAOI* or tricyclic* or antidepress* or anti-depress*).mp.

15 10 or 11 or 12 or 13 or 14

16 4 and 9 and 15

(n = 17)

Appendix 14. CENTRAL updated search strategy

Searched to October 2012

#1 MeSH descriptor: [Depressive Disorder] explode all trees

#2 MeSH descriptor: [Depression] explode all trees

#3 MeSH descriptor: [Mood Disorders] explode all trees

#4 depress*

#5 (affective or mood) near disorder*

#6 #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Brain Neoplasms] explode all trees

#8 MeSH descriptor: [Glioma] explode all trees

#9 brain near/5 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)

#10 glioma* or astrocytoma* or meningioma* or oligodendroglioma* or glioblastoma*
 #11 #7 or #8 or #9 or #10
 #12 Any MeSH descriptor with qualifier(s): [Drug therapy - DT] in all MeSH products
 #13 MeSH descriptor: [Antidepressive Agents] explode all trees
 #14 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees
 #15 MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees
 #16 SSRI* or TCA* or MAOI* or tricyclic* or antidepress* or anti-depress*
 #17 #12 or #13 or #14 or #15 or #16
 #18 #6 and #11 and #17
 (n = 6)

WHAT'S NEW

Last assessed as up-to-date: 29 April 2013.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 3, 2010

Date	Event	Description
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
7 April 2013	New citation required but conclusions have not changed	Text updated. One new study added to excluded studies (Caudill 2011). The update has not altered the conclusions from the last publication of this review
26 October 2012	New search has been performed	Updated search of MEDLINE, EMBASE, CENTRAL and PsycINFO.

CONTRIBUTIONS OF AUTHORS

AR developed and wrote the review, supervised by RG.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- NHS Lothian Neuro-oncology Endowment Fund, UK.
Salary for AR

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was changed to specify that the review was of interventions for the treatment of depression (as opposed to prevention).

The British Nursing Index was searched in place of CINAHL, since CINAHL was not available on Ovid. CancerLit was not searched because it is covered by MEDLINE. Applied Science and Technology Plus was not searched as it is an engineering database. General Science Plus could not be accessed from Edinburgh University. The search strategy outlined in the protocol was altered, as necessary, for individual databases; for full details see the Appendices.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [adverse effects; *therapeutic use]; Brain Neoplasms [*psychology]; Depression [*drug therapy; etiology]

MeSH check words

Humans