The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review

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Depression is common in cancer patients, and this often remains undetected and untreated. Depression has been associated with poorer quality of life, in addition to increased impairment of immune response and poorer survival in cancer patients. Previous systematic reviews and meta-analyses of the efficacy of interventions for cancer patients with depression have failed to distinguish between caseness for depression and depressive symptoms. The findings from this systematic review show that there is limited trial data on the efficacy of prescribed antidepressants in reducing the incidence of major depression and depressive symptoms in cancer patients. Contrary to previous reviews that failed to distinguish between depressive symptoms and depression, this review found very little data from clinical trials (without the possibility of confounding factors) to demonstrate that psychotherapeutic interventions are effective in reducing depression in cancer patients. A number of small-scale, single-centre trials indicated that psychotherapeutic interventions (especially cognitive behavioural therapy) can have effects on depressive symptoms in cancer patients. However, given the methodological limitations of studies to date, lack of evidence should not be interpreted as implying lack of efficacy. In conclusion, there is a need for adequately powered studies of pharmacological and psychotherapeutic studies, which are targeted at cancer patients with a diagnosis of depression and include monitoring of the use of other pharmacological/psychotherapeutic and complementary and alternative medicine interventions.

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Studies have reported up to 58% of cancer patients as having depressive symptoms and up to 38% as having major depression (Massie, 2004). Depression may be particularly difficult to detect in patients suffering from cancer, especially those with terminal illness, and is difficult to distinguish from ‘appropriate sadness’ related to cancer diagnosis, treatment and the approach of end of life (Lloyd-Williams, 2000; Bailey et al, 2005). There are also difficulties in deciding which somatic symptoms may be attributable to cancer and its consequences, and which may be due to depression (Lloyd-Williams, 2001; Bailey et al, 2005). Psychological distress, including adjustment problems, anxiety and depression, typically occurs at many points along the cancer trajectory, and may be exacerbated by physical pain, the effects of treatment, family difficulties, financial worries, etc. The importance of detecting and treating depressive illness in cancer patients lies not only in the relief of psychological distress and its impact on quality of life but also on consequent health service and societal costs. In addition, depression has been associated with increased impairment of immune response (Andersen et al, 1998; Newport and Nemeroff, 1998; Reiche et al, 2004) and poorer survival (Buccheri, 1998; Faller et al, 1999; Watson et al, 1999; Faller and Bulzebruck 2002; Herjl et al, 2003; Goodwin et al, 2004).

Psychosocial needs are often inadequately addressed by cancer services, and depression is frequently unrecognised (Newport and Nemeroff, 1998; Passik et al, 1998; Petito and Evans, 1998; Lloyd-Williams, 2000; Sharpe et al, 2004; Somerset et al, 2004). Clinical practice guidelines for the psychosocial care of cancer patients are available in some countries, such as in the USA and Australia (Turner et al, 2005). The National Institute for Clinical Evidence guidelines for the management of depression in primary and secondary care in the UK propose that screening for depression should be undertaken in primary-care and general hospital settings for high-risk groups, which include those with significant physical illnesses (NICE, 2004).

There have been three recent systematic reviews (Barsevick et al, 2002; Newell et al, 2002; Uitterhoeve et al, 2004) and two meta-analyses (Devine and Westlake, 1995; Sheard and Maguire, 1999) of psychotherapeutic interventions for patients with cancer and depression/depressive symptoms, the results of which provide broad support for such interventions. In their meta-analysis of 98 studies, Devine and Westlake (1995) concluded that psychoeducational care is of benefit to adults with cancer and depression. Likewise, Barsevick et al’s (2002) systematic review of 36 studies concluded that psychoeducational interventions reduce depressive symptoms in patients with cancer, and that behaviour therapy or counselling alone or in combination with cancer education is beneficial. However, Sheard and Maguire (1999) in their meta-analysis of 20 trials concluded that preventative psychological interventions in cancer patients do not have a clinical effect upon
depression. Based on a systematic review of 15 randomised controlled trials, Newell et al (2002) made tentative recommendations about the medium-term benefit of group therapy and the long-term benefits of education and structured counselling. Uitterhoeve et al’s (2004) systematic review of 13 trials concluded that psychosocial interventions had positive effects on patients with advanced cancer and depression.

In addition, a meta-analysis by Meyer and Mark (1995) reported on the effects of psychosocial interventions with adult cancer patients in terms of emotional adjustment, which involved measures of such constructs as mood state, fear and anxiety, depression, denial or repression, self-esteem and distress. Although the study did not present findings on efficacy exclusively in terms of depression/depressive symptoms, it found that psychosocial interventions have positive effects on emotional adjustment. There were no significant differences found between types of interventions (behavioural interventions, non-behavioural counselling and therapy, informational and educational methods, organised social support provided by other patients and other nonhospice interventions). Even so, the authors stated that it would be premature to conclude that there were no differences between treatment categories given the possible confounds.

However, none of these systematic reviews and meta-analyses distinguished between the presence of depressive symptoms and caseness for depression in cancer patients, so limiting their applicability to everyday clinical practice.

There have been no systematic reviews or meta-analyses to date published on the efficacy of antidepressant treatments for cancer patients with depression.

The aim of the following study, therefore, was to systematically review the efficacy of psychotherapeutic and antidepressant interventions for cancer patients with depression/depressive symptoms in terms of (i) reduction in depressive symptoms, (ii) reduction in caseness of clinical depression and (iii) adverse effects.

**MATERIALS AND METHODS**

We undertook a systematic review of randomised controlled trials of pharmacological and psychotherapeutic interventions for cancer patients with depression/depressive symptoms. The method was based on established guidelines for conducting systematic reviews (Chalmers and Haynes, 1994; Mulrow, 1994; Oxman, 1994).

**Search strategy**

References were retrieved by manual searches and through searching electronic databases. The following electronic databases were searched for years 1995–2005 for psychotherapeutic interventions and 1960–2005 for pharmacological interventions: PubMed, CINAHL, Cochrane Library databases DARE, CDSR, CCTR and PsycARTICLES. Manual searches were conducted and relevant references retrieved from those listed in key papers, reports, theses and dissertations. Box 1 provides the search strategy terms.

**Box 1** Search strategy terms

Search terms were taken from known articles relevant to the review and the Medical Subject Headings (MeSH) thesaurus of the US National Library of Medicine (NLM). The search terms included: ‘Depression’, ‘Depressive Disorder’, ‘Depressive Disorders’, ‘Disorder, Depressive’, ‘Disorders, Depressive’, ‘Neurosis, Depressive’, ‘Depressive Neuroses’, ‘Depressive Neurosis’, ‘Neuroses, Depressive’, ‘Mental Health’, ‘Mental Health’, ‘Unipolar Depression’, ‘Depression, Unipolar’, ‘Depressions, Unipolar’, ‘Depression, Endogenous’, ‘Depressions, Endogenous’, ‘Endogenous Depression’, ‘Endogenous Depressions’, ‘Depressive Syndrome’, ‘Depressive Syndromes’, ‘Syndrome, Depressive’, ‘Syndromes, Depressive’, ‘Depression, Neurotic’, ‘Depressions, Neurotic’, ‘Neurotic Depression’, ‘Neurotic Depressions’, ‘Depressions, Neurotic’, ‘Depressive Symptoms’, ‘Depressive Syndrome’, ‘Symptom, Depressive’, ‘Symptoms, Depressive’, ‘Emotional Depression’, ‘Depression, Emotional’, ‘Depressions, Emotional’, ‘Psychiatric Morbidity’, ‘Cancer’, ‘Neoplasms’, ‘Neoplasms, Second Primary’, ‘Hypothalamic Neoplasms’, ‘Brain Neoplasms’, ‘Brain Stem Neoplasms’, ‘Spinal Cord Neoplasms’, ‘Meningeal Neoplasms’, ‘Urologic Neoplasms’, ‘Cerebellar Neoplasms’, ‘Supratentorial Neoplasms’, ‘Unрогenital Neoplasms’, ‘Sigmoid Neoplasms’, ‘Infratentorial Neoplasms’, ‘Cerebral Ventricles Neoplasms’, ‘Testicular Neoplasms’, ‘Pharyngeal Neoplasms’, ‘Pelvic Neoplasms’, ‘Ovarian Neoplasms’, ‘Breast Neoplasms’, ‘Antidepressive Agents’, ‘Antidepressive Agents – adverse effects’, ‘Serotonin Uptake Inhibitors’, ‘Fluoxetine’, ‘Cognitive Therapy’, ‘Randomised Controlled Trials’

**Inclusion criteria**

The criteria for selecting studies were randomised controlled trials of pharmacological and psychotherapeutic interventions for depression in cancer patients, published in English. Participants were either adult cancer patients with depression or depressive symptoms receiving a pharmacological or psychotherapeutic intervention for depression/depressive symptoms. Studies investigating the efficacy of psychotherapeutic interventions in the presence of pharmacological therapy (or vice versa) were excluded, as were those evaluating the efficacy of complementary and alternative (CAM) medicine (including meditation) or information/education strategies.

**Data extraction and synthesis**

Data extraction was completed independently by the reviewers (SW) and (JD) and checked through for accuracy. Data were gathered using a data extraction form (Appendix A). The main outcomes were either depressive symptoms or diagnosed clinical depression measured by a separate scale or as part of a composite outcome measure. Study quality was assessed with the Methodological Quality Instrument (Appendix A) developed by Cho and Bero (1994). Studies were assessed as being of low methodological quality if they failed to meet the minimum requirements on each of the following aspects of study design: adequacy of sample size, randomisation, blinding, method of allocation concealment, clear description of treatment, representative source of subjects, use of diagnostic criteria, number of and reasons for withdrawal from intervention and how dealt with in the analysis, outcome measures described clearly, use of validated instruments, and steps taken to control for possible confounding factors.

**RESULTS**

**Study inclusion and characteristics**

Figure 1 shows the numbers of studies yielded by the search strategy. In all, 29 papers reporting pharmacological studies and 63 reporting psychotherapeutic interventions were identified as potentially relevant and were carefully read. Of these, we excluded 65 because they did not meet the inclusion criteria, and a further two were excluded because they were not strictly randomised controlled trials (Holland et al, 1998; Kissane et al, 2003) and one because it failed to measure baseline levels of depressive symptoms (Stieglis et al, 2004). This left a total of 24 studies (Table 1), of which six were trials of pharmacological treatments and 18 were of psychotherapeutic interventions.

**Pharmacological studies**

The six pharmacological studies were randomised placebo-controlled trials conducted in the United States of America (n = 4) (Musselman et al, 2001; Fisch et al, 2003; Morrow et al, 2003; Roscoe et al, 2005) and Belgium (n = 2) (Razavi et al, 1996;
Van Heeringen and Zivkov, 1996). The mean sample size of intervention and control groups was 83 (range 20–277 patients) and 83 (range 20–272 patients), respectively. The average age of patients ranged from 50 to 61 years. Between half to 100% of participants were female. Three studies were multicentre trials (Razavi et al, 1996; Fisch et al, 2003; Morrow et al, 2003) and three were single-centre trials (Van Heeringen and Zivkov, 1996; Musselman et al, 2001; Roscoe et al, 2005).

Methodological quality The methodological quality of these trials is summarised in Table 2. The sample size exceeded 100 patients in two of the six (33%) trials (Fisch et al, 2003; Morrow et al, 2003). The method of randomisation to groups was sufficiently well described in all studies, but the method of allocation concealment was adequately described in only four trials (Razavi et al, 1996; Musselman et al, 2001; Fisch et al, 2003; Roscoe et al, 2005). Blinding of investigators was reported in five trials (Razavi et al, 1996; Van Heeringen and Zivkov, 1996; Musselman et al, 2001; Fisch et al, 2003; Roscoe et al, 2005) and blinding of subjects in all trials. All studies provided a clear description of the intervention, had a representative source of subjects and provided the number and reasons for withdrawals. Dropout rates for intervention and controls ranged from 0 to 56%. Three trials stated that intention-to-treat analyses were used to deal with patients who were lost to follow-up (Razavi et al, 1996; Van Heeringen and Zivkov, 1996; Musselman et al, 2001).

Two trials selected subjects on the basis of a depressive disorder using Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) criteria (Razavi et al, 1996; Van Heeringen and Zivkov, 1996); one selected patients who were to receive high-dose alpha therapy (which has been associated with symptoms of major depression) (Musselman et al, 2001). Three trials reported on the efficacy of the pharmacological treatment in terms of caseness for depression (Razavi et al, 1996; Musselman et al, 2001; Roscoe et al, 2005) with the other three trials reporting on change in the level of depressive symptoms as indicated by scores on questionnaires (Van Heeringen and Zivkov, 1996; Fisch et al, 2003; Morrow et al, 2003). All outcome measures were clearly described and were valid and reliable (Table 1).

Five trials investigated the efficacy of selective serotonin reuptake inhibitors with three investigating paroxetine (Musselman et al, 2001; Morrow et al, 2003; Roscoe et al, 2005) and two fluoxetine (Razavi et al, 1996; Fisch et al, 2003), while the remaining study investigated the tricyclic antidepressant mianserin (Van Heeringen and Zivkov, 1996). All six trials avoided/monitored pharmacological cointerventions by trial design. None of the six studies reported avoiding or monitoring the use of potentially confounding psychotherapeutic or CAM cointerventions by subjects during the study periods.

Effectiveness and tolerability Depression: One trial found paroxetine effective in reducing major depression in cancer patients with malignant melanoma who were to receive high-dose interferon alpha therapy (Musselman et al, 2001). Major depression developed in 11% (two of 18) of the paroxetine and 45% (nine of 20) of the placebo group, and 5% of paroxetine compared to 35% of the placebo group had to discontinue interferon alpha because of severe depressive distress. In terms of tolerability, retinal haemorrhages developed in three patients (severely in one patient) who were taking paroxetine. The sample size was only 40 patients, but no subjects withdrew from the study.

Another trial found paroxetine to be effective in reducing caseness for depression in breast cancer patients receiving chemotherapy (Roscoe et al, 2005). At final follow-up (cycle 4 of chemotherapy), only four of the original 13 patients (31%) in the paroxetine group who had baseline depression (scoring greater than 19 on the Center for Epidemiological Studies Depression scale) had scores above the cutoff, while all 13 (100%) of the initially depressed patients in the placebo group remained above the threshold. Dropout rates were comparable for intervention and controls (25 and 21%, respectively).

Fluoxetine was not effective in reducing caseness for depression in a trial that included patients with breast, gynaecological or haematological cancer who presented with major depressive disorder (Razavi et al, 1996). The successful response rate (defined by Hospital Anxiety and Depression Scale (HADS) score lower than 8 after 5 weeks of treatment) was not significantly higher (11%) in the intervention group than the placebo group (7%). Side effects between groups were not significantly different, although there was a trend towards digestive and neuropsychiatric adverse events in the intervention group. There were, however, significantly more dropouts from the intervention group (33%) compared with controls (15%) ($P = 0.04$).

Depressive symptoms: Paroxetine was found to be effective in reducing depressive symptoms in breast, lung, haematological, gynaecological and gastrointestinal cancer patients who reported fatigue at their second chemotherapy cycle (Morrow et al, 2003). Dropout rates were comparable for intervention and controls.
Table 1 Characteristics of included studies (n = 24)

| Pharmacological studies (cancer various sites) | Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|-----------------------------------------------|----------|-----------------|--------------------------------------------------------|---------|------------------------|
| Morrow et al. (2003), USA                     | I = 549 cancer patients with a diagnosis of any type of cancer reporting fatigue at their second chemotherapy cycle | I = SSRI paroxetine (20 mg day⁻¹) for 8 weeks (n = 277) | Depressive symptoms CES-D and DD | At conclusion (cycle 4) the paroxetine group had a significantly lower mean level of depression than placebo group as measure on the CES-D (P ≤ 0.003) and DD (P < 0.001). Mean decrease in CES-D score from baseline to end point was 18.9% in the paroxetine group and 6.3% in the control group. Tolerability: not reported | Not reported |
| Design: Randomised placebo-controlled trial    | C = 563.2 (12.3) | C = placebo for 8 weeks (n = 272) | Assessments performed at baseline (cycle 2 of chemotherapy), cycle 3 and cycle 4 | | |
| Random allocation to treatment groups: YES     | Gender: I = 80% female C = 71% female | | | | |
| Conception treatment allocation: UNCLEAR       | | | | | |
| Binding of investigators: NO                   | | | | | |
| Binding of subjects: YES                       | | | | | |
| Known confounders accounted for by study design: PARTIAL | | | | | |
| Attrition of subjects and reasons: YES         | Dropout rate: I = 12%, C = 14% | | | | |
| Fisch et al. (2003), USA                       | I = 163 patients with an advanced solid tumour and expected survival between 3 and 24 months | I = SSRI fluoxetine (20 mg day⁻¹) for 12 weeks (n = 83) | Depressive symptoms: 11-item BZSDS | The fluoxetine group improved significantly compared with placebo on depression scale (P ≤ 0.0005). Mean decrease in BZSDS score from baseline to end point was 13.5% in the fluoxetine group and 2.4% in the control group. Tolerability: 9 (33%) of 27 patients in fluoxetine arm reported one or more episodes of emesis at study completion visit compared with two (4.6%) of 43 patients receiving placebo (P ≤ 0.01) although there were significantly more fluoxetine patients receiving radiation therapy | Not reported |
| Design: Randomised placebo-controlled trial    | C = 52.6 (11.3) | C = placebo for 12 weeks (n = 80) | Assessments performed at baseline and every 3 to 6 weeks thereafter. Patients were assessed for 12 weeks and complete assessment involved three to five sessions of data collection. After 12 weeks, patients were given option to continue the study drug blinded for up to 9 months | | |
| Random allocation to treatment groups: YES     | Gender: I = 45% female C = 55% female | | | | |
| Conception treatment allocation: YES           | | | | | |
| Binding of investigators: YES                  | | | | | |
| Binding of subjects: YES                       | | | | | |
| Known confounders accounted for by study design: PARTIAL | | | | | |
| Attrition of subjects and reasons: YES         | Dropout rate: I = 54%, C = 44%, NS | | | | |
| Razav et al. (1996), Belgium                   | I = 91 cancer patients with a major depressive disorder or an adjustment disorder as defined by DSM-III Patients with score of 13 or higher on the HADS at start | I = SSRI fluoxetine treatment (20 mg day⁻¹) (n = 45) | Depression/depressive symptoms MADRS, HADS | HADS, NS | Not reported |
| Design: Experimental randomised placebo-controlled trial | C = Placebo (n = 46) | | Measured at baseline, 1, 3 and 5 weeks after the intervention | | |
| Random allocation to treatment groups: YES     | After a single-blind placebo period of 1 week patients (to exclude early placebo responders and false-positive cases for depression) were randomised to: | | Digestive and neuropsychiatric types of adverse events were more frequent in the intervention group although this was not significant. | | |
| Conception treatment allocation: YES           | | | | | |
| Binding of investigators: YES                  | | | | | |
| Binding of subjects: YES                       | | | | | |
| Known confounders accounted for by study design: PARTIAL | | | | | |
| Attrition of subjects and reasons: YES         | Dropout rate: I = 33%, C = 15% (P = 0.04) | | | Caseness: NS | The successful response rate defined by HADS score lower than 8 after 5 weeks of treatment was not significantly higher (11%) in the intervention group than the placebo group (7%) |
| Pharmacological studies (skin cancer)          | I = 40 patients with malignant melanoma who were to receive high-dose interferon | Interferon alpha has been associated with symptoms that overlap with those | Depression: HAM-D21, CDS, DSM-IV | Tolerability: After 12 weeks, small reversible retinal haemorrhages developed in two patients and one patient had more Paroxetine treatment significantly reduced the incidence of major depression | | |
| Musselman et al. (2001), USA                   | C = 82% female | | Assessment performed at | | |
Symptoms consistent with major depression developed in two of the 18 (11%) patients in the paroxetine group and nine of the 20 (45%) patients in the placebo group.

Effectiveness of treatment for depression/depressive symptoms

Table 1

| Author (date), country of origin and study quality | Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|--------------------------------------------------|----------|-----------------|--------------------------------------------------------|---------|------------------------|
| Random allocation to treatment groups: YES       | I = paroxetine, C = Control | | | severe retinal haemorrhages associated irreversible loss of vision. All three patients were taking paroxetine. Retinal haemorrhage is a rare side effect of paroxetine and high rates of retinal complications occur in patients treated with interferon alpha. Paroxetine significantly decreased the likelihood that interferon alpha therapy would be discontinued because of severe depression or related neurotoxic effects (P = 0.05) | (P = 0.04) Symptoms consistent with major depression developed in two of the 18 (11%) patients in paroxetine group and nine of the 20 (45%) patients in the placebo group HAM-D21 (P = 0.01) |
| Concealed treatment allocation: YES              | | I = SSRI paroxetine: Two weeks before the initiation of interferon alpha therapy SSRI Paroxetine (10 mg day\(^{-1}\) tablet) for one week (20 mg day\(^{-1}\) 2 tablets) for one week. Four weeks after the initiation of paroxetine therapy the dosage could be increased up to 40 mg day\(^{-1}\) 4 tablets (n = 20) C = placebo therapy (n = 20) | | | |
| Binding of investigators: YES                    | | | | | |
| Known confounders accounted for by study design: PARTIAL | | | | | |
| Attrition of subjects and reasons: YES           | | | | | |
| Dropout rate: I = 0%, C = 0%                     | | | | | |

Pharmacological studies (breast cancer)

Roscoe et al (2005), USA
Design: Randomised placebo-controlled trial
Random allocation to treatment groups: YES
Concealed treatment allocation: YES
Binding of investigators: YES
Binding of subjects: YES
Known confounders accounted for by study design: PARTIAL
Attrition of subjects and reasons: YES
Dropout rate: I = 25%, C = 21%

Van Heeringen and Zivkov (1996), Belgium
Design: Experimental randomised placebo-controlled trial
Random allocation to treatment groups: YES
Concealed treatment allocation: UNCLEAR
Binding of investigators: YES
Binding of subjects: YES
Known confounders accounted for by study design: PARTIAL
Attrition of subjects and reasons: YES
Dropout rate: I = 21%, C = 56% (P = 0.014)

Psychotherapeutic studies (cancer various sites)

Kuiper et al (2004), The Netherlands
Design: Experimental randomised controlled trial
Random allocation to treatment groups: YES

59 couples with medical diagnosis of cancer in one partner with an estimated life expectancy of at least 6 months for the ill partner

I = CBT: brief counselling program directed at couples focused on the exchange of social support and help between both partners. Five

Depressive symptoms
Psychological distress – CES-D I = Once before intervention, 1 week postintervention and 3 months postintervention

Among patients psychological distress decreased significantly 1 week after the intervention (P < 0.05). ES = 0.55 Mean decrease in CES-D score for patients from baseline to end point was 31.7%
Table 1 (Continued)

| Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|----------|-----------------|--------------------------------------------------------|---------|-------------------------|
| Author (date), country of origin and study quality | Mean age (years) (s.d.): I = Patient 50 (12), C = Patient 49 (10) | CESD-20 Measured at baseline, time 2 midway through intervention and time 3 one month postintervention (24 weeks) | Patients who received the intervention had significantly fewer symptoms between baseline and time 2. CESD-20 at time 2 (P = 0.03) | Not reported |
| Concealed treatment allocation: UNCLEAR | I = 90 min sessions led by a psychologist held biweekly. The approach was cognitive-behaviourally oriented (n = 20) C = waiting list group (n = 19) | | | |
| Binding of investigators: NO | I2 = twice before intervention, I week postintervention and 3 months postintervention | | in the experimental group and −7.6% in the waiting list group | |
| Binding of subjects: NO | Known confounders accounted for by study design: NO, cointerventions not reported | | Not reported | |
| Attrition of subjects and reasons: YES | Dropout rate: I = 37.5%, C = 40.7% | | | |

**Given et al (2004), USA**
Design: Experimental randomised controlled trial
Random allocation to treatment groups: YES
Concealed treatment allocation: UNCLEAR
Blinding of investigators: NO
Blinding of subjects: NO
Known confounders accounted for by study design: NO, cointerventions not reported
Attrition of subjects and reasons: YES
Dropout rate: I = 32%, C = 27%

**Psychotherapeutic studies (cancer various sites)**
Rawl et al (2002), USA
Design: Experimental randomised controlled trial
Random allocation to treatment groups: YES
Concealed treatment allocation: YES
Blinding of investigators: NO
Blinding of subjects: NO
Known confounders accounted for by study design: NO, cointerventions not reported
Attrition of subjects and reasons: YES
Dropout rate: I = 38%, C = 19%

I = CBT: 10 contact (1 h sessions), 20 week experimental group cognitive behavioural approach for symptom management. Each strategy for addressing a symptom problem was evaluated at follow-up with the patient. If the strategy had been tried and was effective it was retained and if not new strategies were introduced (n = 118) C = conventional care (n = 119)

Depressive symptoms – CES-D
Baseline, 10 and 20 weeks

The intervention had a short-term (10 weeks) but no long-term (20 weeks) effect on patient depressive symptoms (ES = 0.25 – 0.33 at 10 and 20 weeks, respectively)

The intervention was more effective in lowering depressive symptoms at 10 weeks among patients with higher levels of baseline symptom severity. Among patients with high levels of baseline depression, the intervention was less successful in lowering depressive symptoms at 10 weeks than the conventional care control group alone
| Author (date), country of origin and study quality | Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|------------------------------------------------|----------|-----------------|--------------------------------------------------|---------|------------------------|
| McLachlan et al (2001), Australia | 450 cancer patients | **I** = Intervention and **C** = Control | Depression/depressive symptoms | For patient subgroup that were moderately or severely depressed at baseline, significant reduction in depression at 6 months ($P < 0.001$) | At 2 and 6 months, 73 and 90% of patients who were moderately or severely depressed at baseline were still so, whereas in the intervention arm, there were 58 and 45%, respectively |
| Design: Experimental randomised controlled trial | The authors stated that patient demographics were well balanced in the two arms. Median age (years) (range): 61 (18–92) Gender: 41% female | **I** = Computer-based assessment and individually tailored care plans: A computer-generated one-page summary of the questionnaire results (CNQ, EORTC QLQ-30, BDI) was made available immediately for consideration during the consultation with the doctor. After discussion with the doctor and patient the coordination nurse formulated an individualised management plan ($n = 296$) | | |
| Random allocation to treatment groups: YES | | **C** = standard care ($n = 54$) | | |
| Concealed treatment allocation: YES | | | | |
| Binding of investigators: NO | | | | |
| Binding of subjects: NO | | | | |
| Known confounders accounted for by study design: NO; cointerventions not reported | | | | |
| Attrition of subjects and reasons: YES Dropout rate: I = 28%, C = 31% | | | | |
| Depressive symptoms CES-D and SCL-90-R measured at baseline, 8 weeks and 6 months | Subjects who received either cognitive behavioural or social support group interventions had significantly lower CES-D scores than controls at 8 weeks ($P < 0.001$) and at 6 months social support group interventions had significantly lower CES-D scores than controls ($P < 0.001$). Mean decrease in CES-D score for patients from baseline to 6 months was 11% for the cognitive behavioural group, 29% for the social support group and 14% in the control group | Not reported | | |
| Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|----------|----------------|------------------------------------------------------|---------|------------------------|
| Winzelberg et al (2003), USA Design: Experimental randomised controlled trial Random allocation to treatment groups: YES Concealed treatment allocation: NO Blinding of investigators: NO Blinding of subjects: NO Known confounders accounted for by study design: NO, cointerventions not reported Attrition of subjects and reasons: YES Dropout rate: 19% overall | I = Social support/education: web-based psychosocial support group, 12 weeks. The program introduced a new topic related to breast cancer each week and the mental health professional facilitated a discussion on these topics and related concerns. On the website participants were able to read personal stories from survivors, share their own experiences and keep a private web-based personal journal. Participants wrote a brief description of how they were feeling when they logged on (n = 36) C = Wait-list control (n = 36) | Depressive symptoms CES-D Measured at baseline and at end of intervention (12 weeks) | CES-D (P < 0.01), ES = 0.54 Mean decrease in CES-D score for patients from baseline to 12 weeks was 36% in the experimental group and 4% in the control group | Not reported |
| Antoni et al (2001), USA Design: Experimental randomised controlled trial Random allocation to treatment groups: YES Concealed treatment allocation: NO Blinding of investigators: NO Blinding of subjects: NO Known confounders accounted for by study design: NO, cointerventions not reported Attrition of subjects and reasons: attrition but not reason: Dropout rate: 26% overall | I = CBT: 10-week group cognitive behavioural stress management intervention. Weekly for ten 2-h sessions. It included both problem-focused (e.g. active coping and planning) and emotion-focused (e.g. relaxation training, use of emotional support) coping strategies (n = 47) C = Education/information: One-day group seminar approximately 16–18 weeks postsurgery. To provide at least some information on all of the topics covered by the intervention condition (n = 53) | Depressive symptoms POMS, CES-D Measured at baseline, post-intervention (3 months), 3 months and 9 months | POMS, NS CES-D In the intervention group the proportion of women meeting criteria for moderate levels of depressive symptoms fell significantly at 3 months postintervention, 6 months and 12 months (P < 0.04) | Not reported |
| Goodwin et al (2001), Canada Design: Experimental randomised controlled trial Random allocation to treatment groups: YES | I = CBT: Weekly supportive–expressive group therapy (90 min sessions) for at least one year. Groups consisted of 8–12 women and two | Depressive symptoms POMS Measured at baseline and 4, 8 and 12 months after randomisation | POMS Depression dejection was significantly lower in the intervention group (P = 0.002) 1 year after randomisation The psychological intervention was not associated with prolonged survival | Not reported |
Table 1 (Continued)

| Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|----------|-----------------|--------------------------------------------------------|---------|------------------------|
| **Classen et al. (2001), USA**<br>Design: Experimental randomised controlled trial<br>Random allocation to treatment groups: YES<br>Concealed treatment allocation: NO<br>Blinding of investigator: NO<br>Blinding of subjects: NO<br>Known confounders accounted for by study design: NO, cointerventions not reported<br>Attrition of subjects and reasons: YES<br>Dropout rate: 18% overall | I = CBT/education: 1 year of weekly (90 min sessions) of supportive—expressive group therapy and educational materials. The treatment strategy is to facilitate discussion of issues that are uppermost in the patients’ minds rather than imposing topics to be discussed (n = 64)<br>C = Education/information: Education materials only (n = 61) | Depressive symptoms POMS<br>Measured at baseline and every 4 months during the first year | POMS Depression<br>When follow-up assessments undertaken within 1 year of the patients’ death were excluded in the secondary analyses POMS Depression subscale was significantly lower for the treatment group, ES = 0.27 | Not reported |
| **Fukui et al. (2000), Japan**<br>Design: Experimental randomised controlled trial<br>Random allocation to treatment groups: YES<br>Concealed treatment allocation: NO<br>Blinding of investigator: NO<br>Blinding of subjects: NO<br>Known confounders accounted for by study design: NO, cointerventions not reported<br>Attrition of subjects and reasons: YES<br>Dropout rate: 8% overall | I = CBT: Six group sessions of structured psychosocial intervention with a cognitive-behavioural approach. It included health education, coping skills training, stress management and psychological support (n = 25)<br>C = Wait-list control (n = 25) | Depressive symptoms HADS, POMS<br>Measured at baseline, 6 weeks and 6 months | HADS, NS | Not reported |
| **Sandgren et al. (2000), USA**<br>Design: Experimental randomised controlled trial<br>Random allocation to treatment groups: YES<br>Concealed treatment allocation: NO<br>Blinding of investigator: NO<br>Blinding of subjects: NO<br>Known confounders accounted for by study design: NO, cointerventions not reported | I = CBT: Individual psychosocial therapy (cognitive-behavioural) delivered by three female psychology graduate students by telephone. There were a total of ten therapy sessions (average duration 20–25 min) once a week for 4 weeks and then every other week for six more sessions. The intervention focused on four aspects of depressive symptoms: information processing, sense of control, illness beliefs, and psychological support (n = 25)<br>C = Wait-list control (n = 25) | Depressive symptoms POMS<br>Measured at baseline, 1, 4 and 10 months | POMS Depression, NS | Not reported |
| Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|----------|-----------------|--------------------------------------------------------|---------|------------------------|
| Attrition of subjects and reasons: YES Dropout rate: 15% overall | areas: providing support, teaching coping skills, managing anxiety and stress and helping to solve patient generated problems. \( n = 24 \)  
C = No therapy control \( n = 29 \) | | | |
| Psychotherapeutic studies (breast cancer) | | | | |
| Edelman et al (1999), Australia | Design: Experimental randomised controlled trial  
Random allocation to treatment groups: YES  
Concealed treatment allocation: NO  
Blinding of investigators: NO  
Blinding of subjects: NO  
Known confounders accounted for by study design: NO, cointerventions not reported | Attrition of subjects and reasons:  
Attrition but no reasons Dropout rate: 23% overall | After completion of therapy significant improvement in depressive symptoms \( P = 0.008 \) | Not reported |
| Marchioro et al (1996), Italy | Design: Experimental randomised controlled trial  
Random allocation to treatment groups: YES  
Concealed treatment allocation: NO  
Blinding of investigators: NO  
Blinding of subjects: NO  
Known confounders accounted for by study design: NO, cointerventions not reported | Attrition of subjects and reasons: NO | Depression scores improved significantly over time in the intervention group \( ES = 0.27 \) | Not reported |
| McArdle et al (1996), UK | Design: Experimental randomised controlled trial  
Random allocation to treatment groups: YES  
Concealed treatment allocation: NO | | | |

**Table 1** (Continued)
| Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|----------|-----------------|--------------------------------------------------------|---------|------------------------|
| Author (date), country of origin and study quality | | | | |
| | | breast care nurse (information and counselling) (n = 70) | | |
| | I = Intervention (n = 56) | C = Control (n = 57) | | |
| | I = Intervention (n = 56) | C = Control (n = 57) | | |
| | I = Intervention (n = 56) | C = Control (n = 57) | | |
| | I = Intervention (n = 56) | C = Control (n = 57) | | |
| Binding of investigators: NO | | | | |
| Binding of subjects: NO | | | | |
| Known confounders accounted for by study design: NO, cointerventions not reported | | | | |
| Attrition of subjects and reasons: YES | Dropout rate: 17% overall | | | |
| Psychotherapeutic studies (gynaecological cancer) | | | | |
| Burton et al (1995), UK | 200 women awaiting mastectomy or sector mastectomy for breast cancer | | | |
| Design: Experimental randomised controlled trial | Mean age (years): | | | |
| Random allocation to treatment groups: YES | I1 = 61 | | | |
| Concealed treatment allocation: NO | I2 = 62 | | | |
| Binding of investigators: NO | I3 = 64 | | | |
| Binding of subjects: NO | C = 57 | | | |
| Known confounders accounted for by study design: NO, cointerventions not reported | | | | |
| Attrition of subjects and reasons: YES | | | | |
| Attrition unclear and no reasons | | | | |
| Petersen and Quinlivan (2002), Australia | 53 patients with gynaecological cancer | | | |
| Design: Experimental randomised controlled trial | Mean age (years) (s.d.): | | | |
| Random allocation to treatment groups: YES | I1 = 63.0 (9.6) | | | |
| Concealed treatment allocation: YES | C = 61.2 (13.5) | | | |
| Binding of investigators: NO | | | | |
| Binding of subjects: NO | | | | |
| Known confounders accounted for by study design: NO, cointerventions not reported | | | | |
| Attrition of subjects and reasons: YES | | | | |
| Dropout rate: 6% overall | | | | |
| | I = Counselling/relaxation: Individual preoperative interview and a 30 min brief psychotherapeutic intervention (n = 50) | | | |
| I = Counselling/psychotherapy: Individual preoperative interview and a 30 min ‘chat’ to control for the effects of attention (n = 50) | | | | |
| I = Preoperative interview only (n = 50) | | | | |
| C = routine hospital care control (n = 50) | | | | |
| Depression, Depressive symptoms | HADS, GHQ-28, PSE schedule | Measured at baseline, 4 days, 3 months and 1 year after surgery | | |
| More control patients were cases for depression on PSE criteria at one year than patients in the experimental groups (P = 0.037) | | | | |
| The intervention was associated with a significant reduction in total HADS score (P = 0.002), reduction in HADS Mild/moderate Depression subscale (P = 0.02), and lower GHQ-28 scores (P = 0.03) | | | | |
| No significant difference was found in the fourth subscale of major depression | | | | |
| Author (date), country of origin and study quality | Subjects | Intervention (n) | Outcome measures for depression or depressive symptoms | Results | Caseness for depression |
|--------------------------------------------------|----------|-----------------|-------------------------------------------------------|---------|------------------------|
| **Psychotherapeutic studies (testicular cancer)** |          |                 | I = CBT/PST: Adjuvant psychological therapy which uses both cognitive and behavioural approaches includes strategies such as problem solving and regaining control. The intervention consisted of six individual sessions each lasting 1 h by a state registered mental health nurse who was experienced in caring for patients with testicular cancer (n = 36) | Depression/depressive symptoms | HADS Depression scale, NS | The proportion of patients scoring above the threshold on subscale was not influenced by adjuvant psychological therapy |
| Moynihan et al (1998), UK | 73 men with newly diagnosed testicular cancer | I = CBT/PST: Adjuvant psychological therapy which uses both cognitive and behavioural approaches includes strategies such as problem solving and regaining control. The intervention consisted of six individual sessions each lasting 1 h by a state registered mental health nurse who was experienced in caring for patients with testicular cancer (n = 36) | | | |
| | | | C = standard care (n = 37) | | |
| **Prostate cancer** | | | I = Social support: Peer support program – 10 men who were long term survivors of prostate cancer received 2 h training session to act as support partners. Each dyad met eight times during an 8 week period and each dyad determined the focus and direction of its own exchanges (n = 15) | Depressive symptoms | There was a significant difference in depression between groups at 4 weeks (P = 0.02) (ES = 0.99), but no significant difference at 8 weeks Mean decrease in GDS score for patients from baseline to 4 weeks was 88% in the experimental group and 0% in the control group | Not reported |
| Weber et al (2004), USA | 30 men who had recently undergone a radical prostatectomy for prostate cancer Mean age (years) (s.d.): I = 57.5 (6.7) C = 59.7 (6.6) | | | | | |
| | | I = Social support: Peer support program – 10 men who were long term survivors of prostate cancer received 2 h training session to act as support partners. Each dyad met eight times during an 8 week period and each dyad determined the focus and direction of its own exchanges (n = 15) | | | |
| | | | C = usual care (n = 15) | | |

BZSDS = Brief Zung Self-Rating Depression Scale; HAM-D21 = 21-item Hamilton Depression Rating Scale; SSRI = selective serotonin reuptake inhibitor; CES-D = Center for Epidemiological Studies Depression scale; POMS = Profile of Mood States; TCA = tricyclic antidepressant; MADRS = Montgomery Asberg depression rating scale; CES = Carroll Depression Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; DSM III = Diagnostic and Statistical Manual of Mental Disorders III; HADS = Hospital Anxiety and Depression Scale; CESD-20 = 20-item Center of Epidemiological Studies Depression Scale; ES = effect size; Dutch POMS = Dutch version of the shortened Profile of Mood States; GDS short version = Geriatric Depression Scale; BDI = Beck Depression Inventory; GHQ-28 = 28-item General Health Questionnaire; GHQ-30 = 30-item General Health Questionnaire; SCL-90-R = Symptom Checklist 90 Revised; s.d. = standard deviation; PST = problem-solving therapy; CBT = cognitive behaviour therapy; PSE schedule = Present State Examination schedule; CNQ = Cancer Needs Questionnaire – short form; EORTC: QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.
(12 and 14%, respectively). Paroxetine was also found to be effective in reducing depressive symptoms in breast cancer patients undergoing chemotherapy (Roscoe et al, 2003).

Fluoxetine was found to be effective in reducing depressive symptoms in patients with advanced solid tumours (Fisch et al, 2003). Frequency of vomiting was significantly higher in patients receiving fluoxetine (nine of 27 (33%)) compared with patients receiving placebo (two of 43 (4.6%)), but there were significantly more fluoxetine patients receiving radiation therapy. Dropout rates were high with 54% for the intervention group and 44% for the controls.

There was a reduction in depressive symptoms in breast cancer patients who received mianserin compared with those receiving placebo (Van Heeringen and Zivkov, 1996). Tolerability appeared to be good with no significant differences between groups for adverse events and changes in vital signs. There were also significantly fewer dropouts from the intervention group (21%) when compared to controls (56%) (P = 0.014).

### Psychotherapeutic studies

Characteristics of the 18 included trials of psychotherapeutic interventions are shown in Table 1. Studies were conducted in Europe (n = 5) (Burton et al, 1995; Marchioro et al, 1996; McArdle et al, 1996; Moynihan et al, 1998; Kuijer et al, 2004), the United States of America (n = 8) (Evans and Connis, 1995; Sandgren et al, 2000; Antoni et al, 2001; Classen et al, 2001; Rawl et al, 2002; Winzelberg et al, 2003; Given et al, 2004; Weber et al, 2004) and Canada (n = 1) (Goodwin et al, 2001), Australia (n = 3) (Edelman et al, 1999; McArdle et al, 2001; Petersen and Quinlivan, 2002) and Japan (n = 1) (Fukui et al, 2000). The mean sample size in the intervention and control group was 61 patients (range 15–296) and 52 patients (range 15–154), respectively. The average age of patients ranged from 49 to 64 years. The proportion of female participants ranged from between 41 to 100%. Eight studies were multicentre trials (McArdle et al, 1996; Classen et al, 2001; Goodwin et al, 2001; McLachlan et al, 2001; Petersen and Quinlivan, 2002; Rawl et al, 2002; Given et al, 2004; Weber et al, 2004) and 10 were single-centre trials (Burton et al, 1995; Evans and Connis, 1995; Marchioro et al, 1996; Moynihan et al, 1998; Edelman et al, 1999; Fukui et al, 2000; Sandgren et al, 2000; Antoni et al, 2001; Winzelberg et al, 2003; Kuijer et al, 2004).

#### Methodological quality

The methodological quality of these trials is summarised in Table 2. The sample size exceeded 100 in eight of 18 (44%) trials (Burton et al, 1995; McArdle et al, 1996; Edelman et al, 1999; Classen et al, 2001; Goodwin et al, 2001; McLachlan et al, 2001; Rawl et al, 2002; Given et al, 2004). All studies randomly allocated subjects to treatment groups. Binding of investigators was reported in two (11%) trials (Moynihan et al, 1998; Goodwin et al, 2001). All 18 (100%) studies provided a clear description of the intervention and had a representative source of subjects. Reporting of attrition of subjects was provided in 16 (89%) studies and reasons for withdrawal in 13 (72%) (see Table 1). Dropout rates for intervention and controls ranged from 0 to 41%.
et al, 2001; Weber et al, 2004). None of the trials reported avoiding or monitoring the use of pharmacological or CAM cointerventions.

**Depression** Only four of 18 (22%) trials reported the efficacy of psychotherapeutic interventions in terms of caseness for depression (Burton et al, 1995; Moynihan et al, 1998; McLachlan et al, 2001; Petersen and Quinlivan, 2002). Of these, one found counselling/psychotherapy to be effective in reducing caseness for depression in breast cancer patients at 1 year follow-up ($P = 0.037$; Burton et al, 1995), and another found counselling/relaxation to be effective in reducing caseness for depression in gynaecological cancer at 6 weeks follow-up ($P = 0.0001$; Petersen and Quinlivan, 2002). Computer-based assessments and individually tailored care plans were also associated with a reduction in the proportion of moderately or severely depressed cancer patients at 2 and 6 months follow-up (McLachlan et al, 2001); the statistical significance of this finding was not reported. However, in men newly diagnosed with testicular cancer, cognitive behaviour therapy/problem-solving therapy was not found to significantly reduce the proportion scoring above threshold for depression (Moynihan et al, 1998).

**Depressive symptoms** All 18 trials (100%) reported the impact of psychotherapeutic interventions on the level of depressive symptoms as indicated by scores on questionnaires.

**Cognitive behavioural therapy** Several trials reported cognitive behavioural therapy (CBT) to be effective. CBT was found to reduce depressive symptoms in patients with breast, gastrointestinal, lymphoma, brain and lung cancers at 1 week postintervention (ES = 0.55) (Kuijer et al, 2004), and also in depressed patients with lung, bladder, prostate and head–neck cancers receiving radiation treatment at 8 weeks follow-up ($P < 0.01$) (Evans and Connis, 1995). Efficacy was also reported for women with metastatic breast cancer immediately after completion of the intervention ($P = 0.008$) (Edelman et al, 1999); women newly treated for stage 0–II breast cancer at 3 months postintervention, 6 and 12 months ($P < 0.04$) (Antoni et al, 2001); women with metastatic breast cancer assessed for depressive symptoms at 4, 8 and 12 months (ES = 0.27) (Classen et al, 2001); and in metastatic breast cancer at 1 year ($P = 0.002$) (Goodwin et al, 2001). In addition, one study found CBT to have a short-term (10 weeks), but no long-term (20 weeks), effect on depressive symptoms in patients diagnosed with a solid tumour and receiving a first cycle of chemotherapy (ES = 0.25 and 0.33 at 10 and 20 weeks, respectively) (Given et al, 2004). However, patients in the experimental group who entered with higher depressive symptoms had higher levels of depressive symptoms at 10 weeks than patients in the control group. Two other trials found CBT to have no significant effects on depressive symptoms in two studies of women with breast cancer (Fukui et al, 2000; Sandgren et al, 2000), but these both had sample sizes below 100 as compared to only two of the six studies that found CBT to be effective.

**Counselling/psychotherapy** Counselling/psychotherapy was found to be effective in reducing depressive symptoms in newly diagnosed women with nonmetastatic breast cancer assigned to adjuvant chemotherapy after surgery, with persistence over 9 months follow-up (ES = 0.27, Marchioro et al, 1996). Counselling/relaxation was also found to be effective in reducing mild/moderate depressive symptoms 6 weeks after therapy in patients with gynaecological cancer (HADS mild/moderate depression subscale, $P = 0.02$) but not severe levels of depressive symptoms (GHQ-28 Major depressive symptoms subscale, NS; Petersen and Quinlivan, 2002).

**Supportive** The provision of group social support was found to be as effective as CBT in reducing depressive symptoms in depressed patients with lung, bladder, prostate and head–neck cancer who were receiving radiation treatment, when assessed at 8 weeks ($P < 0.01$) and also effective at 6 months follow-up compared with controls ($P < 0.01$) (Evans and Connis, 1995). Peer support from long-term survivors of prostate cancer was found to be effective in reducing depressive symptoms in men who had recently undergone a radical prostatectomy when assessed at 4 weeks ($P = 0.02$), but not at 8 weeks, follow-up (Weber et al, 2004).

A web-based social support group was also found to be effective in reducing depressive symptoms in women with primary breast cancer when assessed at the end of the 12 weeks intervention (ES = 0.54) (Winzelberg et al, 2003).

In a complex trial that compared different levels of support, routine care plus education/information/counselling/support from breast care nurse was found to be more effective than (1) routine care plus education/information/counselling/support from a voluntary organisation, (2) routine care plus education/information/counselling/support from breast care nurse and voluntary organisation or (3) routine care from ward staff ($P = 0.015$, 0.003, 0.072; Mcardle et al, 1996). The failure to reduce morbidity in the combined group is difficult to explain.

Computer-based assessments and individually tailored care plans together with emotional support and counselling by nurses was found to reduce depressive symptoms midway through the intervention in newly diagnosed breast, colon or lung cancer patients who were receiving chemotherapy ($P = 0.05$) (Rawl et al, 2002). Computer-based assessments and individually tailored care plans were also found to reduce depressive symptoms ($P = 0.001$) at 6 months follow-up for patients with lung, head and neck, gynaecologic, haematology/lymphoma, melanoma and other types of cancers unspecified in the paper (McLachlan et al, 2001).

**DISCUSSION**

This systematic review indicates that there is limited trial data on the efficacy/tolerability of antidepressants and psychotherapeutic interventions for patients with cancer and depression. The reviewed studies varied in the type of pharmacological or psychotherapeutic interventions employed, the characteristics of the studied populations, the type, grade and stage of subjects’ cancer, the treatments being received, and the trial design, including outcome measures used. Most were of small size and lacked control for possible confounding factors. Such limitations indicate the need for cautious interpretation of the review’s findings beyond the contexts within which these studies were conducted.

**Pharmacological studies**

Only three of the six trials that involved pharmacological interventions reported the efficacy of antidepressants in terms of change in caseness for clinical depression as opposed to change scores indicating levels of depressive symptoms. Paroxetine was found to be effective in reducing major depression in patients with malignant melanoma who were to receive high-dose interferon alpha therapy (Musselman et al, 2001), and in reducing caseness for depression in breast cancer patients receiving chemotherapy (Roscoe et al, 2005). Fluoxetine was not effective in reducing caseness for depression in a trial that included patients with breast, gynaecological or haematological cancer (Razavi et al, 1996). However, the study by Razavi et al (1996) was only of brief duration (5 weeks) and higher doses of fluoxetine were not used.

Paroxetine and fluoxetine were both effective in reducing depressive symptoms in three trials that included patients with a range of cancers (breast, lung, haematological, gynaecological and gastrointestinal) (Fisch et al, 2003; Morrow et al, 2003; Roscoe et al, 2005), and the tetracyclic antidepressant mianserin was also
shown to be effective in reducing depressive symptoms in breast cancer (Van Heerening and Zivkow, 1996).

Some nonpsychological benefits of antidepressant therapy also emerged, such as improved adherence to cancer treatment. For example, paroxetine significantly decreased the likelihood that interferon alpha therapy in malignant melanoma would be discontinued because of severe depression or related neurotoxic effects (Musselman et al, 2001).

Although tolerability was only reported in four of the six pharmacological studies, overall, the tolerability of antidepressants in patients with cancer appears to be good. Although there was some evidence of adverse effects, these may well have been caused by other aspects of the treatment (e.g. radiotherapy, interferon alpha) that these patients were receiving.

**Psychotherapeutic interventions**

Only four of the reviewed studies reported the efficacy of psychotherapeutic interventions in treating depression. Of these, two trials reported significant benefits of counselling/psychotherapy (Burton et al, 1995) and counselling/relaxation (Petersen and Quinlivan, 2002) in reducing caseness for depression for patients with breast cancer and gynaecological cancer, respectively, and a third found computer-based assessment (including completion of the Beck Depression Inventory) and individually tailored care plans by a nurse to be associated with a reduction in the proportion of patients with moderate or severe depression (McLachlan et al, 2001).

There is more extensive evidence that psychotherapeutic interventions are effective in reducing depressive symptoms in cancer patients, at least in the short-term. Seven trials found cognitive behavioural therapy to be effective in reducing depressive symptoms, with persistence of improvement demonstrated for up to a year (Evans and Connis, 1995; Edelman et al, 1999; Antoni et al, 2001; Classen et al, 2001; Goodwin et al, 2001; Given et al, 2004; Kuier et al, 2004). However, two trials found CBT to have no significant effects on depressive symptoms (Fukui et al, 2000; Sandgren et al, 2000), and one study found CBT to have a short-term (10 weeks), but no long-term (20 weeks), effect (Given et al, 2004).

Other psychotherapeutic approaches that may be effective in lowering depressive symptoms include supportive interventions in the form of social support groups, supportive dyads or web-based support groups (Evans and Connis, 1995; Winzelberg et al, 2003; Weber et al, 2004), computer-based assessments and individually tailored care plans (McLachlan et al, 2001; Rawl et al, 2002), and counselling/psychotherapy and counselling/relaxation (Burton et al, 1995; Marchioro et al, 1996).

**Methodological limitations**

A major limitation of all 24 trials reviewed was the lack of consistent avoidance/monitoring of the use of psychotherapeutic, pharmacological or CAM cointerventions by subjects. In general the reviewed studies had small sample sizes, and had not attempted to control for confounding, so limiting the validity of findings. Many patients being treated for cancer will be receiving other aspects of the treatment (e.g. radiotherapy, interferon alpha) that these patients were receiving.

A large proportion of the psychotherapeutic studies were single-centre trials, so limiting the generalisability of findings beyond the context of the trial setting. Psychotherapeutic interventions are likely to be highly dependent on the practitioners’ training, skills and other attributes. Hence, multicentre trials are needed to confirm the applicability and effectiveness of interventions. Furthermore, many of the studies report findings that only just achieve statistical significance, suggesting the likelihood of publication bias that needs to be considered in the interpretation of their findings.

There was only one trial that selected patients on the basis of a diagnosis of depression (Evans and Connis, 1995), but the change in caseness for depression was not reported in this study. The negative findings of some studies may reflect that recruited subjects did not have significant psychological morbidity; psychotherapeutic and pharmacological interventions should be offered to patients with clinically meaningful levels of depression/depressive symptoms.

Given the small number of studies on the efficacy on antidepressants with cancer patients in general, there is a need for further work with specific groups of cancer patients. Tolerability data were not always recorded and reported. It is important that future studies include recording and reporting of adverse effects, especially as such effects are likely to have an impact on compliance (Stokes, 1993). Concerns that antidepressants may lead to or accelerate the development of cancer also need further investigation (Brandes et al, 1992; Wallace et al, 2001).

Finally, while the randomised controlled studies in this review may be of relevance to palliative care, no studies were conducted with palliative care patients as subjects. Controlled studies including such subjects are even more difficult to conduct than those on nonpalliative cancer patients. Depression is difficult to diagnose in such patients, and depressive symptoms are very similar to the general symptoms of end-stage cancer. While high attrition rates, together with high heterogeneity, would lead to the need for very large sample sizes, recruitment is difficult for practical and ethical reasons (Grande and Todd, 2000; Addington-Hall, 2002). There is also a lack of reporting on syndromal depression and this too requires further work.

**CONCLUSION**

The sparse number of studies of pharmacological interventions for cancer patients with depression provides some evidence that antidepressants are effective in reducing depression/depressive symptoms in cancer patients. Although more data are needed regarding the safety and efficacy of antidepressants, there is some evidence that cancer patients with depression are responsive to treatment. Overall, the small number of trials of pharmacological interventions for cancer patients with depression/depressive symptoms, high dropout rates in some trials and lack of reporting of adverse events/tolerability should caution against drawing definitive conclusions about which antidepressants are most effective or well tolerated by cancer patients in general or by patients with specific types of cancer.

There is limited trial data on the efficacy of psychotherapeutic interventions in treating depression/depressive symptoms in cancer patients. Cognitive behavioural therapy appears to be effective in reducing depressive symptoms in cancer patients. Social support for cancer patients may also be effective in reducing depressive symptoms.

However, there is a need for more rigorous investigation of the efficacy of both pharmacological and psychotherapeutic interventions, including avoidance/monitoring of the confounding factors and control of confounding factors that these patients were receiving.
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Cohen AJ, Menter A, Hale L (2005) Acupuncture: role in comprehensive treatment for depression and depressive symptoms because of a lack of trial data on effectiveness. The review indicates that there remains a pressing need for more thorough and extensive investigation of the effectiveness and consequences of different approaches to managing depression in cancer patients to inform the design and delivery of effective healthcare services.

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Appendix A

Data Extraction Form  Methodological Quality Instrument (Cho and Bero, 1994) (Table A1).

Table A1

| Reviewer | Article |
|----------|---------|
|          |         |

1. Study design (choose 1 only):
   Experimental randomised:
   - Placebo-controlled trial
   - Controlled trial
   - Comparative trial, no placebo
   - Time series trial
   - Crossover trial
   Experimental, unrandomised:
   - Placebo controlled trial
   - Comparative trial, no placebo
   - Time series trial
   - Crossover trial
   Nonexperimental:
   - Cohort, prospective
   - Cohort, retrospective
   - Cross-sectional
   - Case–control
   - Case reports or case series
   - None of the above (describe):

2. What was the study question? (please use space below)
   - Yes
   - Partial
   - No
   - N/A

3. Was the study question sufficiently described?
4. Was the study design appropriate to answer the study question?
5. Were both inclusion and exclusion criteria specified? (If case study, check N/A)
6. For case studies only: Were patient characteristics adequately reported? (If not case study, check N/A)
7. Were subjects appropriate to the study question?
8. Were control subjects appropriate? (If no controls were used, check No)
9. Were subjects randomly selected from the target population?
10. If subjects were randomly selected, was the method of random selection sufficiently well described? (If subjects were not randomly selected, check N/A)
11. If subjects were randomly allocated to treatment groups, was the method of random allocation sufficiently described? (If subjects were not randomly allocated, check N/A)
12. If blinding of investigators to intervention was possible, was it reported? (If not possible check N/A)
13. If blinding of subjects to intervention was possible, was it reported? (If not possible, check N/A)
14. Was measurement bias accounted for by methods other than blinding?
15. Were known confounders accounted for by study design? (If no known confounders, check N/A)
16. Were known confounders accounted for by analysis? (If no known confounders, check N/A)
17. Was there a sample size justification before the study?
18. Were post hoc power calculations or confidence intervals reported for statistically nonsignificant results?
19. Were statistical analyses appropriate?
20. Were statistical tests stated?
21. Were exact P values or confidence intervals reported for each test?
22. Were attrition of subjects and reason for attrition recorded?
23. For those subjects who completed the study, were results completely reported?
24. Do the findings support the conclusions?
Data Extraction Form: Pharmacological intervention/psychosocial intervention (Table A2).

### Table A2

| Study details | Authors/date | Country of origin: |
|---------------|--------------|-------------------|
| Patient groups similar at baseline? No sig. diffs. | Gender | Yes | No | Unclear |
| | Age | | |
| | Ethnicity | | |
| | Disease distribution | | |
| | Cancer treatment | | |
| | Depression/Depressive symptoms | | |

### Setting/s

**Screening/diagnostic procedure for depression or depressive symptoms**  
(consider issues for access to healthcare treatment)

**Intervention treatment**

1. Description of intervention and implementation?
2. Measure of compliance?
3. Cointerventions: avoided by trial design/monitored  
   (Also consider issues for access to healthcare treatment)

### Possible adverse effects

**Use of diagnostic criteria for depression?**

Outcome measures used (adequately described, valid/reliable?)

**Dropout rates and reasons for withdrawal**

**Noneligible patients**

See table

### Data analysis

Economic analysis as part of trial?

### Conclusion

Effectiveness of treatment for depression/depressive symptoms