The treatment of depression in patients with advanced cancer undergoing palliative care
Annabel Price and Matthew Hotopf

Introduction
Depression is common in patients with advanced cancer and affects function, symptoms, prognosis and service use [1]. A systematic review of depression in palliative populations by Hotopf et al. in 2002 [2] identified 10 studies that used psychiatric diagnostic interviews on populations receiving palliative care and found that the median prevalence estimate of major depression was 15% (range 5–26%).

Concepts of depression in palliative populations need to take into consideration the particular set of circumstances experienced by patients facing terminal illness, including loss of role and previous function. Efforts have been made to recognize and manage emotional distress [3,4] and demoralization [5]; and novel therapeutic interventions aimed at restoring dignity [6,7], meaning [8] and hope [9–11] are being developed, which include therapies for both the individual, couples [12] and the family.

Research into effective treatments for depression in advanced disease presents considerable methodological challenges, including losses to follow-up, changes in disease status, heterogeneity in clinical populations and reluctance to enter patients into trials. The majority of patients with advanced disease do not find participation in psychosocial research burdensome, and many welcome the opportunity to participate [13,14]. Nonetheless, research on the treatment of depression in specific palliative care cancer populations is sparse, and it is necessary to make informed decisions on the basis of research on depression in other physical illnesses.

Barriers to treatment of depression in palliative care populations
Despite the recognition of depression as a common condition in patients with advanced cancer, there are barriers to the detection and effective timely treatment of the condition. Barriers to detection include misattribution of symptoms of depression to those of the underlying disease [15], underconfidence in eliciting psychiatric morbidity by palliative care clinicians and the mistaken belief that depression is an inevitable consequence of terminal illness [16]. In their 1999 survey of antidepressant prescribing in the terminally ill, Lloyd-Williams et al. [17] found that antidepressants were prescribed ‘too
little, too late’. Most patients were within the last 2 weeks of life, and inadequate dosing was common. Palliative care providers lack access to specialist expertise in detecting and managing depression. Price et al. [18] found that 45% of UK hospices had access to neither a psychiatrist nor a psychologist.

**Pharmacological management**

Recent efforts have been made to synthesize the available literature on pharmacological management of depression and generate clinical practice guidelines and recommendations for treatment. Qaseem et al. [19*], in their clinical practice guideline from the American College of Physicians, have assessed the evidence for treatment of depression at the end of life and found good evidence for the effectiveness of the long-term use of tricyclic antidepressants (TCAs) or specific serotonin reuptake inhibitors (SSRIs) and gave a ‘strong recommendation’ for their use in practice. The evidence was classified as ‘moderate on average’ using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) classification because it was derived from studies using patients with cancer, not all of whom were at the end of life.

Miovic and Block [1], following their review of the evidence for treatment of depression in advanced cancer, recommend a combination of antidepressant medication, supportive psychotherapy and patient and family education, although these recommendations were not based on a systematic review of the literature.

When assessing the evidence from studies specifically looking at palliative populations, the conclusions are less clear. Ly and Hotopf [20], in their 2002 systematic review, found only three published trials, two of which were placebo controlled and were unable to draw conclusions about treatment of depression in the palliative setting. They recommended using the wider literature to inform the treatment of depression in this group pending further evidence. In 2000, Gill and Hatcher [21] conducted a Cochrane review of antidepressants for patients with depression and physical illness and identified 18 trials, only two of which studied patients with cancer. The authors concluded that antidepressants led to improvement of depression for adults with medical illness. This review has now been withdrawn and is currently being updated by Rayner et al. [22]

Rodin et al. [23*] have published a more recent systematic review of treatment of depression in cancer patients that identified seven trials of pharmacological agents up to 2005. Only one of these trials involved a population with advanced cancer [24] that compared 12 weeks of treatment with fluoxetine with placebo. The trial had several methodological difficulties, which are described in detail in the review, including a high-attrition rate in both the treatment and placebo groups (54 and 44%, respectively). No significant difference was found in depressive symptoms between the two groups after treatment. On the basis of evaluation of all seven trials, the authors concluded that there was limited evidence for the effectiveness of pharmacological interventions in treatment of depression in cancer patients and stressed the need for further research.

**Antidepressants**

A recent study has been conducted in order to evaluate the effectiveness of the antidepressant sertraline in patients with advanced cancer. Stockler et al. [25*] carried out a multicentre placebo-controlled, double-blind, randomized controlled trial (RCT) of the SSRI sertraline for symptoms of depression and survival in patients with advanced cancer in whom the oncologist ‘doubted the benefits of treatment with an antidepressant’. The study was conducted because previous evidence suggested survival benefits for psychosocial interventions designed to improve well being [26,27]. The investigators hypothesized that antidepressants may improve psychological well being and survival for patients with advanced cancer.

One hundred and eighty-nine patients were recruited, the majority of whom scored low on depression using the Center for Epidemiologic Studies Depression scale. The trials monitoring committee suspended the trial because in interim analyses, the sertraline group appeared to have a shorter survival time, although the final analysis did not show a difference between groups. Sertraline had no significant effect on depression or anxiety in this group.

In addition, a study assessing an algorithm for pharmacological treatment of depression in advanced cancer found that a discontinuation of antidepressants was most often because of their causing delirium [28].

**Psychostimulants**

Psychostimulants have been recommended as a rapid onset treatment of depression, especially suitable to those with a very short life expectancy.

Miovic and Block [1] identified three papers (one review and two uncontrolled trials, not primarily studying depression outcomes) looking at the effectiveness of psychostimulants for people with cancer [29–31]. They concluded that there were several indications for their use, including improving mood, appetite, energy and cognition. They warned, however, about the potential risk of cardiac death with methylphenidate.

Orr and Taylor [32] in their 2007 review of psychostimulants for treatment of depression concluded that
in general populations, psychostimulants were not to be recommended due to concerns about dependency, but that a role for them could not be ruled out for certain groups, in which antidepressants would not be practical to use, highlighting palliative populations.

Fulcher et al. [33], in their 2008 review of treatments for depression in cancer, identified one uncontrolled prospective study with 41 participants [34] and one systematic review of methylphenidate in advanced cancer, not containing any randomized controlled trials for treatment of depression [35]. They found, on the basis of the Oncology Nursing Society Putting Evidence into Practice (ONS PEP) Weight-of-Evidence Classification Schema, that methylphenidate is likely to be effective.

Candy et al. [36‡] conducted a Cochrane review of psychostimulants for treatment of depression in any context and assessed 24 RCTs, of which 13 contributed data. None of the studies included patients with advanced cancer, but some were in physically ill populations. Three trials demonstrated that oral psychostimulants significantly reduced symptoms of depression compared with placebo; no significant difference was found between modafinil and placebo. The authors concluded, however, that there was insufficient evidence to recommend psychostimulants for depression in practice, and that there was no evidence to support the use of modafinil for treatment of depression.

**Psychological therapies**

Psychological interventions are increasingly seen as part of a comprehensive package of psychosocial input for patients with advanced cancer, but as with pharmacotherapy are challenging to evaluate using rigorous methodology. There have been several recently published reviews of psychological interventions in cancer, but fewer assessing interventions for advanced cancer patients. Four recent reviews specifically assessed interventions for this group, two of them using Cochrane review methodology.

First, Lorenz et al. [37‡] carried out a systematic review of interventions to improve palliative care at the end of life. They synthesized the evidence using the GRADE classification. They found that there was ‘strong, consistent efficacy from RCTs of various psychosocial interventions’. These included behaviour therapy, cognitive behaviour therapy (CBT), informational interventions and individual and group support. No data on the comparative effectiveness of these interventions were reported.

Second, Qaseem et al. [19‡] found evidence to recommend the use of psychosocial interventions for treating patients with cancer who have depression. They classified the strength of evidence as ‘moderate on average’ as with their recommendation for antidepressants using the GRADE system.

Third, Akechi et al. [38‡] reported a Cochrane systematic review of randomized controlled trials of psychotherapy among incurable cancer patients. Ten RCT’s were identified with 780 participants and six contained sufficient data to enter into a meta-analysis (four studies of supportive psychotherapy, one CBT trial, and one trial of problem-solving therapy).

Treatment with psychotherapy was associated with a significant decrease in depression score [effect size −0.44 (−0.80 to −0.08)], but no included study focused exclusively on patients with clinically diagnosed depression. This review provided evidence for treating patients with incurable cancer and depressive states with psychotherapy, but did not provide conclusive evidence that such approaches are effective in patients with major depressive disorder.

Lastly, Edwards et al. [39‡] carried out a Cochrane review of the effects of psychological interventions on psychological and survival outcomes for women with metastatic breast cancer, again assessing RCTs. Five studies were identified: two trials of CBT and three of Supportive Expressive Group Therapy. The studies had a wide variation in duration and psychological outcome measures and were, therefore, not amenable to meta-analysis of psychological outcomes. Benefits were only evident for psychological outcomes in the short term, and the authors concluded that there was insufficient evidence to advocate for group psychological therapies being available to all patients with metastatic breast cancer.

**Cognitive behavioural therapy**

CBT has been developed in palliative populations using the model adapted by Moorey [40]. Attempts have been made to evaluate the training of palliative care practitioners to deliver the therapy to their own patients. Mannix et al. [41] in their 2006 study showed that brief training in CBT techniques and supervision over 6 months provides a suitable skill base for delivery of an appropriate standard of psychological support to patients at all stages of cancer, and a small uncontrolled mixed methods feasibility study of CBT by Anderson et al. [42] showed significant reductions in depression and anxiety scores after treatment.

Moorey et al. [43‡] have more recently carried out a larger cluster RCT on the effect of nurse training in CBT on the outcome of anxiety and depression in palliative care patients with advanced cancer. Fifteen nurses were randomized to a brief CBT training course and 1 year of weekly supervision or treatment as usual. Individuals assigned to CBT-trained nurses had a significantly lower
anxiety score over time, but depression scores were not significantly different between groups, although they reduced in both groups over the trial period. This study addressed the challenge of conducting a RCT of psychological therapy for patients with advanced cancer by adapting the standard study design. Despite a high attrition rate due to deteriorating health and death, the study gained a comparable participation rate to studies of patients with less advanced disease [44].

**Couples therapy**

McLean et al. [45] conducted a one-arm preintervention and postintervention prospective study evaluating marital therapy for couples (n=16), using emotionally focused couple therapy for patients with metastatic cancer or recurrence and their partners. Depression was measured as a secondary outcome. Participants attended 8 weekly sessions of therapy, and self-report measures were completed at baseline, four and eight sessions and at 3 months postintervention. For both the couples and patients, there was a significant reduction in Beck Depression Inventory-II (BDI-II) score after eight sessions compared with baseline, although patients showed a greater improvement than couples overall.

**Supportive expressive group therapy**

Kissane et al. [46] conducted a RCT of supportive expressive group therapy (SEGT), a therapy originally developed by Spiegel et al. [47] for women with metastatic breast cancer. Two hundred and twenty-seven women under the age of 70 years, with metastatic breast cancer and a prognosis of greater than 1 year were randomized to attend at least 1 year of weekly SEGT sessions and three sessions of relaxation or three sessions of relaxation only. The primary outcome of interest was survival, but depression was a secondary outcome measure. At baseline, one-third of the 227 patients randomized had a diagnosis of depression, evenly distributed between the two study groups. In those with depression at baseline, there were significant differences in the depression rates between groups at 6 months, favouring the treatment arm. In those without depression at baseline, significantly more patients remained free of depression in the treatment compared with the control group at 6 months. These differences did not remain significant at later time points.

This study provided evidence for SEGT in both improving and preventing depression in women with metastatic breast cancer. However, the results may not translate well to populations with more advanced cancer as the therapy was prolonged.

**Complementary therapies**

Over the past 2 years, there has been an increased contribution to the research literature on the treatment and go beyond the traditional biological or psychological frameworks and delivery models. In a RCT of ‘Depression Care for People with Cancer’ [48], a nurse delivered complex intervention; 200 patients with a cancer prognosis of more than 6 months and a major depressive disorder of at least a month’s duration were randomized to usual care or usual care as well as the intervention. The intervention consisted of 10 individual sessions, comprising education about depression, teaching of coping strategies and communication about management of depression with patients’ oncologists and general practitioners. The intervention was delivered by nurses with no specialist mental health experience. Patients in the intervention group scored significantly lower on the primary outcome (depressive symptoms measured at 3 months), and this difference persisted over the 12-month follow-up period. There was also a significant reduction in anxiety scores compared with usual care. Although this study was of patients with relatively good prognoses, complex multimodal interventions may be effective in more advanced disease.

Palliative care providers in UK frequently offer complementary therapies [18]. There is little systematic evidence for most such techniques, but one exception is a trial by Wilkinson et al. [49] who assessed the effectiveness of aromatherapy massage for management of depression and anxiety for patients with cancer. In a pragmatic, multicentre two-arm RCT, 288 patients were randomized to treatment with 4 weekly sessions of aromatherapy massage or treatment as usual. Over half the participants were described as having advanced cancer. Participants of sufficient concern, as to require a psychiatric assessment, were excluded from the trial. Patients receiving aromatherapy massage had no significant improvement in clinical anxiety or depression or both, compared with those receiving usual care at 10-weeks postrandomization [OR (odds ratio 1.3 (0.9–1.7)], but a benefit was seen at 6 weeks [OR 1.4 (1.1–1.9)]. Patients in the treatment arm reported greater improvement to self-reported anxiety at both 6 and 10 weeks.

This is the first study of a complementary therapy for a physically ill population to use rigorous clinical trial methodology. It was not possible to blind the participants, and as with the psychotherapy trials, no account was taken of the nonspecific components of the treatment, but other elements of a RCT were adhered to, but the trial has the advantage of having randomized large numbers.

**Conclusion**

Over the past 2 years, there has been an increased contribution to the research literature on the treatment
of depression for patients with advanced disease, including cancer. The existing literature has been synthesized, and new studies highlight promising interventions and future research directions.

Recent research efforts have paid particular attention to psychological interventions, with CBT approaches being most evaluated and showing some encouraging results.

Pharmacological interventions remain challenging to assess using rigorous clinical trial methodology, and clinicians still rely upon data derived from studies using general populations and those with less advanced disease or other physical illness. Methodologically sound trials of pharmacological interventions for treatment of depression in advanced disease remains an area of research need.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 86–87).

A balanced evaluation of the evidence base for treatment of depression at the end of life.
A thorough systematic review of the evidence for treatment of depression in cancer patients looking at both pharmacological and nonpharmacological interventions.
A multicentre RCT of sertraline in advanced cancer patients with advanced cancer, showing that clinical trial methodology is feasible in this group.
A systematic review of the evidence for use of psychostimulants using rigorous Cochrane review methodology that addresses a controversial area of clinical practice.
A thorough systematic review of the evidence for treatment of depression at the end of life.
Psychotherapy for depression among incurable cancer patients. Cochrane Database Syst Rev 2008:CD005537. This study systematically reviews the evidence for psychotherapy in advanced cancer using rigorous Cochrane review methodology. The evidence suggested that a range of psychotherapies reduced symptoms of depression, although no included studies were limited to patients with major depressive disorder.


Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. Psychooncology 2007; 16:277–288. A RCT of a psychosocial intervention whose design was able to detect both treatment and prevention outcomes.

