Management of depression for people with cancer (SMaRT oncology 1): a randomised trial

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See **Comment** page 8

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Summary

Background **Major depressive disorder severely impairs the quality of life of patients with medical disorders such as cancer, but evidence to guide its management is scarce. We aimed to assess the efficacy and cost of a nurse-delivered complex intervention that was designed to treat major depressive disorder in patients who have cancer.**

Methods **We did a randomised trial in a regional cancer centre in Scotland, UK. 200 outpatients who had cancer with a prognosis of greater than 6 months and major depressive disorder (identified by screening) were eligible and agreed to take part. Their mean age was 56·6 (SD 11·9) years, and 141 (71%) were women. We randomly assigned 99 of these participants to usual care, and 101 to usual care plus the intervention, with minimisation for sex, age, diagnosis, and extent of disease. The intervention was delivered by a cancer nurse at the centre over an average of seven sessions. The primary outcome was the difference in mean score on the self-reported Symptom Checklist-20 depression scale (range 0 to 4) at 3 months after randomisation. Analysis was by intention to treat. This trial is registered as ISRCTN84767225.**

Findings **Primary outcome data were missing for four patients. For 196 patients for whom we had data at 3 months, the adjusted difference in mean Symptom Checklist-20 depression score, between those who received the intervention and those who did not, was 0·34 (95% CI 0·13–0·55). This treatment effect was sustained at 6 and 12 months. The intervention also improved anxiety and fatigue but not pain or physical functioning. It cost an additional £5278 (US$10 556) per quality-adjusted life-year gained.**

Interpretation **The intervention—Depression Care for People with Cancer—offers a model for the management of major depressive disorder in patients with cancer and other medical disorders who are attending specialist medical services that is feasible, acceptable, and potentially cost effective.**

Funding **Cancer Research UK.**

Introduction

Depression is rapidly becoming one of the most pressing public health challenges in the world.[1] A 2007 WHO survey reported that depression had an especially large effect on health when it was comorbid with a chronic medical disorder.[2] Despite its importance, management of depression in patients with medical disorders has been shown to be inadequate—with failure to diagnose depression, to provide evidence-based treatment, or to actively follow up treatment to ensure that a response has been achieved.[3–5] If we are to improve outcomes for patients who have depression that is comorbid with a medical disorder, we need a system of care that addresses all these failings, is acceptable to medical patients, and is feasible and cost effective to deliver.

We developed a system of care that combines systematic screening with a complex intervention, and integrates management of depression into patients' cancer care. Screening is needed to identify patients with major depressive disorder,[5] but on its own does not improve patients' outcomes.[6] The complex intervention,[7] called Depression Care for People with Cancer,[8] was based on an intervention for the management of depression in primary care (known as collaborative care),[9,10] and was designed to be delivered by a nurse to patients who attended a specialist cancer centre.

We aimed to investigate whether adding this intervention to usual care could achieve a greater reduction in depressive symptoms at 3 months than could usual care alone, and whether this would be sustained at 6 and 12 months. This is the first in a series of trials of complex interventions for various symptoms in medical patients: Symptom Management Research Trials (SMaRT).

Methods

Study design and patients

Between October, 2003, and December, 2005, we used a screening system to identify patients with major depressive disorder. We screened patients attending clinics for breast, colorectal, gynaecological, genitourinary, haematological, lung, and mixed cancers in a regional tertiary National Health Service (NHS) cancer centre that served a geographically defined population of 1·5 million people in the southeast of Scotland, UK. The screening system had two stages. First, patients completed the Hospital Anxiety and Depression Scale questionnaire, on a touch-screen computer.[11] Second, patients who had a score of 15 or more were interviewed by telephone[12] with use of the major depression section of the Structured Clinical Interview for

the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[13] Patients who had major depressive disorder, according to these criteria, were invited to be assessed for eligibility to participate in the trial. Assessment was by initial telephone screen, then a face-to-face interview.

Eligible patients had to have: a cancer prognosis of at least 6 months (to ensure that they could complete the trial); major depressive disorder of at least a month's duration that was not associated with major changes in the patient's cancer or its management (to ensure that we did not include patients with transient adjustment disorders); and a minimum severity of major depressive disorder, defined by a score on the Symptom Checklist-20 (SCL-20) depression scale[14] of at least 1·75 (higher than the 1·5 which is usually regarded as equivalent to major depressive disorder, to allow for physical symptoms of cancer).

We excluded patients who were unlikely to be able to adhere to the intervention: reasons included major communication difficulties such as severe deafness or dementia, inability to attend the cancer centre, concurrent intensive anticancer treatment such as frequent chemotherapy or radiotherapy, or another poorly controlled medical disorder such as epilepsy that dominated their care. We also excluded those who were receiving, or were judged to need, specialist psychiatric care (eg, chronic major depressive disorder of more than 2 years' duration, severe substance or alcohol misuse, comorbid severe psychiatric disorder such as psychosis, or risk of suicide). Our justification was that we aimed to supplement the care of depression in the cancer centre, not to treat problems requiring specialist psychiatric care, which is freely available in the UK.

We recorded written informed consent from all eligible patients who agreed to take part. We then randomly assigned these patients to either usual care alone or usual care supplemented with the intervention. After baseline data were gathered, the assessing nurse faxed details to the trial unit. A computer programme was used to allocate patients to the two groups, with minimisation for sex, age (≤39, 40–79, and ≥80 years), primary cancer site (breast, colorectal, gynaecological, and other cancer), and extent of disease (disease-free after initial treatment, local disease, and metastatic disease). The aim was to minimise specific differences in known or suspected determinants of outcome between the groups. The nurse was informed of the assignment for each patient by telephone. The local research ethics committee approved the trial protocol.

Procedures

All patients in the trial received usual care. Every patient in the UK has a primary-care doctor (referred to as a general practitioner). Patients who attend specialist medical services can receive treatment for depression either from their primary-care doctor or from a hospital specialist. Both primary-care and specialist NHS medical services are free at the point of delivery. We informed each patient's primary-care doctor and oncologist of their diagnosis of major depressive disorder and provided advice on choice of antidepressant drug if requested.

In addition to usual care, patients in the intervention group were offered a maximum of 10 one-to-one sessions over 3 months, preferably in person at the cancer centre but occasionally by telephone or at patients' homes if they were unable to attend the centre. The content of the intervention, Depression Care for People with Cancer, comprised education about depression and its treatment (including antidepressant medication); problem-solving treatment[15] to teach the patients coping strategies designed to overcome feelings of helplessness; and communication about management of major depressive disorder with each patient's oncologist and primary-care doctor. For 3 months after the treatment sessions progress was monitored by monthly telephone calls. This monitoring used the nine-item Patient Health Questionnaire (PHQ-9)[16] to assess the severity of depression. We offered one or two additional sessions to patients who had increasing PHQ-9 scores.

Each 45 min treatment session was delivered by one of three cancer nurses, who followed a detailed manual (available from the corresponding author). All sessions were video-recorded, and 10% of sessions were randomly selected to be independently assessed for their adherence to the treatment manual. No further intervention was given after 6 months.

The nurses (who had experience equivalent to that of a charge nurse) had no previous experience of psychiatry, and were trained to deliver the intervention using written materials, tutorials, and supervised practice over at least 3 months. Patients were allocated to nurses on the basis of the nurses' workloads. A psychiatrist reviewed patients' progress with the nurses every week. Nurses presented each patient's scores on the Patient Health Questionnaire, their antidepressant dose, and their progress with problem-solving treatment. The patient's management was then briefly discussed. If necessary, video recordings of sessions were reviewed.

Primary-care doctors prescribed all antidepressant medication. If the patient decided, during discussions with the nurse, to start or change antidepressant medication, they were encouraged to contact their primary-care doctor for this purpose. The patient's doctor was then contacted by the nurse (by fax or telephone) before their appointment to provide information about the patient and offer advice from a study psychiatrist.

Outcome measures

The primary outcome measure was the difference in depressive symptoms, as self-reported by patients with the SCL-20 questionnaire, at 3 months after each patient was randomly assigned. The SCL-20 depression score, which is derived from the SCL-90 scale,[14] is a valid and

reliable self-reported measure.[17] The score is the mean of ratings for 20 items, and ranges from zero to four. Questionnaires were mailed to patients, and returned by mail. Data were collated at the cancer centre. Telephone interviews were used to obtain any data that were missing from responses to the questionnaire, to assess if a patient still had a diagnosis of major depressive disorder, and to record health-care use.

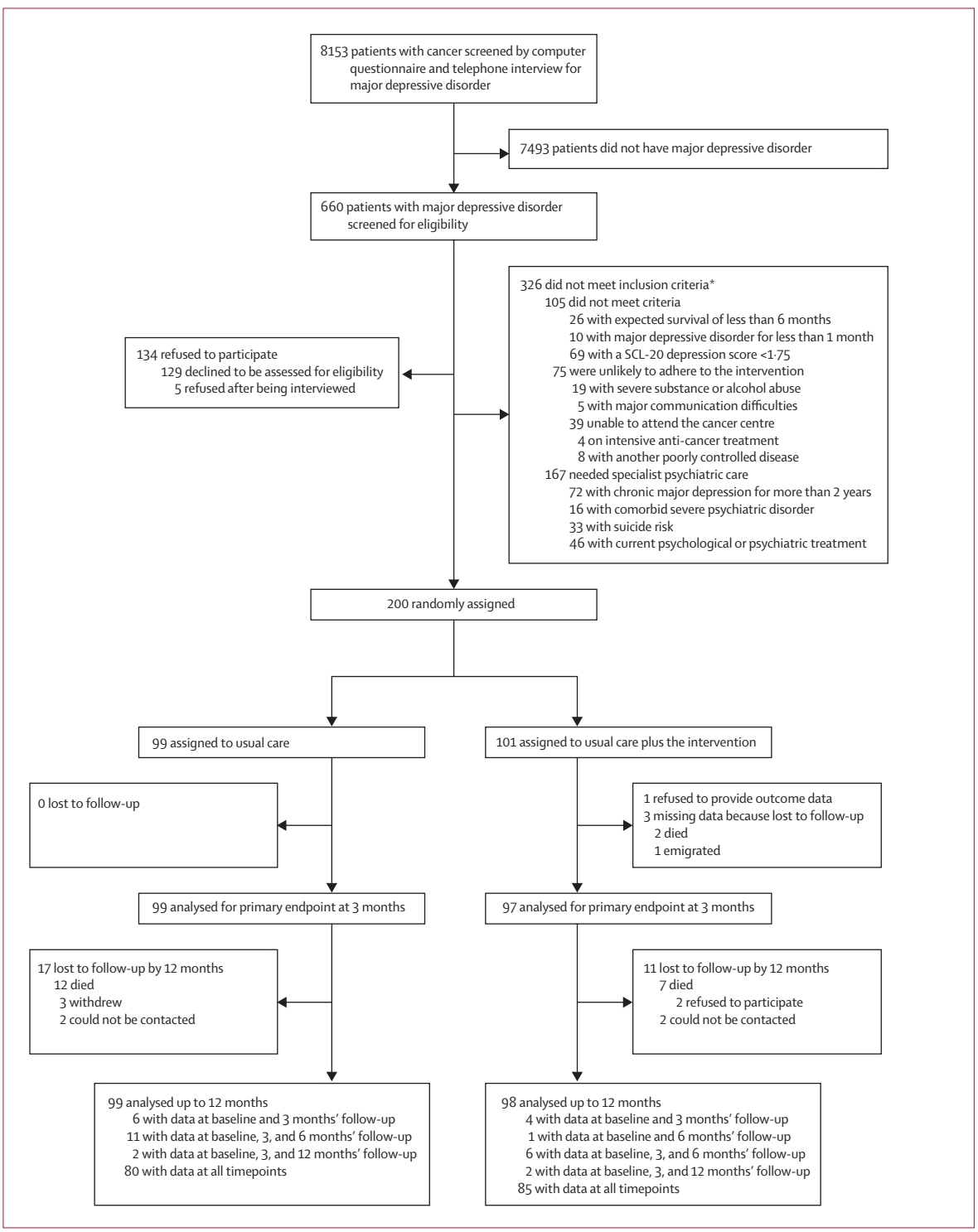

Figure 1: **Trial profile**
*Some patients had more than one reason for exclusion.

Secondary outcomes included response to treatment, which was defined as a 50% reduction in the SCL-20 depression score from baseline, and remission, which was defined as an SCL-20 score of less than 0·75 (compared with the 0·5 used in primary-care trials,[17] to allow for cancer-related somatic symptoms). We also measured the SCL-20 depression score at 6 and 12 months' follow-up to assess the effect of the intervention over time. Persistence of a diagnosis of major depressive disorder was assessed, by interviewers who were unaware of treatment allocation, using the major depression section of the Structured Clinical Interview for DSM-IV.[13] These interviews were by telephone—a method which has been shown to have good agreement with face-to-face interviews.[18] Telephone interviewers did not attempt to judge whether symptoms were related to cancer; but used the so-called inclusive approach to diagnosis. To compensate for possible bias caused by the interviewers discovering treatment allocations during interviews, all the interviews were audio-recorded and edited to remove such information. An independent investigator reassessed these recordings; these reassessments were used in the analysis.

We measured anxiety with a ten-item subscale of the SCL-90 questionnaire[14] (which is scored in the same way as the depression scale); pain, fatigue, and physical functioning with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30);[19] and quality of life for the economic analysis with the Euroqol-5D questionnaire.[20] This quality-of-life scale assesses mobility, self-care, usual activities, pain or discomfort, and depression or anxiety, on a scale from one (representing no problems) to three (representing major problems).

At 3 and 6 months, all patients recorded their number of visits to primary-care services; any use of antidepressant drugs, with doses; and any contact with community cancer-support services or specialist mental-health services. Therapeutic doses were predefined (webtable). At 6 months, patients rated the quality of care received for their depression on a simple five-point scale from poor to excellent. For patients in the intervention group, the nurses who delivered the treatment sessions recorded their number and duration, and the amount of time with the supervising psychiatrist. We defined serious adverse events as death from any cause and admission to hospital for depression. We monitored serious adverse events by patient report and review of case notes.

Statistical analysis

We planned a sample size of 200 patients, which would provide 80% power, at the 5% significance level, to find a clinically significant difference in mean SCL-20 depression scores of 0·21 (assuming a standard deviation of 0·5) and allowed for 5% loss to follow-up.[21] The primary endpoint was the difference in the mean SCL-20 total score at 3 months. We did all analyses on an intention-to-treat basis, and included all randomised patients for whom outcome data were available.

We did analysis of covariance with the 3 month SCL-20 depression score as the dependent variable, adjusted for baseline SCL-20 score and minimisation variables. The standardised effect size was calculated by dividing the effect size by the standard deviation, pooled across the two groups. No covariate data were missing. To account for missing outcome data, we did a sensitivity analysis on the conservative assumption of no change from baseline. To assess the stability of the treatment effect, we fitted a mixed model for SCL-20 depression scores at 3, 6, and 12 months, adjusted for baseline SCL-20 and minimisation variables. We analysed 197 patients for whom we had an SCL-20 score at any of these times. The model treated time as a fixed categorical effect, allowing for non-linear trends; we used a general covariance structure, since it substantially improved the log likelihood when compared with compound symmetry ($p=0·06$). We did three sensitivity analyses, checking the fit of the model against (1) single timepoint analyses, (2) a linear random coeffiecient model, and (3) data collected in specified time windows. None of these affected our results.

Binary secondary outcomes were analysed with logistic regression, adjusted for baseline SCL-20 depression score and minimisation variables. Continuous secondary outcome variables were analysed with analysis of covariance, with 3 month scores as the dependent variable adjusted for the baseline outcome and minimisation variables. Statistical significance was chosen as $p<0·01$ for all secondary outcomes to allow for the multiple testing. For partly complete data, we handled missing items according to the scale-specific scoring manuals. We used EQ-5D scores to generate quality-adjusted life-years,[22] to adjust the time spent during the follow-up period according to quality of life.

We only gathered data on costs for up to 6 months, since this was the period over which the intervention was given. The costs of all treatments except cancer treatment in hospital were assessed (since changes in cancer treatment were not expected during this period). The costs of the intervention (treatment sessions, administration and supervision time, follow-up telephone calls, and psychiatrist time) and costs of health-care contacts in usual care (eg, visits to primary-care doctor) were calculated by combining the data on contacts with established unit-cost information.[23] We obtained prices of antidepressant drugs from the 2006 British National Formulary.[24] We then calculated the incremental cost per quality-adjusted life-year as the average excess cost of the intervention divided by the average quality-adjusted life-year gain (of the intervention compared with usual care alone). Costs of training and screening to detect cases were not included. No discounting was used. We analysed all data with SAS software (version 9.1).

See Online for webtable

Role of the funding source
The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows that, of the 660 patients with major depressive disorder whom we identified, 326 were not eligible for the trial and 134 patients did not agree to participate. Of the 83 who gave a specific reason for refusal, most reported scepticism about whether the intervention would help them. Those who participated and those who declined did not differ in their demographic or cancer characteristics (data not shown). 200 patients were enrolled and randomly assigned; 99 to usual care, and 101 to usual care plus the intervention. Table 1 shows the demographic and clinical characteristics of patients at their entry to the trial.

Of the 101 patients in the group who had usual care plus the intervention, three did not attend any of their one-to-one sessions and the remainder had a mean of seven sessions (range two to ten). Most of the sessions were at the cancer centre, but six (6%) were by telephone and five (5%) were in patients' homes. Nurses gave a total of eight additional booster sessions between 3 and 6 months to six patients who had worsening PHQ-9 depression scores. Independent assessment of video recordings of 14% of the sessions showed that 89 (96%) were consistent with the treatment manual.

At baseline, similar numbers in each group were taking therapeutic doses of antidepressant drugs: 17 (17%) in the intervention group and 20 (20%) in the usual care group. By 3 months, 68 (69%) in the intervention group were taking a therapeutic dose, compared with only 42 (42%) of those given usual care alone (p=0·0002). This difference persisted at 6 months (62 [65%] *vs* 32 [34%]; p<0·0001).

In the first 3 months, patients in the intervention group had a mean of 2·0 (SD 2·0) visits to the primary-care doctor, compared with 1·7 (2·3) in the usual care group; in the second 3 months they made 1·2 (1·8) and 1·0 (1·6) visits, respectively. Very few primary-care doctors asked study psychiatrists for advice on prescription of antidepressants. Only 22 (11%) of patients were seen by mental-health specialists (such as psychiatrists, psychologists, or psychiatric nurses) during the first 6 months of the trial (nine in the intervention group and 13 in the usual care group).

Of the 200 who were randomly assigned, we analysed the primary outcome in the 196 patients for whom data were available at 3 months (figure 1). Figure 2 shows that depression scores on the SCL-20 fell between baseline and 3 months in both groups, but fell more in the intervention group. The median baseline depression score was 2·35 (IQR 2·05–2·75) in the intervention group and 2·25 (1·95–2·75) in those given usual care alone; after 3 months, this fell to 1·20 (0·70–1·70) and 1·55 (0·90–2·00), respectively. The mean reduction at

	Usual care group (N=99)	Usual care plus intervention group (N=101)
Age	56·6 (12·3)	56·6 (11·4)
<40 years	11 (11%)	10 (10%)
40–79 years	84 (85%)	89 (88%)
≥80 years	4 (4%)	2 (2%)
Sex		
Male	28 (28%)	31 (31%)
Female	71 (72%)	70 (69%)
Primary cancer		
Breast	44 (44%)	43 (43%)
Gynaecological	15 (15%)	16 (16%)
Colorectal	6 (6%)	7 (7%)
Other	34 (34%)*	35 (35%)†
Time since most recent cancer diagnosis‡ (months)	20·0 (9·1–44·7)	13·0 (5·5–33·7)
Extent of disease		
Disease-free	67 (68%)	65 (64%)
Local disease	22 (22%)	20 (20%)
Metastatic disease	10 (10%)	16 (16%)
Cancer treatment stage		
Pretreatment	2 (2%)	0
Under investigation	15 (15%)	4 (4%)
Active treatment	15 (15%)	19 (19%)
Post-treatment assessment	3 (3%)	2 (2%)
Monitoring	64 (65%)	76 (75%)
Cancer treatment		
No active treatment	84 (85%)	82 (81%)
Chemotherapy	10 (10%)	9 (9%)
Radiotherapy	3 (3%)	7 (7%)
Both	2 (2%)	3 (3%)
Duration of current depressive episode (months)	6 (3–12)	8 (4–16)
Antidepressant use at trial entry		
At any dose	29 (29%)	25 (25%)
At therapeutic dose	20 (20%)	17 (17%)
Symptoms		
Depression score§ (0–4)	2·25(1·95–2·75)	2·35 (2·05–2·75)
Anxiety score¶ (0–4)	1·3 (0·7–2·1)	1·5 (0·9–2·2)
Pain score|| (0–100)	33 (17–67)	33 (17–67)
Fatigue score|| (0–100)	56 (44–78)	56 (44–78)
Physical functioning|| (0–100)	73 (53–87)	67 (53–87)

Data are number (%), mean (SD), or median (interquartile range). *Other primary cancers included 9 prostate, 10 haematological, 8 testicular, 2 urinary tract, 1 lung, 2 skin, and 2 sarcoma. †Other primary cancers included 10 prostate, 10 haematological, 8 testicular, 3 urinary tract, 3 lung, and 1 skin. ‡Diagnosis of cancer, of recurrence, or of metastases. §Symptom Checklist-20.[14] ¶Symptom Checklist-10.[14] ||European Organisation for Research and Treatment of Cancer quality of life questionnaire.[19]

Table 1: **Baseline characteristics**

3 months in the intervention group compared with usual care, adjusted for baseline SCL-20 score and minimisation variables, was 0·34 (95% CI 0·13–0·55; p=0·002). The standardised mean difference, or effect size, was 0·43 (0·16–0·71). No interactions of minimisation factors (including cancer type) with the intervention were significant at the 5% level.

For the four patients for whom outcome data at 3 months were missing, we used their baseline SCL-20 depression scores as the 3 month scores. When this was done the difference between groups was 0·30 (95% CI 0·08–0·51) and remained significant (p=0·007).

Figure 3 shows the unadjusted SCL-20 depression scores at each timepoint. Depression scores for patients in the intervention group remained lower than scores in patients given usual care alone at both 6 and at 12 months after randomisation (at 6 months, they were 1·03 [SD 0·79] *vs* 1·51 [0·81]; and at 12 months, 1·12 [0·89] and 1·43 [0·94]).

In the mixed model the adjusted mean difference between SCL-20 depression scores in the group was largest at 6 months (–0·59, 95% CI –0·81 to –0·37). Although the difference was less at 12 months (–0·42, –0·67 to –0·17) it was still larger than at 3 months (–0·34, –0·55 to –0·12).

Secondary outcomes are shown in table 2. The SCL-20 depression score fell by at least 50% between baseline and 3 months for 51 (53%) patients in the intervention group, compared with 34 (34%) of those given usual care alone (p=0·008). The proportion who met our predefined criterion for remission—an SCL-20 score of less than 0·75—was 15% greater with the intervention than without. If we defined remission as an SCL-20 score of less than 0·5, as did previous non-cancer trials, 7% more patients in the intervention group had this result (OR 2·8, 95% CI 1·1–7·5, p=0·04). The effect of the intervention was also evident in the proportion of patients who no longer met criteria for major depression on the Structured Clinical Interview for DSM-IV after 3 months. Patients in the intervention group had a greater reduction in anxiety and in fatigue than did those given usual care alone, but not in pain or physical functioning at 3 months. These findings were similar at 6 months (data not shown). At 6 months, 68 (79%) of the 86 patients in the intervention group for whom we had data rated their care as very good or excellent.

The gain in quality of life associated with the intervention over the first 6 months was 0·063 quality-adjusted life-years (95% CI 0·032–0·095, p<0·001). Over the whole 12 month follow-up period it was 0·103 of a quality-adjusted life-year (0·025–0·182, p=0·01)

The average direct cost of the intervention including nurse time and psychiatrist supervision (but not the cost of nurse training or screening for depression), was £261·65 [US$523] per patient. Patients who received the intervention also had slightly greater costs for health care than did those who had usual care (£175·33 *vs* £151·44, difference £23·89) and for antidepressant drugs (£70·11 *vs* £20·79, difference £49·32). The total average extra cost of the intervention was therefore £334·86 [$670] (95% CI £276–£393) per patient over 6 months, which corresponds to £5278 [$10 556] per quality-adjusted life-year gained. A conservative sensitivity analysis, taking the lower limit of the 95% CI for the effect size (0·032 QALYs) and the upper limit for the additional cost (£393) gives a cost of £12 300 per quality-adjusted life-year gained. Taking the upper limit for the effect size (0·095 QALYs) and the lower limit for the additional cost (£276) gives a cost of £2900 per quality-adjusted life-year gained.

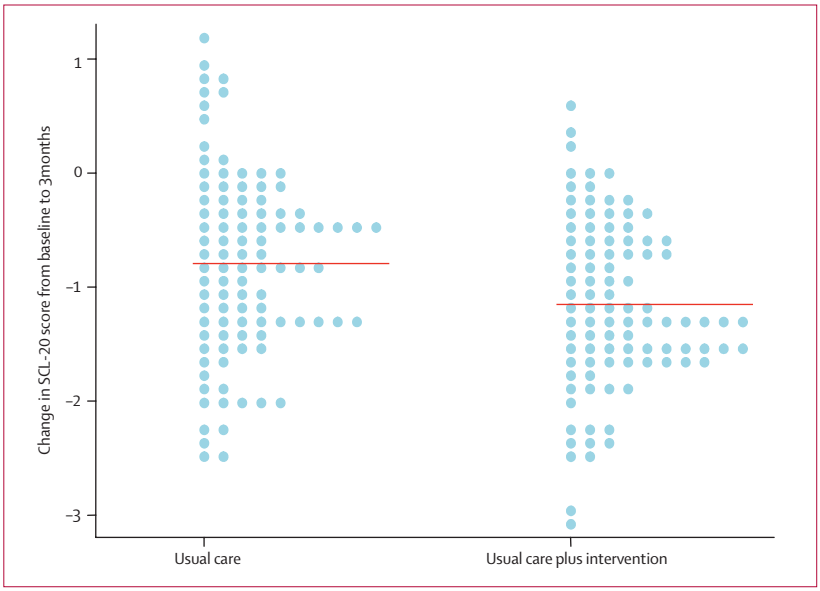

Figure 2: **Change in SCL-20 depression scale* over first 3 months**
*Checklist of depressive symptoms.[14] The mean for each group is shown in red.

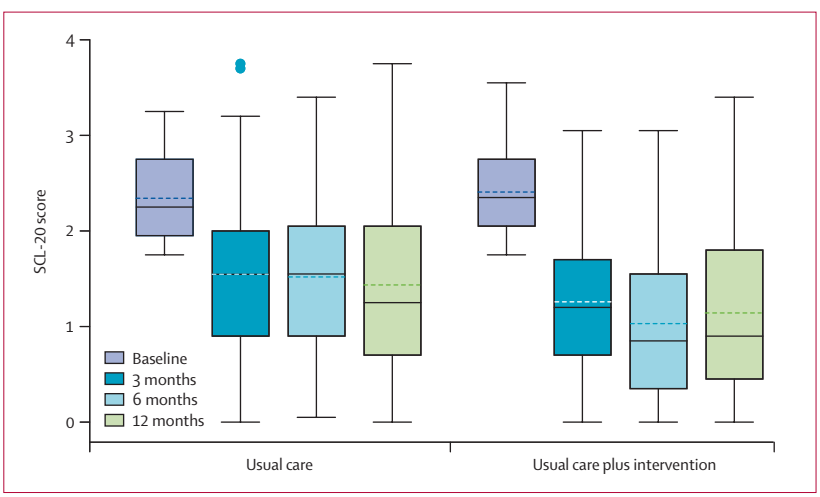

Figure 3: **SCL-20 depression scale* at each timepoint**
*Checklist of depressive symptoms.[14] Boxes show the interquartile range (IQR), with continuous lines for median scores, and dotted lines for means. Whiskers indicate range. Dots beyond the whiskers are outliers, defined as any point outside the IQR by any more than 1·5 times the IQR.

	Usual care group (N=99)	Usual care plus intervention group (N=97)	Effect size	p value
ANCOVA (mean difference as effect size)				
SCL-20 depression score (0–4)*	1·54 (0·80)	1·25 (0·77)	−0·34 (−0·55 to −0·13)	0·002
SCL-10 anxiety score (0–4)*†	0·97 (0·78)§	0·78 (0·82)¶	−0·20 (−0·32 to −0·09)	0·0008
Pain score (0–100)‡	37·8 (33·1)§	36·8 (31·0)¶	−2·2 (−10·2 to 5·9)	0·597
Fatigue score (0–100)‡	55·4 (27·6)§	49·7 (27·1)¶	−9·4 (−15·5 to −3·4)	0·003
Physical functioning (0–100)‡	67·6 (23·6)‖	66·8 (24·4)¶	1·0 (−3·4 to 5·5)	0·643
Logistic regression (odds ratio as effect size)				
Treatment response (50% reduction on SCL-20)*	34 (34%)	51 (53%)	2·2 (1·2 to 4·0)	0·008
Remission of major depressive disorder (<0·75 on SCL-20)*	14 (14%)	28 (29%)	2·9 (1·4 to 6·3)	0·005
Remission of major depressive disorder (SCID)**	44 (45%)††	65 (68%)‡‡	3·0 (1·6 to 5·5)	<0·001

Data are number (%), mean (SD), or difference (95% CI). *Both subscales derived from Symptom Checklist-90.[14] †To achieve a normal distribution for ANCOVA the scores for this measure were square root transformed; the treatment effect cannot, therefore, be interpreted as actual scores. ‡European Organisation for Research and Treatment of Cancer quality of life questionnaire. §N=93. ¶N=91. ‖N=92. **Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). ††N=98. ‡‡N=96.

Table 2: **Comparison of outcomes at 3 months**

At 3 months, the only serious adverse events recorded were two cancer-related deaths in the group that had usual care plus the intervention. During the remaining 9 months of follow-up, there were 11 cancer-related deaths and one death by suicide in the usual care group, and seven cancer-related deaths in the intervention group.

Discussion

For patients with major depressive disorder identified by screening who attended a cancer centre, supplementation of usual care with a nurse-delivered complex intervention improved the symptoms of depression more than did usual care alone. The size of the treatment effect that we recorded in both the self-rated and interview-based secondary outcomes at 3 months, and its persistence to 12 months support the clinical significance of this improvement in the primary outcome. We also noted evidence that the intervention caused an improvement in anxiety and fatigue, but not in pain or physical functioning, perhaps because anxiety and fatigue are more closely related to depression. Furthermore, the intervention proved to be feasible to deliver, acceptable to the patients who received it and also cost effective in terms of the increase in quality-adjusted life-years achieved.

The complex intervention, Depression Care for People with Cancer, was designed to address the well-documented failings in the care of depressed patients who have comorbid medical disorders. The components were chosen because they have each been proven to be effective for the treatment of depression; we did not therefore aim to assess them individually or to identify active ingredients. Rather, we aimed to assess whether the intervention was feasible, acceptable, and cost-effective.

Since we wanted to know if we could improve on the usual care that such patients would receive, all patients received usual care. In the UK, usual care for this patient group includes both specialist cancer care and primary care. However, for ethical reasons, we optimised usual care by informing primary-care doctors whose patients were taking part in our study that these patients had major depressive disorder. Therefore, prescription of antidepressants was higher in both groups than we have previously reported for patients who receive usual care alone.[5] Consequently the relative benefit of the intervention could have been even greater if the doctors who provided the usual care had not been informed of the diagnosis of major depressive disorder. Very few patients in either group were referred to specialist mental-health services.

A systematic review in 2006 concluded that there was little evidence to guide management of depressive disorder in patients with cancer.[25] A pilot trial of a nurse-delivered complex intervention for patients with cancer was done in socially deprived Latin American women in the USA.[26] Similar interventions for depression, in patients with other comorbidities have been trialled in primary care,[17] including one in patients with coexisting diabetes mellitus,[27] and one in elderly people who had various chronic diseases.[21] We aimed to test such an intervention in cancer patients.

The finding that the treatment effect was sustained at 12 months was surprising to us, since the intervention was very brief (consisting of 3 months of sessions and a further 3 months' follow-up), and the patients had no monitoring or additional treatment in the second 6 month period. Sustained treatment effects have been reported in primary-care trials of similar interventions.[28] We might have recorded a bigger treatment effect at 12 months if we had continued to monitor, and intervened if patients relapsed after 6 months.

We chose to employ specially trained cancer nurses as care managers, supervised by psychiatrists. A systematic review of complex interventions for depression in

primary care concluded that the most effective variants of this type of intervention had care managers with mental-health training who were supervised by psychiatrists.[10] Our justification for training cancer nurses to deliver the intervention, rather than mental-health nurses, was to maximise acceptability to patients and integration with their existing medical care.

The incremental cost associated with the intervention was £334 (US$668) over 6 months. The cost per quality-adjusted life-year gained, of £5278 ($10 556), was well within what is usually considered to be cost-effective[29] and compared with a median cost per quality-adjusted life-year of at least £10 000 ($20 000) for anticancer treatments. We did not include the one-off cost of training the nurses, the cost of quality assurance and control procedures used in the trial, or the cost of the screening system used to identify patients with depression. However, even if these costs were included, the intervention would still probably be a relatively cheap and acceptable model for effective treatment of comorbid depression in patients who attend medical services.

The findings of this trial need to be set in the context of potential limitations: the first is the validity of the diagnosis and measurement of major depression in medically ill patients. Although low mood and anhedonia are specific to depression, the physical symptoms of depression can overlap with those caused by medical disorders. However, evidence suggests that this potential difficulty has been overestimated.[30] Furthermore, all patients in our trial had the diagnosis of major depressive disorder confirmed at interview and patients were also required to have a high symptom score on the SCL-20 depression scale. Moreover, the two groups of patients had similar severity of cancer and associated physical symptoms, so that even if these symptoms did affect the assessment of depression they were unlikely to have accounted for the difference in outcomes.

A second limitation is the possibility of bias in the self-rated outcome assessments. Because of the type of trial, patients knew their treatment allocation. However, both the self-reported and independently assessed results were similar.

Third is the question of generalisability of the findings. We excluded patients who had cancers with poor prognoses and patients who had treatment needs that we considered could be more appropriately met by readily available specialist psychiatric services (such as chronic depression, that antedated the diagnosis of cancer). About 40% of eligible patients declined to take part—a rate of participation which is similar to that in other trials which have recruited depressed patients by screening those attending specialist medical services.[31] However, most of these patients refused to be assessed for eligibility; very few withdrew after the interview. We do not know if as many patients would refuse the intervention outside a trial setting, or whether a better explanation at an early stage of recruitment might reduce the number of refusals. We did the trial at only one major cancer centre, and in the UK NHS, where all patients are registered with a primary-care doctor and have free access to specialist services including psychiatry. Since the UK NHS is not typical of all health services, implementation of this approach in other health care systems might necessitate adaptations such as having the antidepressant medication prescribed by the oncologist, and including patients with more complex needs such as chronic depression and substance misuse.

This initial proof-of-concept trial raises many questions. In further trials (SMaRT oncology 2 and 3), we aim to investigate whether Depression Care for People with Cancer is cost effective if implemented on a large scale and if screening, training of nurses, and other costs are fully assessed and whether this intervention can also benefit patients who have cancers with poor prognoses, such as lung cancer. Other questions still to be addressed are whether the benefit for quality of life would improve if other symptoms, such as pain, were treated at the same time;[32] and whether this approach is effective for patients who attend specialist services for other medical disorders or for patients being treated in other health care systems. This proof-of-concept trial provides preliminary evidence that such a system of delivering care for depressed patients who attend specialist medical services such as cancer centres offers a feasible, acceptable, and cost-effective way to improve patients' quality of life.

Contributors

MS and VS conceived and designed the study; MS obtained funding and supervised the study; VS, CH, and LW participated in acquisition of data; CH provided technical support; VS provided administrative and material support; RW, GM, and GMcH did statistical analysis; AW advised on the economic analysis; and VS, RW, and MS wrote the draft, with critical revision from all other authors. All authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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