Evidence Report on the Occurrence, Assessment, and Treatment of Depression in Cancer Patients

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This evidence-based report reviews the empiric literature on depression in people with cancer with a focus on three areas: occurrence, assessment, and treatment. More than 350 studies were identified through searches of the English-language literature published between 1966 and September 2001. Reports of occurrence are limited to prevalence studies, and prevalence rates vary widely despite standardized assessments. Rates of major depressive disorder and depressive symptoms comorbid with cancer appear to be 10%–25%. Although multiple instruments are available for assessing depressive symptoms, a clinical interview using *Diagnostic and Statistical Manual of Mental Disorders* criteria is the standard to which assessments are compared. Some data exist for the efficacy of psychosocial and pharmacologic treatments for depression in this population. No randomized, controlled studies of alternative medicine interventions were identified. [J Natl Cancer Inst Monogr 2004;32:32–9]

A substantial literature on the psychosocial aspects of cancer has been developing over the last 20 years. Depression associated with cancer has received much of the attention in this literature. This evidence-based review examines the empiric studies on depression in people with cancer, with a focus on three areas: occurrence, assessment, and treatment.

"Depression" in comparison to other symptoms associated with cancer, such as pain or fatigue, can be a set of symptoms as well as clinical syndromes. Depressive symptoms are present in several psychiatric disorders, with the most common disorders in cancer patients being major depressive disorder (MDD), adjustment disorder, and depression secondary to a medical condition. Depressive symptoms can also be present in the absence of a psychiatric disorder. To avoiding limiting the report to only major depressive disorder, studies that assessed depressive symptoms, regardless of diagnosis, were also reviewed.

Methods

The Office of Medical Applications of Research at the National Institutes of Health requested an evidence-based report on the topics of pain, depression, and fatigue in cancer for a National Institutes of Health for a State-of-the-Science Conference entitled "Cancer Symptom Management: Pain, Depression, and Fatigue." The Evidence-Based Practice Center at the New England Medical Center prepared the report.

Studies used in the evidence report were identified through searches of the English language literature published between 1966 and September 2001. The searches were completed by the National Library of Medicine. No restrictions were placed on the patients' age, gender, ethnicity, or stage of the primary disease or presence of metastases.

An initial search was conducted with the subject headings "neoplasms" combined with "depression," "depressive disorder," or "antidepressant agents," using the search engines of PubMed, PsycInfo, CINAHL, and Biosis. This initial search found more than 3000 abstracts related to depression and cancer. A second search limited to citations that contained the term "depression" as a descriptor or in the title yielded about 1000 articles. Review articles, letters, news, and editorial citations were eliminated. Abstracts were screened for relevance according to the three topic areas, and pertinent articles were retrieved. Data from the articles were extracted into tables and then summarized.

Results

Occurrence

Studies on the occurrence of depression in people with cancer are limited to cross-sectional prevalence studies. A few studies of changes in depressive symptoms along the course of a specific cancer treatment exist, but no real incidence studies were identified. Because depression can refer to both "major depressive disorder" and depressive symptoms, a review of prevalence studies was done for each.

Major Depressive Disorder

Eleven studies that used DSM (*Diagnostic and Statistical Manual of Mental Disorders*) criteria to diagnose major depression were identified and reviewed *(1–12).* These studies are summarized in Table 1. Ten of the studies used interviews that incorporated DSM criteria, and one used the Structured Clinical Interview for the DSM. These studies reflect data from 1955 patients, with an average of 177.7 patients in each study (range = 18–1112). The majority of studies (seven) assessed MDD in hospitalized cancer patients. Two studies assessed depression in outpatients, and two had mixed or unspecified hospital status.

Despite using standardized criteria for diagnosis, there appears to be a wide range of reported rates. However, the populations were quite heterogeneous in terms of types of cancers, hospital status, treatment, and disease status. The majority of the rates for MDD fall between 10% and 25% of patients, with 25% of studies reporting rates below and 17% reporting rates above this range.

From these data (summarized in Table 1) it is difficult to draw conclusions about the prevalence rate of MDD in people with cancer and the effects of the variables, such as hospitalization, type of cancer, and disease status on occurrence. It may be noteworthy, however, that the lowest reported rate was in the youngest population. Only one study specifically examined the

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Table 1. Prevalence of major depressive disorder (MDD): 11 cross-sectional studies on prevalence of MDD using DSM criteria*

Author, year (ref)	N	Population/Setting	Mean age ±SD (range) % male	Cancer type	Prevalence
Derogatis, 1983 *(2)*	215	Multi-center, new inpatients and outpatients	50.3 ± 15.5 y 49%	All: 20% lung; 18% breast; 11% lymphoma	13% depressive class; 5.5% MDD
Bukberg, 1984 *(3)*	62	Oncology inpatients	51 y (23–70 y) 53%	All: 38% leukemia/lymphoma; 21% GU, 13% lung	42%; 24% severe
Morton, 1984 *(4)*	48	Patients treated in last 3 y, no evidence of disease	>60 y 100%	Head and neck cancers	39.6%
Evans, 1986 *(5)*	83	Oncology inpatients	53.1 ± 15.6 y (20–86 y) 0%	Gynecologic cancers	23% MDD; 24% non-major depression
Grandi, 1987 *(6)*	18	Consecutive surgical oncology inpatients	(29–75 y) 0%	Breast cancer	22.2%
Colon, 1991 *(7)*	100	Routine evaluations of hospitalized BMT patients	30 y 65%	Acute leukemia, BMT	1% MDD; 6% adjustment disorder with depressed mood
Golden, 1991 *(8)*	65	Oncology inpatients	54.2 ± 2.0 y (20–86 y) 0%	Gynecologic cancer	23%
Alexander, 1993 *(9)*	60	Oncology inpatients	55.0 ± 13.3 y 60%	Various, not specified	13% MDD; adjustment disorder with depressed mood 10%
Sneeuw, 1993 *(10)*	1112	Early stage, patient status not noted	NR 0%	Breast cancer	5.4%
Bereard 1998 *(11)*	100	Oncology outpatients	51.8 ± 13.3 16%	55% breast; 43% lymphoma	19%
Breitbart 2000 *(12)*	92	Hospitalized palliative care oncology patients	65.9 ± 15.6 40%	Various, not specified	16%

*BMT = bone marrow transplant; NR = not reported.

rate of MDD in survivors—that of head and neck cancer survivors—and this sample had one of the highest rates of depression, at 39.6% *(4)*. Although MDD is more common in women in the general population, there did not appear to be a consistent strong association between female gender and depression in these data. However, this comparison is confounded by not having more precise estimates for the rates of depression. A gender differential could be hidden within the range of 10%–25%.

Depressive Symptoms

Studies of the rate of depressive symptoms in people with cancer use multiple instruments in the assessment of depression. To compare data from many studies, a decision was made to identify the instrument most frequently used to measure depressive symptoms in research and then to review studies with that particular instrument. In citations from our literature search, the Hospital Anxiety and Depression Scale (HADS) was the most commonly used instrument to measure depressive symptoms.

Twelve cross-sectional prevalence studies were identified that used the HADS *(13–26)*. These studies are summarized in Table 2. Rates of "depression" are reported that reached threshold scores for probable "cases" of clinically meaningful depressive symptoms. When specified, rates of subthreshold (or "borderline" cases) are also reported in the evidence table.

These studies tended to be more focused on outpatient populations than were the studies of MDD. Seven studies assessed depression in outpatients; three included homecare, mixed, or unspecified hospital status; and two assessed depressive symptoms in hospitalized cancer patients. The studies included various types of cancers and patients at various stages, from new patients to survivors. These studies include data from 3598 patients, with a mean of 299.8 patients in each study (range = 41–987).

Again, even using one standardized instrument, a wide range of rates was reported. It appears that the majority of reports fall into the 7%–21% range for probable cases of depression, with a higher rate for "borderline cases" of depression. Of the 14 studies quantifiable for depression, 14% lay below this range of rates and 14% lay above this range. Two studies provided data on depressive symptoms in populations considered survivors, and these rates also varied: 3.5% and 17% *(13,21)*.

These reports are complicated by populations heterogeneous by hospital status, cancer type, treatment, and disease status. Although a standardized instrument was used, another complication with these data is the authors' variance in choosing a cutoff score to define clinically meaningful depressive symptoms. Guidelines for the instrument state that a depression score of 8–10 corresponds to mild depression and a score of 11–14 corresponds to moderate depression. Cutoff scores were not explicitly identified in all reports. When stated, the cutoff points ranged from 8 or greater to 11 or greater. Higher cutoff criteria did not result in lower prevalence rates. The two highest rates were from studies that used a cutoff score of 11 or greater.

Assessment

The physical symptoms that are associated with both depression and cancer can confound the assessment of depression in this population. Although some assessments attempt to limit the contribution of these symptoms, such as the

Table 2. Prevalence of significant depressive symptoms in adults: Cross-sectional studies using the HADS

Author, year (ref)	N	Population/Setting	Cancer type	Mean age ±SD (range) % male	Prevalence
Espie, 1989 *(13)*	41	Outpatients follow-up at least 6 mo after treatment	Head and neck	64 y (43–78 y) 66%	17%
Razavi, 1990 *(14)*	210	Inpatients	Various	55.30 ± 14.50 y 32.9%	7.8% random, 25.5% referred
Hopwood, 1991 *(15)*	204	Consecutive ambulatory patients	Breast	NR 0%	9% probable cases, 1% borderline, and 9% mixed depression and anxiety
Hopwood, 1991 *(16)*	81	Ambulatory patients	Advanced breast, no brain mets	NR 0%	34.6%
Maraste, 1992 *(17)*	133	Ambulatory patients	Breast	61 y (32–84 y) 0%	1.5% probable cases, 3.75% borderline
Pinder, 1993 *(18)*	139	Inpatients and outpatients	Advanced breast cancer	60.5 y (27–90 y) 0%	12%
Grassi, 1996 *(19)*	86	Home care patients	Various		45%
Roth, 1998 *(20)*	113	Outpatients	Prostate	NR 100%	15.2%
Groenvold, 1999 *(21)*	538	Ambulatory survivors	Breast	55 y 0%	3.5% probable cases, 6.5% borderline
Newell, 1999 *(22)*	195	Outpatients	Various	56% are 50–69 y 41%	8% probable cases, 15% borderline
Chen, 2000 *(23)*	203	Inpatients	Various	NR 49.8%	20.2% probable cases, 23.7% borderline
Cliff, 2000 *(24)*	164	Outpatients	Prostate	73.9 y 100%	8.1%
Hopwood, 2000 *(25)*	987	Data from 3 multicenter treatment studies	Lung cancer	NR NR	17% probable cases, 16% borderline
Pascoe, 2000 *(26)*	504	Outpatients	Various	62 y median (20–93 y) 45%	7.1% probable cases, 11.0% borderline

BMT = bone marrow transplant; NR = not reported.

HADS, the prevalence estimates described above may still contain some bias.

A clinical interview appears to be the standard for diagnosing MDD in patients with cancer. Although DSM criteria for MDD contain symptoms that overlap with cancer and cancer treatments, the rates of diagnosing MDD in patients with cancer using substitute criteria, such as the Endicott criteria, are highly correlated to that with DSM criteria *(27)*.

Depressive symptoms, in contrast, have no clear standard for assessment. Multiple instruments exist for the measurement of depression. Some instruments are commonly used in psychiatric research, some are for use in medically ill populations, and some were created for cancer patients. These instruments also have a wide range of complexity, from comprehensive quality-of-life instruments with mental health domains to simple visual analogue scales. The HADS appeared to be the most frequently used instrument to measure depressive symptoms in this literature search.

Because of the multiple instruments available to measure depression, a decision was made to focus this review on comparing instruments. Table 3 compares 10 forms of assessment that were found to have direct comparisons to others in our literature search *(14,16,27–35)*. Although other instruments, such as the Brief Symptom Inventory, Center for Epidemiologic Studies Depression Scale, and the Mental Adjustment to Cancer Scale, had studies demonstrating their validity, internal consistency, and reliability, no direct comparisons to other assessments were identified *(36–38)*.

One interesting study found a single-item screener asking "Are you depressed?" to have a promising predictive rate for depression in terminal cancer patients *(35)*. However, there have been no other studies to replicate the findings of this small study.

TREATMENT

Psychosocial Interventions

Most of the studies on the treatment of depression in people with cancer have used psychosocial interventions. Hundreds of studies on the effects of psychosocial interventions on depressive symptoms in cancer patients have been published. This body of research itself could have been the focus of an evidence-based report. Because of the broad nature of this report, the large number of studies, and our available resources, we limited our review to three published meta-analyses of these studies.

Although these meta-analyses were not done exclusively on studies of patients with clinical thresholds of depressive symptoms at baseline, there does appear to be a small to moderate effect size from these treatments. One of the meta-analyses did not note a significant difference in effect size among different types of treatments, but the limitations of that study make interpretations of that observation difficult.

Despite its title as a meta-analysis of psychoeducational care, Devine and Westlake's paper is actually a meta-analysis of psychosocial interventions in adult cancer patients *(39)*. It included 98 studies, with 5326 subjects, published from 1976 to 1993. Of these studies, 47% were published in a journal or book, 45% were doctoral dissertations, and 6% were theses published in a journal. Inclusion criteria were a provision of a psychosocial intervention with adults with cancer; use of an experimental,

Table 3. Assessment of depression in adults: Direct comparisons of instruments to each other or standardized interviews*

Author, year (ref)	Population	N	Instruments
Kathol, 1990 *(27)*	Patients with terminal solid tumors reporting depressive symptoms	152	BDI: Score <11, 93% chance not depressed, positive predictive value 94%; if prevalence 15%, negative predictive value is 99%. HDRS: Positive predictive value 95%
Sutherland, 1989 *(28)*	Various cancers at various stages, over half receiving treatment, all participating in psychosocial intervention	42	POMS and Symptom Checklist 90-R (SCL 90-R) correlated at 0.77
Hardman, 1989 *(29)*	Hospitalized patients with various cancers	126	General Health Questionnaire recognized 79% affective disorders and had 34% false positive rate compared with Standard Psychiatric Interview.
Razavi, 1990 *(14)*	Hospitalized patients with various cancers	226	HADS: With optimal cut off of 13, 75% sensitivity, and 25% false positives with DSM criteria; with cut-off of 11, 54% sensitivity and 25% false positives.
Hopwood, 1991 *(15)*	Outpatients with breast cancer	81	HADS: With cut-off of 11, 75% sensitivity. 75% specificity, 24.7% misclassification rate with DSM criteria. RSCL: With cut-off of 11, 75% sensitivity, 80% specificity, 21% misclassification rate with DSM criteria.
Ibbotson, 1994 *(30)*	Outpatients with various cancers, not all patients completed all measures, stratified by disease status	514	HADS: Optimal score >14, sensitivity 80%, specificity 76%, PPV 41% compared with DSM criteria; affected by disease and treatment status. RSCL: Optimal score >17, sensitivity 83%, specificity 71%, PPV 37% compared with DSM criteria; affected by disease and treatment status. General Health Questionnaire: Optimal score >8 in disease free population, sensitivity 75%, specificity 92%, PPV 69%.
Lees, 1999 *(31)*	Hospice patients with cancer	25	HADS and visual analogue scale correlated at 0.82.
Skarstein, 2000 *(32)*	Inpatients and outpatients with cancer	568	HADS depression scale correlated with EORTC QOL C33 EF scale at 0.41.
Hall, 1999 *(33)*	Women with early breast cancer	269	HADS: Cut off 11 or more, sensitivity 14.1%, specificity 98.2%, PPV 82%, compared with standardized psychiatric interview. RSCL: Cut-off 11 or greater for psychological distress, sensitivity 30.6%, specificity 95.9%, PPV 90%, compared with standardized psychiatric interview.
Passik 2001 *(34)*	Outpatients with various cancers	60	Zung Self Rating Depression Scale and diagnosis of major depression on MINI (Structured Psychiatric Interview) correlated at 0.66.
Chochinov, 1997 *(35)*	Patients receiving palliative care for advanced cancer	197	BDI Short Form for diagnosis of major depression on structured clinician interview (Schedule for Affective Disorders) with score 8 or greater: sensitivity 0.79, specificity 0.71, PPV 0.27, NPV 0.96, 29% false positives. Single item screening question for depression: Sensitivity 1.0, specificity 1.0, PPV 1.0 NPV 1.0, false positives 0%

*BDI = Beck Depression Inventory; EORTC QOL C33 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression; HDRS = Hamilton Depression Rating Scale; POMS = Profile of Mood States; RSCL = Rotterdam Symptom Checklist.

quasi-experimental, or pre–post single-test design; and outcome measures of physical and emotional well being. Exclusion criteria were studies that had comparison arms to other treatments (such as medications), studies with fewer than five subjects, and all treatment groups not being from the same setting. Interventions included education, behavioral/cognitive counseling, and nonbehavioral/cognitive counseling. The most prevalent intervention was behavioral/cognitive counseling. It was not noted whether both individual and group interventions were included. Although the studies were not necessarily on patients with depression, a positive effect was present in 92% of the studies, with the average effect size being medium.

Meyer and Mark published another meta-analysis of psychosocial interventions in adult cancer patients *(40)*. It included 45 studies with 2840 subjects, and its inclusion criteria were published randomized experiments, psychosocial intervention compared with control or minimal intervention, and the inclusion of behavioral and emotional outcome measures. The only exclusion criterion was hospice or terminal care studies. Interventions included were education, behavioral counseling, nonbehavioral counseling, social support, or other (e.g., music therapy). It is not noted whether both individual and group interventions were observed. Although this meta-analysis showed a small effect size, it was not as stringent in evaluating depressive symptoms. Measures of emotional adjustment were included, rather than measures of depression. This meta-analysis also did not show a significant difference in effect size according to type of intervention.

The last meta-analysis of psychological interventions for anxiety and depression in cancer patients is by Sheard and Maguire *(41)*. It included 20 studies with 1101 subjects. Inclusion criteria were studies of psychosocial interventions for psychological distress in cancer patients, studies having a control condition, and studies published in English in a journal or indexed as a dissertation. The one exclusion criterion was a single-group design without a control. Both individual and group data were included in the analysis. The interventions included individual therapy, relaxation, group therapy, group therapy excluding psychoeducation, and group psychoeducation. Although these studies were not specifically done on patients who were depressed, a small to medium effect size was seen on depressive symptoms, although it decreased with the authors' assessment of the quality of the study.

Medications

Only 13 randomized, controlled trials of medications for depressive symptoms exist in cancer patients. Eleven are primarily treatment studies on depressive symptoms, one is a pain study that also assessed depressive symptoms, and one is a depression prevention study. These data are summarized in Table 4.

Table 4. Psychopharmacologic studies of treatment of depression in cancer double-blind randomized control trials*

Author, year (ref)	N	Medication	Dosage	Depression instruments	Results
Johnston, 1972 *(50)*	50	Thioridazine	25 mg tid	Physician ratings	Better than placebo for depressed mood at week 1, but not weeks 3 and 6. Helpful for insomnia and crying spells at all time points ($P<.05$)
Purohit, 1978 *(42)*	39	Imipramine	25–50 mg qd	Physician ratings, HDRS	80% imipramine patients improved, 42% of controls
Bruera, 1985 *(51)*	40	Methyl-prednisolone	16 mg bid	HDRS	Day 13 MP patients had improved depression ($P<.05$), day 33 no significant difference with placebo
Costa, 1985 *(47)*	73	Mianserin	30–60 mg/day	HDRS, CGI, ZSDRS	Experiment group greater improvement in HDRS ($P<.01$) and ZSDRS ($P<.05$) at 4 wk; significantly more responders on CGI in experiment group ($P<.025$)
Bruera, 1986 *(53)*	26	Mazindol	1 mg tid	HDRS	No significant difference with placebo
Holland, 1991† *(52)*	147	Alprazolam vs. progressive muscle relaxation	0.5 mg tid	DSM-III interview, HDRS, ABS	Both groups improve, alprazolam group significantly more improvemt with ABS ($P = .04$) and HDRS ($P = .08$)
Van Heerigen, 1996 *(48)*	55	Mianserin	60 mg/day	DSM-III interview, HDRS	HDRS scores lower than placebo at 2 wk ($P = .056$), 4 wk ($P = .004$), and 6 wk ($P = .004$), number of responders significantly greater than placebo ($P<.05$) at 4 and 6 wk
Eija, 1996 *(44)*	15	Amitriptyline	25–100 mg/day	Two questions on depression with 4 point scale	No significant differences
Razavi, 1996 *(45)*	115	Fluoxetine	20 mg qd	HDRS, MADRS, Symptom Checklist 90-R(SCL90-R)	Both groups improved, no significant difference with placebo
Holland, 1998 *(43)*	37	Fluoxetine vs. Desipramine	F 20 mg qd D 100 mg qd Both variable with response	DSM-III-R interview, HDRS, CGI	Both groups improved significantly by both scales, no significant differences between drugs
Razavi, 1999 *(49)*	27	Trazodone vs. Clorazepate	T 50–150 mg/day C 10–30 mg/day	DSM-III-R interview, HADS, CGI	By CGI, 91% T group responders, 57% C group, but no significant differences; by HADS scores decreased in both but no significant differences
Musselman, 2001 *(46)*	20 per group	Paroxetine			Paroxetine significantly reduced the incidence of depression ($P = .04$), 11% in paroxetine vs. 45% in control; paroxetine had significant effect on severity of depressive symptoms ($P<.001$)

*ABS = Affects Balance Scale; CGI = Clinical Global Impression; HADS = Hospital Anxiety and Depression Scale; HDRS = Hamilton Depression Rating Scale; ZSDRS = Zung Severity of Depression Rating Scale.

†The Holland, 1991 study is not double-blinded.

These 13 studies were done using patients with various cancers in varying settings. They include data from 755 patients, with an average of 58.1 patients per study (range = 15–147). Medications studies included medications classified as "antidepressants" as well others.

Antidepressants. Nine of the studies used seven different antidepressant medications. The antidepressants can be further divided into three classes: tricyclics, selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants.

Three studies used three different tricyclic antidepressants: amitriptyline, desipramine, and imipramine. Both desipramine and imipramine appeared to have some benefit. In a placebo-controlled trial, Purohit and colleagues found that 80% of the imipramine group improved compared with 42% of the controls, using the Hamilton Depression Rating Scale (HDRS) *(42)*. However, the authors did not analyze their data for the statistical significance of these differences. In a comparison study with fluoxetine, desipramine demonstrated statistical significance within group improvement as measured by both the HDRS and the Clinical Global Impression (CGI) *(43)*. The third study used amitriptyline for pain in cancer patients but also assessed depressive symptoms *(44)*. This shorter, 4-week placebo-controlled study showed no significant differences in depression between groups, but depression was not assessed in a standardized way.

Three studies used two SSRIs, fluoxetine and paroxetine. Two were treatment studies, and both used fluoxetine. A 4-week, placebo-controlled study by Razavi found no significant differences in the numbers of responders, as defined by the HADS <8, and no significant changes in depression scores using the HADS and Montgomery Affective Disorders Rating Scale were found between groups *(45)*. The other study by Holland, a 5-week comparison trial with desipramine that was previously referenced, found that both groups improved significantly by both the HDRS and the CGI scales *(43)*. Although there was significant within-group improvement with fluoxetine, there were no significant differences between groups. Paroxetine was used in a placebo-controlled trial for depression prevention in patients with melanoma receiving interferon alpha *(46)*. Paroxetine statistically significantly reduced the incidence of depression ($P = .04$) and the severity of depressive symptoms ($P<.001$), as measured by the HDRS.

Three studies of two atypical antidepressants, mianserin and trazodone, were identified. The two placebo-controlled trials of mianserin appeared to have the highest methodological quality of all the medication studies. Both studies showed benefit from mianserin. Costa and colleagues found that there were more responders in the mianserin group, as assessed by changes in CGI ($P<0.25$), and that the mianserin group had a greater improvement in the HDRS ($P<.01$) *(47)*. The other study, by Van Heerigen and colleagues, found that the HDRS scores were statistically significantly lower in the mianserin group compared with placebo at weeks 2 ($P<.056$), 4 ($P<.004$), and 6 ($P<.004$) *(48)*. The number of responders was also greater in the mianserin group compared with placebo at weeks 4 and 6 ($P<.05$). The other atypical antidepressant, trazodone, was used in a comparison trial with chlorazepate for depressive symptoms in cancer patients with adjustment disorders *(49)*. Trazodone was dosed 50 to 150 mg per day, which is lower than the therapeutic dose for depression (>400 mg per day). Although there were a greater number of responders by CGI in the trazodone group, this difference was not statistically significant. There was also no statistically significant difference in change in depression scores with the HADS.

Medications Not Classified as Antidepressants. Five of the trials used medications not classified as antidepressants: thioridazine (a neuroleptic), methylprednisolone (a glucocorticoid), mazindol (a stimulant), alprazolam (an anxiolytic), and chlorazepate (an anxiolytic). Four of these studies found either initial positive effects that were not persistent or very small improvements that were not always significant. Although thioridazine appeared to be better than placebo for depressive symptoms (as measured by physician ratings) at the end of the first week, this difference was not statistically significant at weeks 3 and 6 *(50)*. Although methylprednisolone showed greater improvement in the HDRS than placebo ($P<.05$) at day 13, there was no statistically significant difference at day 33 *(51)*. Alprazolam, in a comparison study with progressive muscle relaxation, was found to have some within-group improvement in the HDRS and the Affects Balance Scale *(52)*. However, the alprazolam group had greater improvement in the Affects Balance Scale ($P<.04$) and displayed an improvement trend with the Hamilton Depression Scale ($P<.08$). In a comparison study with trazodone that has been previously referenced, chlorazepate showed some improvement in the HDRS *(49)*. Although there were a greater number of responders by CGI in the trazodone group, this difference was not statistically significant. There was also no statistically significant difference in change in depression scores with the HADS. Mazindol, a stimulant that is now used for muscular dystrophy and weight loss, had no statistically significant improvement in depressive symptoms compared with placebo, but it did have a statistically significantly higher rate of medication toxicity *(53)*.

Alternative/Complimentary Treatments

Although there have been descriptive reports of alternative or complementary treatments, such as acupuncture and aromatherapy, for depression in people with cancer, there have been no randomized, controlled trials.

Discussion

Major depressive disorder and depressive symptoms occur frequently in patients with cancer. Rates of occurrence are limited mainly to prevalence studies. Despite using standardized measures, there is a wide range of reported prevalence. From our review of the literature, the prevalence rates appear to be between 10% and 25% for MDD and in a similar range for clinical thresholds of depressive symptoms regardless of psychiatric diagnosis. Given that the estimated point prevalence of MDD is 2.2% in the general population, these rates in cancer patients may be at least four times greater *(54)*. This range may be the result of several factors that include the timing of the assessment, concurrent treatment, medical morbidity and pain, and age. Cancer patients are a heterogeneous population with different sociodemographics, cancer types, treatments, and responses to treatment. More accurate estimates might be obtained in studying the rates in more homogeneous subgroups.

The clinical interview, using DSM criteria, is the standard of care for diagnosing MDD and other depressive syndromes in people with cancer. However, many instruments are available for the assessment of depressive symptoms. The most frequently used instrument in our literature search was the HADS. Although these assessment tools may have been validated in studies, there is currently no evidence on how widely they are used clinically or to suggest that they affect clinical care and outcomes.

The current evidence shows that interventions are beneficial for depressive symptoms in cancer patients. There appears to be some benefit from psychosocial interventions, although the magnitude of the effect size seems to be in the small to medium range. However, in limiting our review to meta-analyses, the contributions of effects from preventative studies and depression treatment studies were not able to be separated. The effects of psychosocial interventions may vary in these two different types of studies.

Although the results of pharmacologic studies appear mixed at first glance, all studies that used medications classified as antidepressants and that conformed to usual practices for antidepressant trials did show benefit. Because antidepressants typically can take 4–6 weeks to exert their full effect to take place, studies of the use of antidepressants for under 5 weeks tended to show less benefit. There appeared to be some efficacy data for SSRIs and tricyclic antidepressants. Another antidepressant that showed benefit, mianserin, is an atypical antidepressant not available in the United States. Although trazodone, an atypical antidepressant, showed some benefit in treating depressive symptoms, it is not commonly used as an antidepressant because it often causes sedation at therapeutic doses.

No randomized, controlled studies on alternative treatments for depression in cancer patients were identified.

Conclusion

Depression appears to be highly prevalent in people with cancer. Although reported prevalence rates vary widely, it appears to affect 10%–25% of cancer patients. More research is needed on factors that may cause varying rates of depression and that predict which patients are most at risk. Longitudinal studies are needed to estimate the incidence of depression starting at the time of or, ideally, before diagnosis of cancer.

Many instruments with a wide range of complexity are currently being used to measure depressive symptoms. Researchers can choose instruments on the basis of the ease of use versus the instrument's performance. However, multiple methods of assessment make it difficult to compare studies. A consensus choice of instruments may help to standardize research on depression that is comorbid with cancer. Although some of these instruments are currently being used in clinical practices, there are currently no published studies of their effect on outcome. Outcome research, both psychological and medical, needs to be done on using the instruments as clinical information in the same manner as laboratory tests.

Psychosocial and pharmacologic interventions offer some benefit on treatment for depressive symptoms with cancer patients. Hundreds of studies exist on psychosocial interventions for cancer patients and depression, but a meta-analysis specifically of treatment studies on depressed patients remains to be done. This will probably change the effect sizes estimated in the meta-analyses reviewed in this report, which included large numbers of prevention trials. This meta-analysis may better differentiate between the effectiveness of types of psychosocial interventions.

Antidepressants appear to be beneficial in the treatment of depression in cancer patients. As the use of medications is becoming increasingly common, more research needs to be done to support current clinical practices in the prescription of medications for depression in cancer patients. Newer antidepressants and stimulants also should be studied in this population.

Finally, randomized, controlled trials on alternative therapies for depression in cancer patients need to be performed.

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