Depression occurs in about 15% of the general population and is at least two to three times more common in patients with cancer. Depression is often difficult to diagnose in these patients because of the complexity and constraints of cancer care, patient and family reluctance to acknowledge distress, and the presence of multiple other symptoms. Both antidepressants and psychotherapy are effective in treating depression in patients with cancer, much like in patients with other significant medical problems. Precise assessments of the benefits of treating depression in these patients are important in weighing them against the costs and potential adverse effects. Such estimates are limited by a paucity of randomized, placebo-controlled trials and methodological problems in the existing studies that reflect some of the clinical difficulties in case-finding, treatment, and follow-up of patients with cancer. The existing body of research about depression in cancer patients is extremely limited in terms of the number of studies published and the number of total patients reported over the last 30 years. Moreover, these limited data may not generalize well because of high rates of patient dropout and the very limited enrollment of children, adolescents, older adults, and minority groups. There is an emerging trend toward simplifying the assessment of depression in outpatient cancer care settings and studying depression therapies in cohorts of patients with cancer other than those with fully characterized depressive disorders. [J Natl Cancer Inst Monogr 2004;32:105–11]

Patients with cancer are often burdened by serious physical and psychological symptoms. The length and quality of their life are influenced not only by their cancer but also by comorbid medical conditions and multiple concurrent symptoms, including those of depression. The complexity of care in patients with cancer makes it particularly challenging to determine what treatments are effective for depression in this population. To better understand the treatment of depression during cancer care, it is useful to first review the existing paradigms for finding and treating cases of depression in the primary care setting. The relevant differences between treating depression in this setting and treating it in the cancer care setting will then be explored. The existing data regarding treatment will also be reviewed. Finally, emerging trends in depression research and treatment will be identified.

**Depression in General Medical Patients: Prevalence, Effect, and Assessment Models**

Large, prospective studies have shown that the prevalence of major depression in the outpatient primary care setting is 6%–14%, and the lifetime incidence of major depression is approximately 15% (1). Depression is at least two to three times more common in hospitalized patients or patients with chronic illness (2). Physicians recognize psychological distress in about two-thirds of the general medical patient population and prescribe antidepressants for about half of them (1). Depressive symptoms are associated with a higher-than-normal risk of physical decline and with long-term mortality in older adults (3–6). It is also a risk factor for coronary heart disease and stroke (7,8) and is associated with greater use of health care services (9,10).

The standard paradigm for finding cases of depression in the primary care setting is to view depression as a syndromal diagnosis based on patient history and exclusion of competing diagnoses, using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (11). Major depression is defined as a depressed mood or anhedonia that lasts for at least 2 weeks accompanied by at least three to four (for a total of five or more) specific psychological or somatic symptoms. If two to four rather than five or more symptoms are present, then the patient may be defined as having minor depression, a research criteria diagnosis in the DSM-IV (12). A recent review of case-finding instruments used in primary care showed that at least 11 questionnaires, ranging in length from one to 30 questions and ranging in time of administration from 1 to 5 minutes, have performance characteristics comparable to those of a semistructured interview applying standard diagnostic criteria (12).

The decision of whether to treat a patient for depression in the primary care setting is not always made on the basis of rigid diagnostic criteria; it is often made on the basis of a clinical judgment about the severity and duration of the patient’s symptoms and the likelihood of a spontaneous recovery within a supportive environment (13). Between 50% and 60% of patients with major depression respond to initial therapy with antidepressants, psychotherapy, or both (13). Those with minor depression and dysthymia have similar response rates (14). Depression may be treated by a patient’s primary physician, who can use either a collaborative care model that involves augmentation with one or more visits with a mental health care provider or a stepped care approach, wherein patients whose depression does not respond to initial therapy are referred to a mental health care provider (15). Patients who do not respond to initial antidepressant therapy after 4 weeks usually are treated with an escalation of the dose of the same antidepressant. No response to dose escalation usually prompts a switch to a different antidepressant (16).

Physicians and patients show considerable variation in how they think depression should be treated. This variation depends on not only the preferences of the physician, patient, and spouse or caregiver but also on health system variables, such as the availability of mental health care providers and reimbursement for mental health care (15). Unfortunately, the vast majority of depressed patients who receive antidepressants are not prescribed an adequate dose for a long enough time (1). Likewise,
the duration of psychotherapy is often too brief; proper therapy requires between six and 16 visits (13). In cancer care, the sheer complexity of patient care and the existence of multiple concomitant symptoms are factors that probably contribute to inadequate length of exposure to the chosen depression treatment. More research is needed to better understand such barriers.

Depression is associated with increased morbidity and health care costs, but it is treatable, so cost-effective interventions to improve the detection and treatment of depression are needed. A randomized trial to determine the cost-effectiveness of a specific quality improvement program in 46 primary care clinics and six community-based managed care organizations found that the cost per quality-adjusted life-year associated with the specific quality improvement program was in the range of from $15,000 to $35,000, comparable with that of other accepted medical interventions (17). Moreover, employment retention for depressed patients improved over a 1-year period without an overall increase in the number of medical visits (18).

**TREATMENT OF DEPRESSION IN GENERAL MEDICAL PATIENTS**

Antidepressant therapy and psychotherapy seem to be equally effective for treating mild to moderate depression in the general medical population (16,19). For treating severe depression, antidepressant therapy combined with psychotherapy may be better than psychotherapy alone (19). Antidepressants are also effective for treating depression in patients with concomitant physical illness. In 1998, a systematic review of randomized trials comparing antidepressants to placebo to treat depression in physically ill patients was published; the review comprised 18 studies including more than 800 patients with a range of chronic diseases (20). Depression treated with antidepressants was significantly more likely to abate than that treated with placebo (odds ratio 0.37; 95% confidence interval [CI] = 0.27 to 0.51). Results also showed that depression needed to be treated in approximately four patients to produce one recovery that would not have occurred with placebo alone (number needed to treat 4.2; 95% CI = 3.2 to 6.4). Approximately 10 cases of depression needed to be treated with antidepressants to cause one treatment dropout relative to placebo (20).

Interestingly, the response rates to both antidepressants and placebo are substantial, having increased considerably over the last 20 years (21). This may reflect a “stage migration” effect, where the inception cohorts have tended to have less severe depressive symptoms over time. Evidence indicates that severe depression is less likely than mild or moderate depression to respond to placebo (22,23). Of note, the widely used herbal remedy St. John’s Wort (*Hypericum perforatum*) has not been found to be more effective than placebo for treating moderately severe depression (24).

More than 24 antidepressants, which work by at least seven distinct pharmacologic mechanisms, are available (25). However, no single drug (or category of drugs) has proved most effective for relieving depressive symptoms or treating the syndrome of major depression (13,26). In the United States, many adults take medications to improve their health and well being; in any given week, most American adults take at least one medication, and 7% take five or more (27). This growing affinity for taking pills also is manifested in a national trend in the outpatient treatment of depression. Specifically, the proportion of depressed patients receiving antidepressant medications nearly doubled between 1987 and 1997 (from 37.3% to 74.5%), whereas the proportion of depressed patients receiving psychotherapy declined (from 71.1% to 60.2%) (28).

**UNIQUE CHALLENGES IN ASSESSING DEPRESSIVE SYMPTOMS IN PATIENTS WITH CANCER**

What is unique about depression in patients with cancer? Are patients with cancer substantially different from patients in primary care settings? Are they similar enough to patients with other serious chronic illnesses that one could generalize the existing evidence regarding depression treatment in patients with chronic illnesses to those with cancer? Is late-life depression or depression in children and adolescents distinct from adult depression treated in the primary care or cancer care settings? These are difficult questions for which there are few data. It is possible that the biology and risk factors for depressive symptoms and disorders differs across these age groups, and the most appropriate therapeutic approaches may also differ. In adolescent depression, for example, suicidal behavior is of particular concern, so tricyclic antidepressants (which can be fatal in overdoses) are no longer considered first-line agents (29). Another age-related difference is that children and adolescents metabolize serotonin-reuptake inhibitors more rapidly than adults, so careful dose titration is particularly important (30).

In addition to differences in the age of depressed patients, the disease-specific and treatment-specific physiological milieu certainly vary across the spectrum of patients with cancer. For example, a 27-year-old woman hospitalized for a stem cell transplant for large-cell lymphoma may not have the same expression of depressive symptoms, effect of symptoms, and response to therapy as a 60-year-old man with high-risk melanoma receiving adjuvant therapy with interferon alpha. Figure 1 provides an illustration of how symptom expression can differ between patients. These patients differ in sex, age, cancer biology, and cancer treatment. It is difficult to generalize depression treatment data to a broad spectrum of cancer patients such as these, as the importance of inclusion criteria related to comorbid illnesses, cancer site, sex, age range, and other factors is not yet clear.

Regarding research in patients with cancer, it is not clear how to select and follow such patients for a depression study. The standard criteria-based syndrome of major depression is notoriously difficult to diagnose in patients with cancer. First, patients, family members, and health care providers sometimes believe that feeling down, depressed, or hopeless is perfectly natural and understandable in the context of living with cancer. Clinicians are encouraged to acknowledge the difficulty and disappointment that often confronts these patients and families (31), but depression and hopelessness are not accepted by expert clinicians as an inevitable consequence of living with cancer. Second, patients with cancer often have physical symptoms of depression such as sleep disturbance, psychomotor retardation, appetite disturbance, poor concentration, and low energy (so-called neurovegetative symptoms) as a consequence of their underlying illness or treatment, thus confounding the diagnosis of depression. Indeed, depression is just one of many symptoms that clinicians must recognize and manage in inpatients and outpatients with cancer. Roughly two-thirds of outpatients with cancer experience pain, and more than one-third report notice-
able disruption in daily function associated with the pain (32). For patients with advanced cancer, the median number of symptoms expressed by self-report is generally from five to 10 (33–35). It may be that the problem of concurrent symptoms is the most relevant difference between depression in the general medical setting and that in the cancer care setting. Relatively few cancer care providers have sufficient knowledge and skill to assess and treat depression in this context, and it is often difficult to decide whether the depressive symptoms should be the primary focus of treatment or whether these symptoms might improve if other problems are better managed. Returning to the example shown in Fig. 1 (symptom scores on a 0–10 scale provided by two outpatients with cancer), both patients had depression, but their patterns of symptom expression were different, and the problem of concurrent symptoms was also evident in both cases. It is not surprising that clinicians vary considerably in their initial approaches to managing depression in such patients. Clinicians sometimes use verbal or nonverbal cues from patients to focus on symptoms they are more comfortable assessing and treating. At present, cancer providers are most comfortable, in general, treating somatic symptoms such as pain, nausea, constipation, or dyspnea.

Several barriers to treating depression still exist in the cancer care setting. In some instances, behavioral health professionals are available for consultation, but there is a paucity of qualified personnel who can see patients with cancer on a timely basis, often because of inadequate reimbursement for care in this area. In addition, even if depressive symptoms are noted or strongly suspected, the perceived stigma of a “psychiatric” problem is sometimes a barrier for patients or their families. There may be a strongly held belief in patients or families that a positive attitude or “fighting spirit” is important to either the health outcome or the clinician’s willingness to treat the cancer aggressively; this kind of belief can translate into a perceived risk in disclosing depressive symptoms or negative emotions. Finally, numerous factors have made the pace of cancer care particularly brisk, leaving less time for important interactions between patients or families and their providers. Although some of these issues are similar for patients in the primary care setting and for patients with other comorbidities, these barriers are particularly relevant for patients with cancer.

**Strategies for Choosing Patients with Cancer for Treatment of Depression**

Who should an investigator choose as an appropriate inception cohort for a study of depression in patients with cancer? The patients could be identified as depressed by the presence of a cardinal symptom (such as depressed mood or anhedonia), by a threshold score on a depression self-report instrument, or by a diagnostic interview administered by trained personnel. The overall approach to selecting patients with depression involves one of several strategies: screen, diagnose, grade severity, and treat; screen, diagnose, and treat; or screen and treat. Each approach gathers a different patient population, especially when one considers the myriad of patients that might be excluded (e.g., those with suicidal ideation, a prior history of depression, concurrent exposure to drugs that might have antidepressant activity, comorbid psychiatric disorders, or poorly controlled symptoms other than depression). The more intensive screening strategies will tend to be associated with fewer participants, because fewer physicians will support these studies for their patients and fewer patients will accept the longer, more complicated investment of their time and energy. The less intensive strategies face scientific criticism from psychiatrists and psychologists who are accustomed to more rigorous patterns of patient selection, depression assessment, depression treatment, and follow-up.

Symptom research is an emerging interest within the discipline of academic general medicine (36–38). Within this new paradigm, symptoms are conceptualized in terms of a functional disturbance of the nervous system. There is a growing appreciation for the physical changes in the nervous system associated with depression and its treatment (39,40). Understanding depressive symptoms in the context of symptom science rather
than solely within the standard psychiatric paradigm is being explored in the cancer care setting in an attempt to break down some of the barriers to recognition and management of depression in this population.

**TREATMENT OF DEPRESSION IN THE CANCER CARE SETTING**

Drugs used to treat depression in patients with cancer are quite similar to those used in the primary care setting; these include tricyclic antidepressants, serotonin-reuptake inhibitors, newer antidepressants, and psychostimulants. There is considerable interest in the use of psychostimulants (particularly methylphenidate) to treat depression in cancer patients (41–46). This interest is driven by the potential of these agents to rapidly produce clinical effects and to alleviate other concomitant symptoms such as fatigue, sedation, and poor concentration. Psychological therapies include psycho-educational interventions, cognitive behavioral therapy, interpersonal therapy, and problem-solving therapy. The basis of psychological therapy is to foster a very personal and respectful communication with the patient with a focus on careful listening. The focus is more on rehabilitation and less on the etiology of the symptoms. As such, patients are encouraged to express their feelings, share their experiences, and find successful strategies for dealing with their problems. Although psychological therapies are often used to treat depression in patients with cancer, there are barriers to their use. The sheer complexity of patient care (multiple providers, laboratory and radiographic tests, and scheduled treatments such as radiation or infusions) can make the scheduling of these interventions difficult. Moreover, such therapy is poorly reimbursed in most instances. Finally, electroconvulsive therapy is a distinct invasive modality known to be effective for severe depression; this modality is rarely used and has not been adequately studied for depression in the context of cancer care.

Difficult issues for designing interventions for cancer-related depression include identifying an acceptable “gold standard” for depression treatment in cancer, choosing an appropriate duration of therapy, and finding a feasible strategy to assess for compliance to the intervention. In addition, assessment of outcomes is particularly challenging, because the researcher must choose feasible numbers and types of outcome measures and decide the importance of depression-specific outcomes relative to more distal outcomes such as quality of life. Other difficulties in researching depression in patients with cancer include the lack of a standard primary endpoint; the high frequency of missing data; the clash of expectations and paradigms inherent to interdisciplinary review of depression research proposals; the shortage of patient access to behavioral health specialists; and the relative aversion of patients, family members, and some providers to placebo-controlled study designs. Finally, limited patient access to behavioral health is a barrier to both patient care and depression research in the cancer care setting.

**CONTROLLED TRIALS TO TREAT DEPRESSION IN PATIENTS WITH CANCER**

With all of these challenges in mind, it is not surprising that data from controlled trials regarding the efficacy of treatment of depression in patients with cancer are sparse. Only seven randomized, placebo-controlled trials comparing an antidepressant drug (a tricyclic antidepressant or serotonin-reuptake inhibitor) with placebo for the treatment of depression in patients with cancer have been reported (Table 1) (47–53). Only 476 patients were included; none of these studies included children, and three of the studies (47,48,50) only included women. The trend in these studies favors the treatment arm, but the small sample size of the individual trials, short follow-up duration, and heterogeneity of outcome measures limits any strong conclusions about this body of research. There are a handful of other randomized controlled trials involving patients with cancer and assessment of depression outcomes that are equally difficult to interpret. Three placebo-controlled, randomized trials assessed depression outcomes but used drugs (such as methylprednisolone, thioridazine, and mazindol) that are not typically used to treat depression (54–56). These studies included a total of 116 patients. The literature also includes three double-blind, randomized trials comparing two interventions without a placebo control (57–59). This group of trials included comparisons of alprazolam and muscle relaxation (57), fluoxetine and desipramine (58), and trazadone and clorazepate (59), with a total of 211 patients enrolled. Finally, a recent randomized-controlled, double-blind trial comparing a serotonin-reuptake inhibitor to placebo has been conducted in the outpatient oncology setting and has been recently published (60). The University of Rochester Cancer Center research base study included 479 patients and compared paroxetine and placebo with fatigue as the primary endpoint (60). This study also found alleviation of depressive symptoms in the treatment arm relative to placebo. Overall, research related to drug therapy for depression in patients with cancer spans 30 years and includes 14 studies involving 1541 patients. Nevertheless, these studies include a myriad of endpoints, and most of the trials had small sample sizes and short duration of follow-up. The trend in these data indicates that antidepressants probably improve depression in patients with cancer much like they do in other medically ill patients. Further research is needed to better define the magnitude and duration of the treatment effect and to improve the precision of the estimate of this effect. In addition, the toxicities and cost utility of drug therapy for patients with cancer who express depressive symptoms have not been adequately studied.

Psychological therapies are most often applied in conjunction with medications, but they can be used alone to treat moderate to severe depression (15). There are no data regarding whether psychological therapies plus antidepressants are more effective than antidepressants alone for treating depression in patients with cancer. In fact, very few studies in medically ill populations have described the effect of psychotherapy with sufficient methodological detail (61). Several meta-analyses of controlled trials of psychological interventions for decreasing psychological distress in patients with cancer have been published (62–65). Shear and Maguire (62) reported the results of 20 trials targeted for reducing distress in patients with cancer comprising 1101 patients and showing a combined effect size of 0.36 (95% CI = 0.06 to 0.66). This study did not reveal a difference in efficacy between group therapy and individual therapy in cancer patients. Meyer examined 45 randomized trials comprising 2840 patients comparing a psychosocial intervention and a control. An overall effect size of 0.24 was found for measures of emotional adjustment and slightly larger effect sizes for global measures and disease-specific symptoms (65). The largest meta-analysis included all trials that provided psychoeducational care to adults.
with cancer including randomized, nonrandomized, and quasi-experimental designs (64). This analysis included 98 studies and 5326 subjects and reported a significant, moderate effect size (standard mean difference between treatment and control groups measured in standard deviation units = 0.54; 95% CI = 0.43 to 0.65). The most recent systematic review of psychological therapies for patients with cancer was completed by the New South Wales Cancer Council Cancer Education Research Program; 627 eligible papers published since 1954 were evaluated, and 129 trials were identified that involved psychosocial outcomes (63). Only 24 of the 114 studies showed an advantage for the intervention in terms of the endpoint of depression (Table 2). None of these meta-analyses focused on psychological interventions specifically for patients with depressive disorders or depressive symptoms. Overall, the data regarding the efficacy of psychological interventions for the treatment of depressive symptoms in patients with cancer remain equivocal.

CONCLUSION

Despite research spanning several decades and including hundreds of clinical trials, no strong conclusion can be made about the effectiveness of antidepressants or psychological interventions for improving depression outcomes for patients with cancer. Research related to depressive symptoms has been fraught with methodological challenges and has involved disproportionate representation of adult women 45–65 years of age. There is little information about the treatment of depression in children, adolescents, or older adults with cancer. Clinical expectations about the assessment and treatment of depressive symptoms in patients with cancer is largely based on existing data from general medical populations and from clinical experience and the opinions of key leaders in psycho-oncology.

More prospective research is needed to evaluate treatment strategies for depression in patients with cancer. One direction for future interventional research would be to pursue both less rigid ways of defining depression in patients with cancer and broad inclusion criteria with respect to age, comorbid conditions, and concurrent somatic symptoms. Another research intervention worth exploring would be prevention of depressive symptoms in high-risk patients. A large longitudinal survey study is needed to provide appropriate descriptive data about the

Table 1. Randomized trials comparing antidepressants to placebo in patients with cancer*

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Antidepressant (No. of subjects)</th>
<th>Patient description</th>
<th>Study duration, wk</th>
<th>Outcome measures</th>
<th>Outcomes that improved compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirohit, 1978 (49)</td>
<td>Imipramine (39)</td>
<td>Hospitalized patients receiving radiation therapy</td>
<td>4</td>
<td>HDRS</td>
<td>No statistical evaluation</td>
</tr>
<tr>
<td>Costa, 1985 (50)</td>
<td>Mianserin (73)</td>
<td>Adult women with cancer</td>
<td>4</td>
<td>CGI HDRS</td>
<td>CGI (77% vs. 50%) HDRS at days 7, 21, and 28</td>
</tr>
<tr>
<td>Eija, 1996 (48)</td>
<td>Amitriptyline (15)</td>
<td>Breast cancer patients with neuropathic pain</td>
<td>4</td>
<td>2 questions about depression on a 4-point scale</td>
<td>No statistical evaluation (mostly a pain study)</td>
</tr>
<tr>
<td>Van Herringen, 1996 (47)</td>
<td>Mianserin (55)</td>
<td>Adult women with early stage breast cancer treated with radiation</td>
<td>7</td>
<td>HRSD</td>
<td>HRSD at 4 wk and 7 wk</td>
</tr>
<tr>
<td>Razavi, 1996 (51)</td>
<td>Fluoxetine (91)</td>
<td>Adults with depression or adjustment disorder in relation to cancer</td>
<td>5</td>
<td>HADS MADRS SCL90-R HAS SQOLI HDRS</td>
<td>SCL-90 at 5 wk</td>
</tr>
<tr>
<td>Musselman, 2001 (52)</td>
<td>Paroxetine (40)</td>
<td>Adults with melanoma receiving adjuvant interferon alpha</td>
<td>14</td>
<td>HAS NRS DSM-IV criteria</td>
<td>HDRS, HAS, and NRS at weeks 8 and 12 Major depression (11% vs. 45%)</td>
</tr>
<tr>
<td>Fisch 2003 (53)</td>
<td>Fluoxetine (163)</td>
<td>Adults with advanced solid tumors and depressive symptoms</td>
<td>12</td>
<td>FACIT-G BZSDS</td>
<td>Quality of life (FACIT-G) and depressive symptoms</td>
</tr>
</tbody>
</table>

*CGI = Clinical Global Impression scale, HDRS = Hamilton Depression Rating Scale, ZSRDS = Zung Self-Rating Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SCL-90 = Revised Symptom Checklist, BZSDS = Brief Zung Self-Rating Depression Scale, FACIT-G = Functional Assessment of Chronic Illness Therapy (General), HADS = Hospital Anxiety Depression Scale, HAS = Hamilton Anxiety Scale, SQOLI = Spitzer Quality of Life Index, DSM-IV = Diagnostic and Statistical Manual of Mental Disorder, 4th edition, NRS = Neurotoxicity Rating Scale.
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