

Diagnosis and treatment of depression in patients with advanced illness

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Abstract. This article reviews common sources of suffering in patients with advanced illness, identifies challenges in appropriately diagnosing and treating depression in this setting, and examines the relationship between depression and other key clinical outcomes in the setting of advanced disease. A systematic literature review was conducted. Most of the existing research on patients with advanced illness has been conducted with cancer patients. Approximately 18 percent of patients with advanced illness meet criteria for major or minor depression; multiple psychiatric co-morbidities occur frequently. Prevalence rates increase as patients become sicker. However, depression is frequently underdiagnosed and undertreated in the setting of advanced illness. One of the key clinical challenges is differentiating depression from grief. Both psychosocial and psychopharmacologic interventions have been shown to be effective in treating depression in patients with advanced cancer. In conclusion, depression is a regular complication of advanced illness, reduces quality of life, compromises family member function, interferes with treatment decisions, and may shorten survival. However, numerous effective treatment approaches, including both medications and psychotherapy, exist and can be used to alleviate depression.

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Sadness and depression are virtually-universal experiences for patients with advanced illness and their families. These symptoms exist on a continuum and have many sources: grief about current and anticipated losses, fear and uncertainty about the future, unresolved issues from the past, and concerns about loved ones. Pre-existing and new psychiatric disorders (depression, anxiety, post-traumatic stress disorder, personality disorders, substance abuse, other major psychiatric disorders), difficult family dynamics, inadequate social support and/or coping resources, personal vulnerabilities related to past experiences, and existential and spiritual concerns may also amplify suffering. Physical symptoms, difficulties in relating to the health care team, financial concerns, and other practical matters may also contribute to patients' and families' emotional distress.

THE SPECTRUM OF NORMAL RESPONSES

Feelings of grief, sadness, despair, fear, anxiety, loss and loneliness are present, at times, for nearly all patients

facing the end of their lives. Yet, in spite of such painful emotions, many patients, even those with significant vulnerabilities, are able to achieve some degree of peace and acceptance at the end of their lives. Being at peace is associated with positive clinical outcomes, including higher quality of life in the last week of life, less emotional distress, more advance care planning, and improved post-death outcomes among survivors (Ray *et al.*, 2006). The usual conditions for effective coping and the attainment of a degree of peace at the end of life include good communication and trust among patient, family, and clinical team, the ability to share fears and concerns, as well as meticulous attention to physical comfort and psychological and spiritual concerns.

Each patient brings a characteristic mode of coping and an array of strengths and vulnerabilities to the experience of a life-threatening illness. Thus, each individual's psychological experience with a terminal illness will be unique and will be affected by multiple different factors.

All patients with a life-threatening illness benefit from a comprehensive psychological, social and spiritual assessment, as well as evaluation of physical symptoms. Systematic psychological assessment allows the clinician to support effective coping, to identify persons at risk of experiencing high levels of difficulty during their illness, and to proactively address vulnerabilities. The basic domains of a psychosocial and spiritual assessment are:

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- Developmental issues
- Meaning and impact of illness
- Coping style
- Impact on sense of self
- Relationships
- Stressors
- Spiritual resources
- Economic circumstances
- Physician-patient relationship

Depression: Prevalence rates of depression in cancer patients range widely, depending on diagnostic criteria used and patient population studied. Rates of depression range from 3-38% among cancer patients (Massie, 2004; Akechi *et al.*, 2004; Hotopf *et al.*, 2002). The wide variability in reported rates is explained by the lack of agreement on appropriate criteria for diagnosis of depression, differences in patient populations (both in relation to disease and staging), and variation in assessment methods used. Research by Derogatis *et al.* (1983) showed that 47% of patients with cancer (all types, all stages) fulfilled diagnostic criteria for psychiatric disorders. Of those 47%, 68% had adjustment disorders with depressed or anxious mood, 13% had major depression, and 8% had organic mental disorders. Akechi *et al.* (2004), in a prospective study in a Japanese palliative care setting, found that, using the Structured Clinical Interview for DSM, 16% of patients had adjustment disorder, 7% had major depression, and none had PTSD. They also found that 31% of patients in their study either developed a new diagnosis of adjustment disorder and/or major depression, or experienced a remission in follow-up with a median of 58 days. More recent data, using the Structured Clinical Interview for DSM-IV, and including diverse patient populations, showed that 39% of advanced cancer patients either fulfilled criteria for a major psychiatric disorder and/or utilized mental health services for psychological distress following the cancer diagnosis. Twelve percent of the patients met criteria for a major psychiatric disorder: 7% major depression, 3% generalized anxiety, 5% panic disorder, 2% post-traumatic stress disorder. An additional 11% of patients fulfilled criteria for minor depression. Over one third of patients with a psychiatric diagnosis met criteria for two or more diagnoses (Kadan-Lottick *et al.* 2005). Prevalence rates appear to increase as patients become sicker (Evans *et al.*, 1999; Ciaramella & Poli, 2001). The highest rates of depression are seen in patients with cancers of the pancreas, oropharynx, and breast (McDaniel *et al.*, 1995). Recent data suggests that depression is associated with an elevated risk of death in patients with

cancer (Stommel *et al.*, 2002; Faller *et al.*, 1999; Loberiza *et al.*, 2002). Depression impairs the patient's ability to enjoy life, interferes with connection, is associated with feelings of emptiness and meaninglessness, and causes anguish to family and friends. In addition, depression is associated with decreased adherence to treatment, prolonged hospital stays, and reduced quality of life (Pelletier *et al.*, 2002; Breitbart *et al.*, 1995). It is a major risk factor for suicide and for requests to hasten death (Cochinov *et al.*, 1995) and influences will to live in cancer patients receiving palliative care (Cochinov *et al.*, 1999). As many as 59% of patients requesting assisted suicide are depressed (Cochinov *et al.*, 1995; Emanuel *et al.*, 2000). Lloyd-Williams (2002) carried out a prospective study to evaluate incidence of suicidal ideation in a palliative care population, mostly with very late stage disease, and found that 3% had such thoughts often, 10% experienced them sometimes, 17% hardly ever experienced them, and 70% never had thoughts of self-harm. Younger patients were more likely to report suicidal thoughts. Several studies suggest that the prevalence of depression in cancer has declined over the past twenty years, perhaps related to improvements in medical care and outcomes (Van't Spijker *et al.*, 1997), and de-stigmatization of the diagnosis of cancer (Spiegel & Giese-Davies, 2003).

Similarly, patients with other medical illnesses, also appear to have elevated rates of depression (Cassem, 1999; Evans *et al.*, 1999). Patients seeking to stop dialysis have rates of depression of between 5% and 25% (Cohen *et al.*, 2002); those with end-stage heart disease are reported to have prevalence rates of 36% for major depression and 22% for minor depression (Gibbs *et al.*, 2002). Fewer than half received treatment for depression (Koenig, 1998). Depression in patients with heart failure is associated with elevated hospital readmission and mortality (Jiang *et al.*, 2001).

Other "syndromes": In recent years, Kissane has proposed that demoralization syndrome be considered a separate entity. He characterizes demoralization as "incompetence through loss of meaning or purpose (Kissane, 2001);" additional proposed criteria for demoralization include existential distress, pessimism, helplessness, hopelessness, absence of drive, isolation and lack of support. However, evidence in support of this as a distinct syndrome is lacking.

Rates of mental health service use: A small number of studies have examined how clinicians assess and manage mental health issues in patients with advanced disease. Recent data suggest that palliative care clinicians and oncologists tend to under-recognize and underestimate

the severity of patients' depression (Meyer *et al.*, 2003; Passik *et al.*, 1998). Lawrie *et al.* (2004) found that 73% of palliative care physicians routinely assess patients for depression, and that 75% prescribed selective serotonin reuptake inhibitors (SSRIs), 25% prescribed tricyclic antidepressants, 6% prescribed psychostimulants, and 3% prescribed St. John's wort. When asked whether they would prescribe complementary or psychological therapies for depression, 35% reported that they would refer

patients for aromatherapy, and only 8% would refer for counseling. Kadan-Lottick *et al.* (2005) found that nearly half of patients who met criteria for psychiatric illness did not receive mental health services, and that non-white patients were significantly less likely to receive mental health care than white patients.

Differentiating depression from grief is a major clinical challenge in palliative care. Characteristics of grief and depression are presented in Table I.

Table I – Characteristics of Grief and Depression.

	Grief	Depression
Definition	Feelings and behaviors that result from a particular loss*	Depressed mood, decreased interest and pleasure, appetite and sleep disturbance, psychomotor agitation or retardation, decreased concentration, loss of energy, feelings of worthlessness, guilt, hopelessness, helplessness, and thoughts of death with impairment of functioning lasting at least two weeks
Symptoms and signs	Somatic distress, sleep and appetite disturbance, diminished concentration, social withdrawal, sighing	Hopelessness, helplessness, anhedonia, worthlessness, guilt, suicidal ideation most useful diagnostic clues Somatic distress, sleep and appetite disturbance, diminished concentration, social withdrawal, sighing are also common
Other differentiating factors	Patient retains capacity for pleasure Comes in waves Passive wishes for death Able to look forward to the future Crying leads to relief	Nothing is enjoyable Constant Intense, persistent suicidal thoughts No sense of anything to look forward to No relief from crying

* Prigerson H.G. & Jacobs S.C. (2001). Perspective on care at the close of life, caring for bereaved patients: "all the doctors just suddenly go". *Journal of the American Medical Association* 286, 1369-1376.

There is considerable overlap between the neurovegetative symptoms of depression and those associated with any serious illness. Different approaches to diagnosis have been espoused; most experts agree that for clinical purposes, using an "inclusive" set of diagnostic criteria that incorporates both neurovegetative and psychological symptoms of depression is most appropriate for this patient population (Raison & Miller, 2003). Asking patients directly about depressed mood has been shown to be sensitive and specific for the diagnosis of depression, although there are differences across populations (Cochinov *et al.*, 1997; Watkins *et al.*, 2001). Some patients may readily verbalize that they are depressed; others, no matter how despairing, may never acknowledge it, or may call it something else (e.g., nervousness). Although some clinicians may be concerned that exploration of feelings of depression may worsen patient distress, recent research suggests that this is not the case (Meyer *et al.*, 2003). Hopelessness, helplessness, worthlessness, guilt, lack of pleasure, and suicidal ideation are the key psychological symptoms of depression. In addition, social withdrawal, irritability, and anxiety may also be present. Pain, as well as a personal or family history of

substance abuse, depression, or bipolar illness, are major risk factors for depression (Breslau *et al.*, 1996). Similarly, treatment with particular medications – interferon, corticosteroids, cyclosporine, L-asparaginase, tyrosine kinase inhibitors (Quek *et al.*, 2009), tamoxifen, vinblastine (Raison & Nemeroff, 2000), for example – also predispose to the development of depression. Prophylaxis with antidepressant medication has been shown to be effective in dramatically reducing the incidence of depression in patients receiving interferon (Musselman *et al.*, 2001). Recent research suggests that depression in cancer patients may be part of a larger "sickness syndrome" that involves depression, pain, fatigue, and sleep disturbance, and that is believed to be associated with chronic immune activation.

In addition to these diagnostic criteria, other clues to the presence of depression are: insomnia (particularly with early morning awakening), intractable pain and/or other symptoms, excessive somatic preoccupation, disability out of proportion to the patient's medical condition, and hopelessness, aversion, or lack of interest in the clinician (Maltseberger & Buie, 1974). Poor adherence or treatment refusal have also been associated with depres-

sion (Goldberg, 1983; Pirl & Roth, 1999); however other studies have shown increased adherence to cancer treatment in depressed patients (Ayres *et al.*, 1994). The use of complementary therapies by cancer patients may also be an indicator of feelings of desperation, fear, hopelessness, depression, and increased symptom burden as patients recognize advancing illness (Soliner *et al.*, 1997; Burstein *et al.*, 1999; Verhoef *et al.*, 1999).

Depression: Contrary to much popular and professional opinion, depression is a treatable condition, even in patients who are terminally ill. Effective treatment of depression in the context of distressing symptoms, however, is difficult; thus, the first step in treating depression is effectively controlling physical symptoms. Some patients may be concerned that being labeled as “depressed” will lead their physicians to take their physical problems less seriously, to treat them less aggressively, or to stigmatize them; it is often essential for the physician to address these issues before the patient will be willing to accept treatment. A combination of antidepressant medication, supportive psychotherapy, and patient and family education are viewed as the “gold standard” of treatment (Block, 2000). Effective treatment of depression has been shown to improve symptoms of both patients and their caregivers (Martire *et al.*, 2010).

There is an accumulating body of moderate quality evidence suggesting that psychotherapeutic interventions are effective in reducing depressive symptoms in patients with advanced cancer (Williams & Dale, 2006; Akechi *et al.*, 2009). In particular, cognitive behavior therapy appears to offer significant benefit to this population (Moorey *et al.*, 2009).

Because antidepressant therapy is usually relatively well-tolerated, recent expert consensus statements recommend having a low threshold for initiating treatment. Psychostimulants, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants are the main pharmacologic treatment modalities for depression at the end of life. Evidence about the effectiveness of antidepressants in patients at the end of life is poor; although one study describes some effectiveness in as many as 80% of cancer patients (Chaturvedi *et al.*, 1994), the lack of clear criteria for effectiveness and appropriate study design significantly compromise these data. There are few randomized, controlled trials of antidepressants in the palliative care setting. The small number of randomized controlled trials have showed some positive response to fluoxetine (Fisch *et al.*, 2003) and modafinil (Lundorff *et al.*, 2009); open label trials have demonstrated positive effects of paroxetine, sertraline, and mirtazapine

(Theobald *et al.*, 2002). Because of these gaps in the evidence base, trials from general oncology, primary care, geriatrics, and HIV provide much of what we know about antidepressant effectiveness in palliative care. Several randomized, controlled trials comparing antidepressants with placebo for depression in cancer patients suggest a benefit of treatment (Razavi *et al.*, 1996; Van Heeringen & Zivkov, 1996; Theobald *et al.*, 2003); high dropout rates and narrow patient populations limit generalizability. A recent randomized controlled study of paroxetine in an ambulatory oncology population demonstrated effectiveness for fatigue and depression (Morrow *et al.*, 2003). A trial of a simple 2-question symptom screening tool for depression followed by fluoxetine treatment for depressed patients demonstrated improvement in patients’ quality of life and depressive symptoms. Randomized controlled trials in primary care have demonstrated the effectiveness of mirtazapine and paroxetine (Wade *et al.*, 2003). RCTs in geriatric settings demonstrate the effectiveness of combined modalities (community-based psychosocial interventions and antidepressant medication) for major and minor depression (Ciechanowski *et al.*, 2004; Bruce *et al.*, 2004); the results of these findings have been incorporated in recent treatment guidelines and algorithms for geriatric depression (Alexopoulos *et al.*, 2001; Mulsant *et al.*, 2001; Lapid & Rummans, 2003). A recent meta-analysis of SSRIs for the treatment of HIV-associated depression suggested some therapeutic benefit and acceptable tolerability, but did not identify any agent(s) as particularly effective (Caballero & Nahata, 2005). Other investigators have demonstrated effectiveness of treatment with sertraline, paroxetine, and mirtazapine in open-label trials (Ferrando *et al.*, 1997).

Several non-randomized studies document the effectiveness of methylphenidate for depression in cancer patients (Olind & Masand, 1996; Macleod, 1989); however, a recent RCT found no improvement in fatigue and quality of life from treatment with dextroamphetamine (Auret *et al.*, 2009). In patients with HIV, a RCT has shown stimulants to be effective in patients with low energy and apathy (Wagner & Rabkin, 2000). Another recent randomized, double-blind, controlled trial of psychostimulants for fatigue in HIV patients showed statistically significant improvements in fatigue, quality of life, and psychological distress (including depression), with minimal side effects (Breitbart *et al.*, 2001). A recent open-label study of HIV positive patients that evaluated modafinil as a treatment for fatigue showed evidence of effectiveness for both fatigue and depression (Rabkin *et al.*, 2004).

Because of their rapid onset of action, psychostimulants (methylphenidate, dextroamphetamine) deserve special consideration in treating depression near the end of life (Dein, 2002). Therapeutic benefits can be achieved within 24-48 hours of starting medication. SSRIs are also valuable drugs in the palliative care setting and may be used alone, or in combination with a psychostimulant. Choosing among SSRIs is not yet an evidence-based decision in this setting. Tricyclic antidepressants are not first-line agents for depression in the terminally ill because they are not as well-tolerated as SSRIs, due to autonomic and sedating effects. Electroconvulsive therapy is a highly effective treatment for depression and should be considered in patients with psychotic depression, those who can't tolerate antidepressant medications, or treatment-resistant depression who have a prognosis of several months or more (Bosworth *et al.*, 2002; O'Connor *et al.*, 2001).

In general, patients with suicidal ideation, treatment-resistant depression, diagnostic uncertainty, co-morbid psychiatric disorder (e.g., anxiety, substance abuse) should be referred to a psychiatrist (Lebowitz, 1996). Refractory, treatment-resistant depression may occur in the palliative care setting. Appropriate treatment planning for such patients requires not only an intensive interdisciplinary dialogue including a psychiatrist, but involvement of the patient and his/her family, in defining appropriate care. Very occasionally, in spite of state-of-the-art medication, psychotherapy, and palliative care, depression may be intractable; in such circumstances, clinicians are called upon to respond to depression as part of a terminal illness syndrome that is causing profound suffering. In these rare circumstances, limitation of further aggressive intervention, as well as other palliative care approaches (e.g., palliative sedation) to the patient with extreme and irremediable suffering, should be considered.

CONCLUSIONS

Emotional distress, especially depression, commonly adds to the burden of suffering for patients with advanced illnesses. While diagnosis of depression is often challenging in this setting, having a low threshold for initiating treatment will help assure that suffering due to depression is minimized. Effective psychosocial and pharmacologic treatments for depression in the setting of terminal illness now exist and are a core element of high quality care for patients approaching the end of life.

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