The Psychopharmacological Management of Depression in Patients with Cancer

Polyxeni Mangoulia[1]

Abstract

Introduction: The patient with a physical illness is affected emotionally and spiritually. The patient with an emotional illness is affected physically and spiritually. It is therefore important to view the patient in a holistic sense. Cancer and depression are responsible for enormous human suffering on a global scale. When cancer and depression are comorbid, symptom burden and mortality are each magnified, as one disease complicates the management of the other. **Aim:** This paper aimed to explore and summarize recent relevant data concerning the rates of depression and other psychiatric disorders in cancer patients and the use of antidepressants and other psychotropic drugs.**Methods:** PubMed, Google Scholar, Web of science and SCOPUS databases were searched for peer-reviewed publicationsondepression in cancer patients. **Results:** Depressive spectrum disorders, including major depression, persistent depression, minor and sub-syndromal depression, and other forms of depressive conditions, such as demoralization, are among the most common psychiatric consequences of cancer patients, affecting up to 60% of patients. The availability of new drugs, with less side-effects and safer pharmacological profiles, has been a major advance in clinical psychooncology. **Conclusions:** It is mandatory that health care professionals working in oncology receive training in the diagnosis and management of depression.

Keywords: Antidepressants; Cancer; Depression; Psychopharmacology; Psychooncology; Oncology

1. Introduction

A frequent misconception is that depression and anxiety are normal and expected for patients with cancer; this attitude minimizes the significance of the patient's suffering from these psychiatric disorders. Depression and anxiety are more common in cancer patients than in the general population and are at least as prevalent as in other medically ill patients. Depression influences treatment compliance and efficacy, quality of life, functional status, hospital length of stay, and possibly prognosis and mortality (Reich, 2008; Miller & Massie, 2006).

Although emotional distress needing clinical attention can affect 40%-60% of cancer patients (Brocken, Prins, Dekhuijzen & van der Heijden, 2012), a formal diagnosis of a psychiatric disorder according to the usual nosology psychiatric systems, such as the International Classification of Disease of the World Health Organization or the Diagnostic and Statistical Manual of Mental Health Disorders of the American Psychiatric Association, can be made in about 25-30% (Mitchell et al., 2011; Singer, Das-Munshi & Brähler, 2010). Among these, adjustment and stress-related disorders and major depression have been most studied in terms of prevalence, consequences and treatment in oncology (Caruso et al., 2017a; Caruso et al., 2017b; Cordova, Riba & Spiegel, 2017; Krebber et al., 2014; Walker et al., 2013).

While many would like to maintain a positive view of the diagnosis and treatment for cancer, for many a diagnosis of cancer constitutes a trauma analogous to experiencing a physical assault, accident, or natural disaster. Many patients remember the date and time they received their cancer diagnosis, exactly where it was discussed, who said it, the specific words that were used, and how they felt.These life-altering, life-changing moments are, psychologically riveting. In the initial period of diagnosis and treatment, the term acute stress disorder or post traumatic stress disorder (PTSD) may best describe the psychological problems that occur (Spiegel &Riba, 2015; APA, 2013).

---

[1] RN, RMHN, MSc, PhD, Faculty of Nursing, University of West Attica, Department of Liaison Psychiatry, "Evaggelismos" General Hospital, Athens, Greece. e-mail: pmangoulia@gmail.com

Such patients experience intrusive thoughts, disbelief, avoidance, inability to sleep, fears, and physiological hyperarousal. Their lives change suddenly from the mundane routine of work or family activities, to a string of doctors' appointments, receiving life-altering news and data in technical language, making appointments for surgery, blood draws, chemotherapy, and radiotherapy (Mangoulia & Baizanis, 2014; Spiegel & Riba, 2015).

According to the World Health Organization (WHO), depression is expected to be the leading cause of disability by 2030 and it is the most significant contributor to the overall global burden of disease (Lépine & Briley, 2011; WHO, 2011). In patients with medical illness, the burden of depression is even more serious. The WHO World Health Survey (WHS), involving 245.404 participants with one or more chronic physical diseases had comorbid depression and that depression had the largest effect on worsening mean health scores and on increasing disability compared with the other chronic conditions (Moussavi et al., 2007).

2. Aim and methods

This paper aimed to explore and summarize recent relevant data concerning the rates of depression and other psychiatric disorders in cancer patients and the use of antidepressants and other psychotropic drugs. PubMed, Google Scholar, Web of science and SCOPUS databases were searched for peer-reviewed publications on depression in cancer patients.

3. Results

3.1 Diagnostic considerations

Many symptoms that occur in the context of cancer overlap with the DSM-IV-TR criteria for major depressive episode (APA, 2000), prompting debate as to whether these shared symptoms should be included or excluded when criteria are considered in making a psychiatric diagnosis. Anorexia, weight loss, fatigue, sleep disturbance, cognitive impairment, and psychomotor slowing can each be caused by pathophysiological processes related to the cancer itself or treatment.

An inclusive approach that includes all symptoms of depression regardless of the possible contributory etiologies is most often used clinically. For research purposes, the exclusive approach improves specificity by removing fatigue and anorexia from the criteria necessary for depression, and instead emphasizing depressed mood, anhedonia and hopelessness (Philbrick, Rundell, Netzel& Levenson, 2012; von Ammon Cavanaugh, Furlanetto, Creech & Powel, 2001).

Despite the fact that all studies used standard diagnostic criteria to define depression caseness, those in which an expert (psychiatrist or clinical psychologist) administered interviews reported a lower estimate of current depression prevalence than studies that employed less expert interviewers (Walker et al., 2013). The most effective and valid methods to correctly screen and assess depression in cancer, including short (and ultra-short) tools, self-report questionnaires, and semi-structured interviews (Caruso et al., 2017a).

In 1997 the National Comprehensive Cancer Network published the Distress Management Guidelines which is updated regularly as a tool for oncology clinicians to develop a differential diagnosis of distress, including common psychiatric disorders and psychosocial and spiritual problems. More recently, the NIH has developed a series of brief reliable and valid measures, the Patient-Reported Outcomes Measurement System (Spiegel &Riba, 2015; O'Hara et al., 2002; Mauricio et al., 2000).

3.2 Prevalence of depression in cancer patients

Limitations in research methodology and lack of standardization in diagnostic criteria contribute to wide variations in prevalence rates of depression in patients with cancer. Age, gender, type of cancer, treatment, severity of illness, social support network and stage of life also influence depression rates.

Depression is one of the most common psychiatric disorders in cancer patients (Smith, 2015; Mangoulia & Baizanis, 2014; Dauchy, Dolbeault & Reich, 2013). An extremely vast literature has examined several issues related to depression including its prevalence, with data showing that 25%-30% of cancer patients suffer from depressive disorders; percentages ranging from 4 to 60% (Mitchell et al., 2011). Risk factors for depression in patients with cancer include: poorly controlled pain, advanced cancer stage, previous history of depression, pancreatic, oropharyngeal and breast cancers, poor functional status, family history of depression/suicide and treatment with medications known to be associated with depression (Miller & Massie, 2006; McDaniel, Musselman, Porter, Reed & Nemeroff, 1995).

In a recent review of 211 studies of cancer patients, in different contexts (outpatient clinics, hospital, palliative care settings), in different stages (early diagnosis, recurrence, survivorship or advanced stages), an extreme variability of prevalence was found, with pooled mean prevalence of depression in cancer patients ranging from 8% to 24% (Krebber et al., 2014).

Those differences can be explained as related to the heterogeneous samples of patients and the different type of the assessment instruments, e.g. questionnaires vs. interviews. Also the quality criteria of assessment methods represents a limitation about prevalence studies, as underlined by Walker et al (2013), who, among 66 relevant papers, identified only 15 studies meeting satisfactory criteria (i.e. random or consecutive sampling, ≥ 70% response rate, sample size ≥ 100) with again prevalence of depression ranging from 5% to 49%. Similar findings were reported in a further review of 31 studies involving 9248 cancer patients, in whom the prevalence of depression was 10.8%, with a range of 3.7% -49% (Ng, Boks, Zainal & de Wit, 2011).

Rates of adjustment disorders with depression or dysthymia vary widely, with prevalence ranging from 16% to 42% (Miller & Massie, 2010). Estimates of minor depression or dysthymia are 20% in all cancer patients (Mitchell et al., 2011). While imprecise, rates of all mood disorders are substantially higher among cancer patients than in the general population, with major depressive disorder (MDD) occurring up to three times more frequently in cancer patients (Li, Fitzgerald & Rodin, 2012). Although prevalence rates vary depending on the methodology employed, recent large and rigorously conducted studies in Europe estimate the point prevalence of MDD between 5% and 15% depending on the site of cancer (Walker et al., 2014; Sharpe et al., 2004). In comparison, a systematic review of community-representative studies suggests a global point prevalence of MDD of 4.7% (Ferrari et al., 2013). In the United States, results from the National Comorbidity Survey Replication, a nationally representative survey using an expanded version of the WHO'S Composite International Diagnostic Interview to assess mental disorders, estimated the 12-month prevalence of MDD as 6.6% in adults (Kessler et al., 2003).

Younger age is consistently associated with higher rates of psychological distress and psychiatric syndromes in adults with cancer (Park & Rosenstein, 2015; Kroenke et al., 2004; Mor, Allen &Malin, 1994). A recent Danish cancer registry study reported substantially higher rates of hospitalization for depression in patients diagnosed with cancer compared with the cancer-free population. Patients 15 years and older were at highest risk for depression severe enough to warrant hospitalization within the first year following a cancer diagnosisand remained at elevated risk in subsequent years (Dalton, Laursen, Ross, Mortensen& Johansen, 2009).

3.3 Medical consequences of depression

Substantial data have been published regarding the role of psychological factors or stress in cancer onset, progression or survival. Due to methodological limitations, publication bias, and confounding factors, the findings are contradictory and inconclusive (Massie & Miller, 2011). Studies that support an association between psychological factors and cancer outcomes generally are unable to demonstrate a clear causal relationship. The data are mixed, but evidence is available to suggest that depression may be associated with elevated cancer risk, and stronger evidence suggests that depression affects cancer progression (Spiegel & Giese-Davis, 2003). Depression may affect the course of the illness due to the impact on treatment adherence and desire for life-sustaining therapy.

Estimates of suicide risk vary, but compared with the general population, cancer patients have at least a slightly higher risk for suicide (Hem, Loge, Haldorsen & Ekeberg, 2004). Male patients with cancer of the respiratory tract or prostate cancer have been shown to have a fourfold increased risk (Llorente et al., 2005; Hem, Loge, Haldorsen & Ekeberg, 2004). Risk factors include uncontrolled pain, advanced disease, fatigue, male gender, delirium and hopelessness. Hopelessness is a stronger predictor of suicide than depression in patients with advanced terminal cancer (Chochinov, Wilson, Enns & Lander, 1998).

3.4 Pharmacological treatment for depression

Few studies have been reported on randomized placebo-controlled trials of antidepressants in patients with cancer. Selection of an antidepressant often depends on the side-effect profile and drug-drug interactions (Philbrick, Rundell, Netzel & Levenson, 2012). Over the last several decades, mainly as a result of the availability of new classes of antidepressants (ADs) with a better tolerability and a reduced number and severity of adverse effects as compared to tricyclic ADs (TCAs) and monoamine oxidase inhibitors (MAOIs), the use of ADs in the medically ill, including cancer patients, has taken several steps forward. These agents are mainly represented by selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NARIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs) and noradrenergic and specific serotonergic antidepressants (NaSSAs). New classes of ADs, such as agomelatine, which exerts an action through melatonin receptors, are also available but their use in cancer patients deserve more research (Carusso, Grassi, Nanni & Riba, 2013).The selective serotonin reuptake inhibitors (SSRIs) are generally the first-line ADs for the treatment of depression in cancer patients, due to their tolerability.

SSRIs comprise a vast class of drugs with a similar effect profile (e.g. gastrointestinal disturbance, headache, fatigue or insomnia, sexual dysfunction and transient increased anxiety after initiation of treatment), but there are important differences between each SSRI that may impact on treatment selection (Grassi,Nanni, Rodin, Li & Caruso, 2018). SSRIs can cause initial suppression of appetite, but this effect usually subsides within a few weeks. Serotonin-mediated nausea can occur, especially at the onset of treatment, but can be reduced with ondansetron (Carusso, Grassi, Nanni & Riba, 2013).

Inhibitors of cytochrome P450 (CYP450), such as fluoxetine, paroxetine, bupropion, and duloxetine, may prevent conversion of tamoxifen, which is a prodrug, into its active metabolite, thereby reducing its effectiveness, and therefore these drugs should be avoided in patients taking tamoxifen (Henry, Stearns, Flockhart, Hayes &Riba, 2008). Fluoxetine has the longest half-life, which can be advantageous for patients who have periods of inability to take anything by mouth. Although, fluoxetine should be used with caution in cancer patients receiving chemotherapy, to avoid the risk of drug interaction with anticancer agents that are metabolized through the CYP450 system. Similarly,paroxetine has prominent P450 inhibitory effects and antiholinergic effects that should be carefully monitored (Grassi, Nanni, Rodin, Li & Caruso, 2018).

Citalopram, sertraline, fluoxetine, and mirtazapine (a mixed-action antidepressant) have been found effective for depression included by interferon-αin patients with cancer or hepatitis C (Miller & Massie, 2006). Sertraline, citalopram and escitalopram have the fewest drug-drug interactions and are the best first-line treatment option. These drugs tend to be well tolerated, although caution is necessary because of the potential for QTc prolongation at higher doses and for bleeding in patients taking aspirin, nonsteroidal anti-inflammatory drugs, warfarin or heparin, because of the antiplatelet effects of SSRIs (Grassi, Nanni, Rodin, Li & Caruso, 2018).

Also, novel and mixed action antidepressants could be used. Patients with insomnia, anorexia-cachexia or nausea may benefit from mirtazapine because of its sedative properties, appetite stimulation, and antiemetic effect. Venlafaxine and duloxetine have been demonstrated to improve neuropathic pain. Buproprion can be stimulating and decrease fatigue, but I usually should be avoided in patients who are at risk of seizures (Miller & Massie, 2006). The side-effect profile of the tricyclic antidepressants (TCAs) limits their use in patients with cancer, and therefore TCAs should be considered primarily for patients who have comorbid neuropathic pain (Philbrick, Rundell, Netzel& Levenson, 2012).

Psychostimulants such as methylphenidate have been proposed for the treatment of depressed patients because of their rapid onset of action (Kaminski &Sjøgren, 2007; Rozans, Dreisbach, Lertora& Kahn, 2002; Masand&Tesar, 1995). They may have antidepressant effects and may be advantageous due to the rapid onset of action (Candy, Jones, Williams, Tookman& King, 2008; Thomas & Lipsky, 2000). Some studies suggest that they provide a safe and effective treatment of depression in cancer patients (Masand&Tesar, 1995) and alleviate opioid induced somnolence, improve cognitive function and ameliorate pain in cancer patients (Challman& Lipsky, 2000). Another potential advantage of the use of psychostimulant in cancer patients is the ability to improve multiple somatic symptoms irrespective of the etiology (Vigano, Watanable&Bruera, 1995). The rapid onset of action of the psychostimulants (methylphenidate and dextroamphetamine) and modafinil can be a significant advantage over antidepressants in some circumstances, especially for patients very short life expectancies. In patients treated with psychostimulants may counteract sedation and potentiate the analgesic effects. Side effects include insomnia, anxiety and agitation, tachycardia, and rarely psychosis (Philbrick, Rundell, Netzel& Levenson, 2012).

3.5 Factors to be considered regarding psychopharmacology in cancer patients

Some of the main factors to be considered when prescribing ADs in cancer patients are the following (Grassi, Nanni, Rodin, Li & Caruso, 2018): 1. past psychiatric history (e.g. assess for past positive treatment responses to an antidepressant), 2. concurrent medications (e.g. assess for potential drug-drug interactions), 3. Somatic symptoms profile (e.g. a sedating antidepressant may be preferable for those with prominent insomnia; cachectic patients may benefit for antidepressants that stimulate weight gain), 4. potential for dual benefit (e.g. duloxetine for neuropathic pain, venlafaxine for hot flashes), 5. type of cancer (e.g. avoid bupropion in those with central nervous system cancers due to elevated seizure risk), 6. comorbidities (e.g. avoid psychostimulants or tricyclic antidepressants in those with symptomatic cardiac disease), 7. cancer prognosis (e.g. in setting of terminal disease, the rapid onset of action of psychostimulants/ketamine may be preferable).

3.6 Psychosocial interventions

Various psychotherapeutic interventions are used for cancer patients, including psychoeducational, supportive, cognitive-behavioral, existential, psychodynamic, life narrative, dignity-conserving, and meaning-centered therapies. Psychotherapy may be done individually, in a group setting, or with the patient's caregiver (Miller & Massie, 2006). The evidence for efficacy of different psychosocial interventions has varied widely.

The goals of treatment are to reduce emotional distress, provide education, provide social support, improve coping, and facilitate resolution of problems (Philbrick, Rundell, Netzel & Levenson, 2012).

4. Conclusions

Depression is frequent but treatable problem that can complicate the lives of cancer patients and their families. Frequent assessment and early intervention can improve quality of life, adherence to treatment and overall outcome. In oncology there is a marked need for the integration of pharmacological and psychosocial intervention. It is mandatory that health care professionals working in oncology receive training in the diagnosis and management of depression.

References

American Psychiatric Association (2000). Diagnostic and Statistical Manual of MentalDisorders, 4th ed (DSM-5). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of MentalDisorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association.

Brocken, P.,Prins, J.B., Dekhuijzen P.N. &van der Heijden H.F. (2012).The faster the better? A systematic review on distress in the diagnostic phase of suspected cancer, and the influence of rapid diagnostic pathways.*Psychooncology*, 21, 1-10.

Candy, M., Jones, L., Williams, R., Tookman, A. & King, M. (2008). Psychostimulants for depression. *Cochrane Database of Systematic Reviews*, 16, CD006722.

Caruso, R., Grassi, L., Nanni, M.G. &Riba, M. (2013). Psychopharmacologyin Psycho-oncology. Current Psychiatry Reports, 15: 393. doi: 10.1007/s11920-013-0393-0

Caruso, R.,Nanni, M.G., Riba, M., Sabato, S., Mitchell, A.J., Groce, E. & Grassi, L. (2017a). Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review.*Acta Oncologica*, 56, 146-155.

Caruso, R., Nanni, M.G., Riba, M., Sabato, S. & Grassi, L. (2017b). Depressive spectrum disorders in cancer: diagnostic issues and intervention: a critical review. *Current Psychiatry Reports*, 19(6), 33. doi: 10.1007/s11920-017-0785-7): 33.

Challman, T.D. & Lipsky, J.J. (2000). Methylphenidate: its pharmacology and users. *Mayo Clinic Proceedings*, 75, 711-721.

Chochinov, H.M., Wilson, K.G., Enns, M. & Lander, S. (1998). Depression, hopelessness, andsuicidal ideation in the terminally ill. Psychosomatics, 39, 366-370.

Cordova, M.J., Riba, M.B. &Spiegel, D. (2017).Post-traumatic stress disorder and cancer.*Lancet Psychiatry,* 4, 330-338.

Dalton, S.O., Laursen T.M., Ross, L., Mortensen, P.B. & Johansen, C. (2009). Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-basedstudy of cancer patients in Denmark from 1973 to 2003. *Journal of Clinical Oncol*ogy, 27(9), 1440–1445.

Dauchy, S., Dolbeault, S. & Reich, M. (2013). Depression in cancer patients. *European Journal of Cancer Supplement*, 11, 205-215.

Ferrari, A.J., Somerville, A.J., Baxter, A.J., Nornan, R., Patten, S.B., Vos, T. & Whiteford, H.A.(2013). Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological Medicine,*43(3), 471–481.

Grassi, L., Nanni, M.G., Rodin, G., Li, M. &Carusso, R. (2018). The use of antidipressants in oncology: a review and practical tips for oncologists. *Annals of Oncology*, 29, 101-111.

Hem, E., Loge, J.H., Haldorsen, T. &Ekeberg, Ø. (2004). Suicide risk in cancer patients from1960 to 1999. *Journal of Clinical Oncology*, 22, 4209-4216.

Henry, N.L., Stearns, V., Flockhart, D.A., Hayes, D.F. &Riba, M. (2008). Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. *American Journal of Psychiatry*, 165, 1251-1255.

Kaminski, M. &Sjøgren, P. (2007). The use of psychostimulants in palliative and supportivetreatment of cancer patients. *Advances in Palliative Medicine*, 6, 23-31.

Kessler, R.C., Berglund, P., Demler, O., Jia, R., Koret, Z., Merikangas, K.R., … & Wang, P.S.(2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA,* 289(23), 3095–3105.

Krebber, A.M.,Buffart, L.M., Kleijn, G., Riepma, I.C., de Bree, R., Leemans, O.R., . . . & Leeuw, I.M. (2014). Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments.*Psychooncology,* 23, 121-130.

Kroenke, C.H., Rosner, B., Chen, W.Y., Kawachi, I., Colditz,. GA. & Holmes M.D. (2004). Functional impact of breast cancer by age at diagnosis. *Journal of Clinical Oncology,* 22(10), 1849–1856.

Lépine, J.P. & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, 7, 3-7.

Li, M., Fitzgerald, P. & Rodin, G. (2012). Evidence-based treatment of depression in patients with cancer. *Journal of Clinical Oncology,* 30(11), 1187–1196.

Llorente, M.D., Burke, M., Gregory, G.R., Bosworth, H.B., Grambow, S.C., Horner, R.D., …Olsa, E.J. (2005). Prostate cancer: a significant risk factor for late-life suicide. *American Journal of Geriatric Psychiatry*, 13, 195-201.

Mangoulia, P. &Baizanis N. (2014). The shame and stigma of head and neck patients and the relation with their general health and life satisfaction. Thesis. National and Kapodistrian University of Athens, Faculty of Medicine.

Masand, P.S. &Tesar, G.E. (1995). Use of stimulants in the medically ill. Psychiatry, 52, 456-463.

Massie, M.J. & Miller, K. (2011). Oncology. In: J.L.Levenson (Ed.), *The American Psychiatric Association textbook ofpsychosomatic medicine*: *psychiatric care of the medically ill*(2ⁿᵈed), pp. 525-550.Washington, DC: American Psychiatric Publising.

Mauricio, M., O'Hara, R., Yesavage, J.A., Friednan, L., Kraemer, H.C. van de Water, M. &Murphy, G.M. (2000). A longitudinal study of apolipoprotein – E genotype and depressive symptoms in community-dwelling older adults. *American Journal of Geriatric Psychiatry*, 8, 196-200.

McDaniel, J.S., Musselman, D.L., Porter, M.R., Reed, D.A. &Nemeroff, C.B. (1995).Depression in patients with cancer: diagnosis, biology and treatment. *Archives of General Psychiatry*, 52, 89-99.

Miller, K. &Massie, M.J. (2006). Depression and anxiety. *Cancer Journal*, 12, 388-397.

Miller, K. & Massie, M. J. (2010). Depressive disorders. In: J.C. Holland, W.S. Breitbart, P.B. Jacobsen, M.S. Lederberg, M.J. Loscalzo& R. McCorkle (Eds.), *Psychooncology(pp.*311–318). New York, NY: Oxford University Press.

Mitchell, A.J., Chan M., Bhatti H., Halton, M.,Grassi, L.,Johansen, C. &Meader, N. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, hematological and palliative-care settings: a meta-analysis of 94 interview-based studies.*Lancet Oncology*, 12, 160-174.

Mor, V., Allen, S. &Malin, M. (1994). The psychosocial impact of cancer on older versusyounger patients and their families. *Cancer,* 74(7 suppl), 2118–2127.

Moussavi, S., Chatterji, S., Verdes, E., Jandon, A., Patel, V. &Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*, 8 (370), 851-858.

Ng, C.G., Boks, M.P.M., Zainal, N. Z., de Wit, N.J. (2011). The prevalence and pharmacotherapy of depression in cancer patients. *Journal of Affective Disorders*, 13,1-7.

O'Hara, R., Thompson, J.M., Kraemer, H.C., Fenn, C., Taylor, J.L., Ross, L., . . .&Tinkleberg,J.R. (2002). Which Alzheimer patients are at risk for rapid cognitive decline? *Journal of Geriatric Psychiatry & Neurology*, 15, 233-238.

Park, E.M. & Rosenstein, D. L. (2015). Depression in adolescents and young adults with cancer. *Dialogues in Clinical Neuroscience*, 17, 171-180.

Philbrick, K.L., Rundell, J.R., Netzel, P.J. & Levenson, J.L. (2012). Clinical manual of psychosomatic medicine: a guide to consultation-liaison psychiatry. (2ⁿᵈ ed.). Washington, DC: American Psychiatric Publishing, (Chapter 25).

Reich, M. (2008). Depression and cancer: recent data on clinical issues, research challenges andtreatment approaches. *Current Opinion in Oncology*, 20, 353-359.

Rozans, M. Dreisbach, A., Lertora, J.J.& Kahn, M.J. (2002). Palliative uses of methylphenidate in patients with cancer: a review. *Journal of Clinical Oncology*, 20, 335-339.

Sharpe, M., Strong, V., Allen, K., Rush, R., Postma, K., Tulloh, A.,…& Cull, A. (2004). Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs. *British Journal of Cancer,* 90(2), 314–320.

Singer, S., Das-Munshi, J. &Brähler, E. (2010).Prevalence of mental health conditions in cancer patients in acute care: a meta-analysis.*Annals of Oncology* 21: 925-930.

Smith, H. (2015). Depression in cancer patients: pathogenesis, implications and treatment. *Oncology Letters*, 9, 1509-1514.

Spiegel, D. & Giese-Davis, J. (2003). Depression and cancer: mechanisms and disease progression. *Biological Psychiatry*, 54, 269-282.

Spiegel, D. &Riba, M.B. (2015). Managing anxiety and depression during treatment. *The Breast Journal*, 21, 97-103. doi: 10.1111/tbj.12355.

Thomas, C. & Lipsky, J.L. (2000). Methylphenidate: its pharmacology and uses. *Mayo Clinic Proceedings*, 75, 711-721.

Von Ammon Cavanaugh, S., Furlanetto, L.M., Greech, S.D., & Powel, L.H. (2001). Medicalillness, past depression and present depression: a predictive triad for in-hospital mortality. *American Journal of Psychiatry*, 158, 43-48.

Walker, J., Holm Hansen, C., Martin, P., Sawhney, A., Thekkumpurath, P., Beale, C.,…& Sharpe, M. (2013). Prevalence of depression in adults with cancer: a systematic review. *Annals of Oncology*, 24(4), 895-900.

Walker, J., Hansen, C.H., Martin P., Symeonides, S., Ranessur, R., Murray, P.G. & Sharpe, P.M. (2014). Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. *Lancet Psychiatry,* 1(5), 343–350.

World Health Organization (2011). Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. EB130/9, WHO, Geneva.