

2018

Effects of palliative care intervention on depression and anxiety levels in cancer patients

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EFFECTS OF PALLIATIVE CARE INTERVENTION ON DEPRESSION
AND ANXIETY LEVELS IN CANCER PATIENTS**

by

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B.A., Boston University, 2014

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2018

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JOSHUA LYONS

ABSTRACT

Palliative care is branch of medicine, which focuses on improving the quality of life (QOL) of patients with chronic illness such as cancer. Patients suffering from cancer are subjected to physical as well as psychological distress associated with their diagnosis and treatment. The purpose of this study was to introduce palliative care and examine its impact on levels of anxiety and depression in cancer patients. Information regarding the current relevance and growth of the palliative profession, as well as expanding areas of research, was included as part of this study. The literature reviewed in this study found that cancer patients are at high risk for psychological comorbidities such as anxiety and depression. Patients with certain cancer types, social factors, and cognitive makeups may be at the greatest risk for psychiatric problems. The data show a strong connection between high emotional distress levels, low QOL, reduced survival time, and adherence to curative treatment plans. Fortunately, there was significant research showing that palliative intervention can improve psychological distress and avoid unwanted effects on QOL and survival. The results of current studies found promising improvements for patients with cancer; however, there remains a need for replication and development of a universal model of care to validate conclusions.

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LIST OF ABBREVIATIONS

3-HAO.....	3-hydroxyanthranilic acid oxygenase
5-HT.....	Serotonin
5-HTT.....	Serotonin transporter
AMPA.....	2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor
BH4.....	Tetrahydrobiopterin
BDNF.....	Brain-derived neurotrophic factor
CAPC.....	Center to Advance Palliative Care
CES-D.....	Center for Epidemiological Studies-Depression
CNS.....	Central Nervous System
COX-2.....	Cyclooxygenase-2
DAT.....	Dopamine transporter
DSM-III.....	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IV.....	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EAAT.....	Excitatory amino acid transporter
ENABLE.....	Educate, Nurture, Advise, Before Life Ends
EOL.....	End-of-life
FACIT-Pal.....	Functional Assessment of Chronic Illness Therapy-Palliative
FACT-L.....	Functional Assessment of Cancer Therapy-Lung
Glu.....	Glutamate
HADS.....	Hospital Anxiety and Depression Scale

HADS-A.....	Hospital Anxiety and Depression Scale for Anxiety
HADS-D.....	Hospital Anxiety and Depression Scale for Depression
HPA.....	Hypothalamic-pituitary-adrenal
IDO.....	Indoleamine 2,3 dioxygenase
IFN.....	Interferon
IL.....	Interleukin
iNOS.....	Inducible nitric oxide synthase
IOM.....	Institute of Medicine
JAMA.....	Journal of the American Medical Association
KAT II.....	Kynurenine aminotransferase II
KMO.....	Kynurenine 3-monooxygenase
LOS.....	Length-of-stay
MAPK.....	Mitogen-activated protein kinases
MBT.....	Mindful-based therapy
MCP-1.....	Monocyte chemotactic protein-1
MDD.....	Major Depressive Disorder
NEJM.....	New England Journal of Medicine
NMDAR.....	N-Methyl-D-aspartic acid receptor
NF-kB.....	Nuclear factor-kappa B
NSCLC.....	Non-small cell lung cancer
NYU.....	New York University
PGE2.....	Prostaglandin E2

PHQ-9.....	Patient Health Questionnaire 9
QOL.....	Quality of life
QUIN.....	Quinolinic acid
RNS.....	Reactive nitrogen species
ROS.....	Reactive oxygen species
SPIKES.....	Setting, Perception, Invitation, Knowledge, Empathy, & Summary/strategy
Sp WB.....	Spiritual well-being
SSRIs.....	Serotonin reuptake inhibitors
STAT.....	Signal transducer and activator of transcription
TH.....	Tyrosine hydroxylase
TNF.....	Tumor necrosis factor
TrkB.....	Tyrosine kinase receptor B
VMAT2.....	Vesicular monoamine transporter 2
U.S.....	United States
UCLA.....	University of California, Los Angeles
WHO.....	World Health Organization

INTRODUCTION

We've been wrong about what our job is in medicine. We think our job is to ensure health and survival. But really it is larger than that. It is to enable well-being. And well-being is about the reason one wishes to be alive. (Gawande, 2014, p. 25)

The quotation by Dr. Atul Gawande (2014) emphasizes the importance of patient-centered care and the physician's responsibility to balance continued treatment with quality of life (QOL). Palliative care is a branch of medicine specifically devoted to improving QOL for those suffering from chronic or terminal illness.

This study introduces and highlights the significance of palliative medicine to aid cancer treatment and QOL of cancer patients. The topics of discussion include background information on cancer, anxiety, and depression, an in-depth definition of palliative care and its relevance to current healthcare issues, economic consequences of palliative care intervention, and novel therapies. For this study, the effect of palliative care on patient psychological symptoms is examined more so than physical symptoms such as pain, nausea, and fatigue. However, the connection and association between physical and psychological symptoms are examined and discussed. The overall goals of this study are to evaluate the prevalence of depression and anxiety in terminal cancer patients and to determine if there is a significant increase in QOL from palliative care intervention.

General Cancer Information

The health system in the United States is facing what some experts call a “silver tsunami” as the baby boomer generation approaches old age and places greater strain on healthcare resources (Bluethmann, Mariotto, & Rowland, 2016). While the U.S. population ages, there will inevitably be an increased incidence of patients suffering from chronic illness and related comorbidities. Over 40% of people living in the United States will be diagnosed with some form of cancer at some point in their lives (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). In 2016 there were about 15.5 million patients with cancer living in the United States, the majority being senior citizens (Bluethmann et al., 2016). Within the next 20 years, the estimated number of cancer survivors will grow to over 26 million (Bluethmann et al., 2016). Figure 1 shows the projected prevalence and growth of cancer diagnoses in the United States by the year 2040.

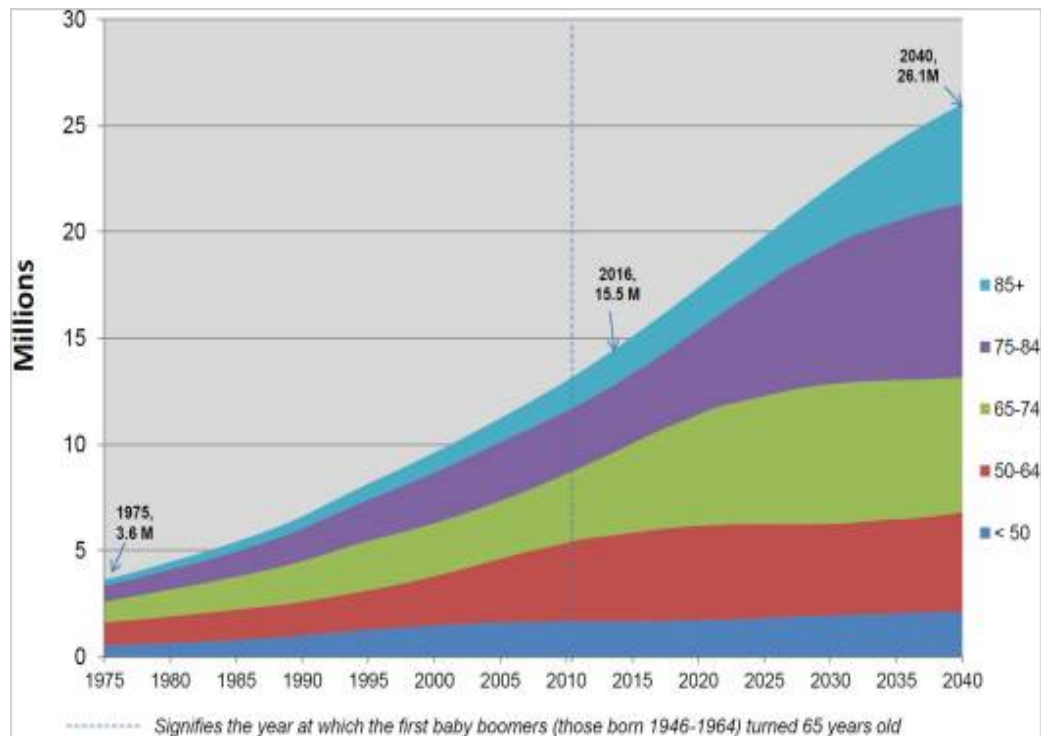


Figure 1. Projected cancer prevalence according to age in the United States. The image depicts a steady rise in the incidence of cancer among United States citizens. This trend is largely due to the aging baby boomer generation and increases in the percentage of the population over 65 years old. Taken from (Bluethmann et al., 2016).

Despite drastic improvements in medical technology and care, incidence and death from cancer continue to rise. According to the World Health Organization (WHO), cancer is the second leading cause of death globally, accounting for 1 in every 6 deaths. In 2015, 8.8 million people worldwide died from various types of cancer. The economic cost is also significant, with the total cost of cancer reaching 1.16 trillion dollars in 2010 (“WHO | Cancer.” *WHO*, February 2017. [http://www.who.int/mediacentre/factsheets/fs297/en/.](http://www.who.int/mediacentre/factsheets/fs297/en/)) As Figure 2 shows, much of this cost comes at the end of life from hospital admissions or trips to the emergency room (Lustbader et al., 2016).

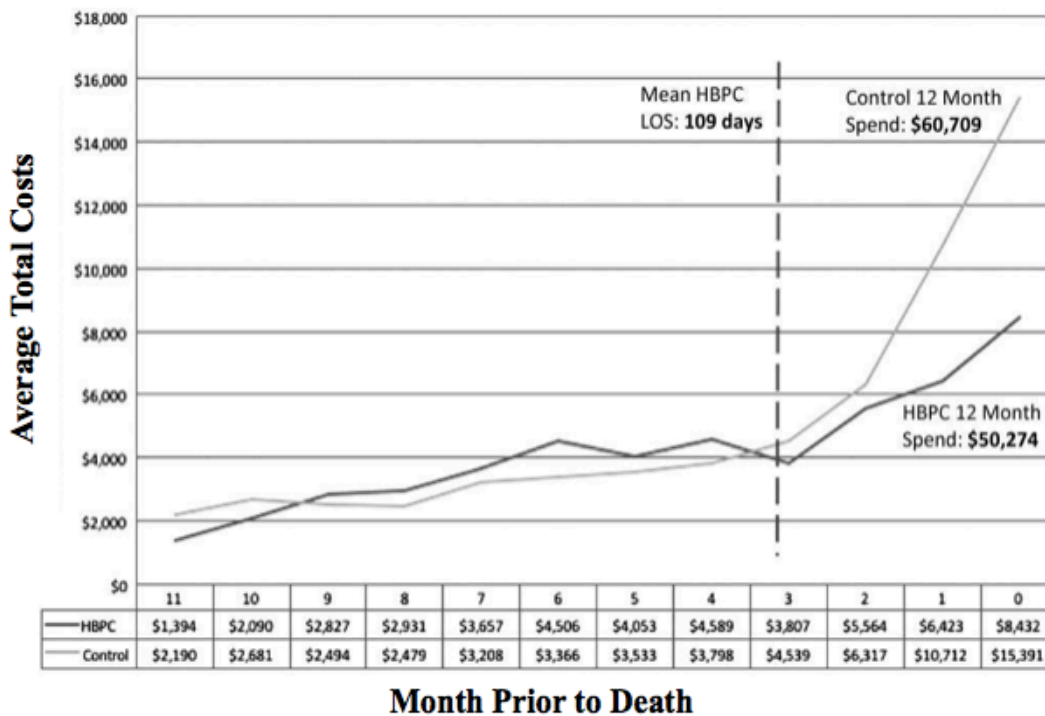


Figure 2. Average cost by months before death in home-based palliative care (HBPC) versus usual care (control). The graph shows over the last year of a patient's life, HBPC is associated with reduced cost in comparison to usual care. HBPC increased hospice length of stay (LOS) and reduced cost of Medicare by over \$10,000 during the last 3 months before death. Taken from (Lustbader et al., 2016)

Not only does this raise the economic burden of cancer, but also the cost can intensify the stress on terminal patients and their families. Although the role of palliative care is to lessen the physical and emotional burden for patients and families, a secondary benefit is to lower the total economic cost of cancer. For these reasons, end-of-life care is of great need to support the millions of people dying each year of cancer.

Palliative Care Definition

Palliative care is best summarized as treatment directed at improving the quality of life (QOL) for patients with chronic and terminal illness. Although hospice is a branch of palliative care, the patient does not need to be dying in the imminent future to receive palliative care. The key distinction between palliative care and hospice is that palliative care can be administered in combination with other curative treatments (Kelley & Morrison, 2015). Insurance companies and government programs like Medicare define both hospice and eligible patients. Currently, in order to receive hospice care, patients must forfeit curative treatment and have a diagnosis of 6 months or less to live (Kelley & Morrison, 2015). According to WHO, a more in-depth description of palliative care includes the following:

- *Provides relief from pain and other distressing symptoms.*
- *Affirms life and regards dying as a normal process.*
- *Intends to neither hasten nor postpone death.*
- *Integrates the psychological and spiritual aspects of patient care.*
- *Offers a support system to help patients live as actively as possible until death.*
- *Offers a support system to help the family cope during the patient's illness and in their own bereavement.*
- *Uses a team approach to address the needs of patients and their families, including bereavement counseling if indicated.*
- *Enhances quality of life, and may also positively influence the course of illness.*
- *Applies early in the course of illness in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.*

(“WHO | Palliative Care.” *WHO*, July 2015.
[http://www.who.int/mediacentre/factsheets/fs402/en/.](http://www.who.int/mediacentre/factsheets/fs402/en/))

Palliative care is a team-based interdisciplinary approach to care, with a focus on the common goal of enhancing QOL to patients (Kelley & Morrison, 2015). There are

several factors in the preceding list, ranging from spiritual crises to pain management, that are addressed in the palliative setting. As a result, palliative care teams utilize a range of medical staff including doctors, nurses, chaplains, social workers, psychologists, and more (Kelley & Meier, 2010). The significance of interdisciplinary care, as opposed to multidisciplinary or other models of care, is that several specialists are utilized to work toward a common goal instead of many entities working toward individual goals. The result is a team that is focused on the single objective to improve QOL and to minimize the suffering of patients and their families.

Palliative Care Growth

Palliative care is a fast-growing field, which has shown a steady increase in availability at U.S. hospitals over the past 20 years. More hospitals are developing palliative care programs as the demands of patients and families increase with better education on the benefits of palliative service (Dumanovsky et al., 2016). Figure 3 shows that as of 2014, palliative care programs were nearly universal at large hospitals with over 300 hundred

beds (Dumanovsky et al., 2016).

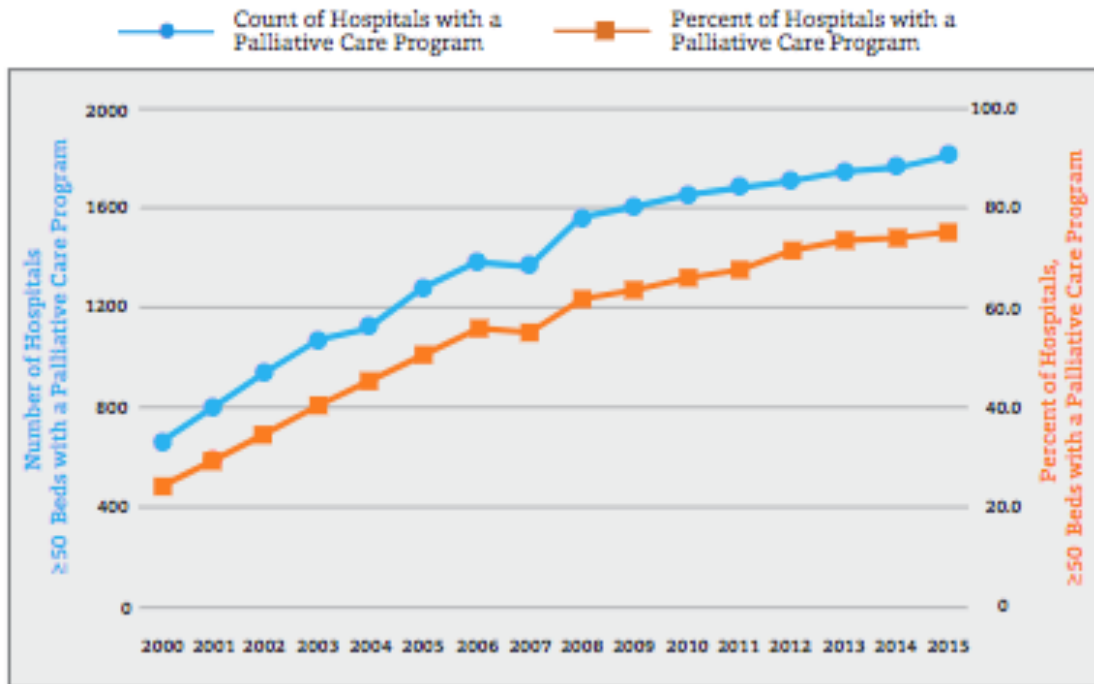


Figure 3. Growth of palliative care in U.S. hospitals from 2000 to 2015. The graph shows a steady increase in the number and percentage of hospitals with palliative care programs. Taken from National Palliative Care (2017)

Unfortunately, although palliative care teams are becoming more frequent, there are regional differences in access to care. Patients outside of the Pacific Northwest and New England, particularly in the South, are faced with a deficiency in palliative programs aimed at addressing end-of-life needs (Dumanovsky et al., 2016). In addition, a study conducted in 2010 determined that the number of hospice and palliative specialists is insufficient (Lupu & American Academy of Hospice and Palliative Medicine Workforce Task Force, 2010). The researchers estimated that an additional 10,000 palliative care physicians are required to fulfill patient demand (Lupu & American Academy of Hospice and Palliative Medicine Workforce Task Force, 2010). Barriers to providing this

palliative care include the deficit in fellowship opportunities that would train physicians to fill current shortages (Lupu & American Academy of Hospice and Palliative Medicine Workforce Task Force, 2010).

Specific Aims

The specific aims of this study are:

1. To determine the effect of anxiety and depression on overall QOL in terminal cancer patients.
2. To identify the role and effect of palliative care on anxiety, depression, and QOL in cancer patients.
3. To examine studies on early palliative care intervention in the oncology setting, and to determine its impact on QOL and survival rate.
4. To discuss the economic advantage of adding palliative care to standard treatment of cancer.
5. To introduce novel and future therapies for anxiety and depression among terminal cancer patients.

BACKGROUND/SIGNIFICANCE

Studies on the Benefits of Palliative Care

In 2010 a landmark study was published in the New England Journal of Medicine (NEJM) highlighting the impact of palliative care in the oncology setting (Temel et al., 2010). The study examined early palliative care intervention in patients with metastatic non-small cell lung cancer (NSCLC), with half of the participants receiving standard curative oncologic care and the other half receiving the same care but with additional palliative care support. The data in Figure 4 show that 12 weeks after baseline assessment, participants in the early palliative care intervention group exhibited significantly higher mood and quality of life (QOL) assessment scores (Temel et al., 2010).

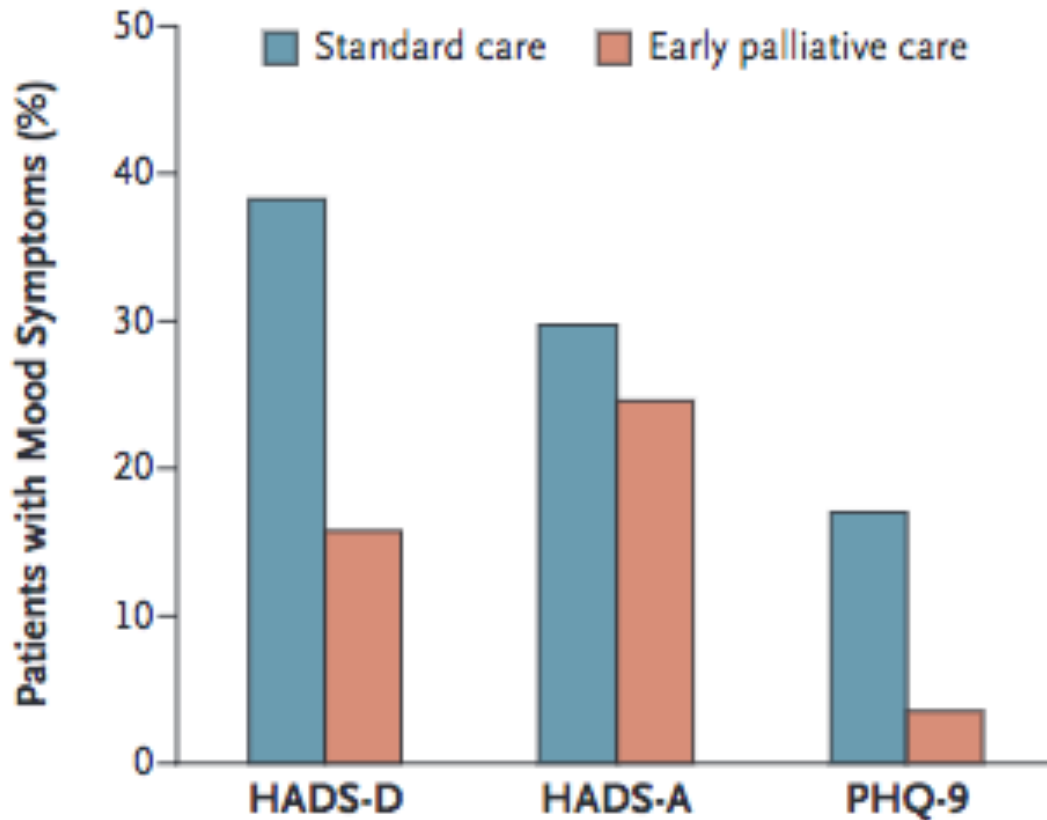


Figure 4. Outcomes of mood assessment for cancer patients in early palliative care after 12 weeks. Mood assessments were made using the Hospital Anxiety and Depression Scale for Anxiety (HADS-A) and for Depression (HADS-D), and the Patient Health Questionnaire 9 (PHQ-9). Higher scores correlate with greater symptoms of depression and anxiety. Palliative care group (N = 77); Standard care group (N = 74). Taken from (Temel et al., 2010).

Interestingly, the data also indicate that those receiving palliative care lived longer (Figure 5) and received less aggressive treatment during their final stage of life (Temel et al., 2010).

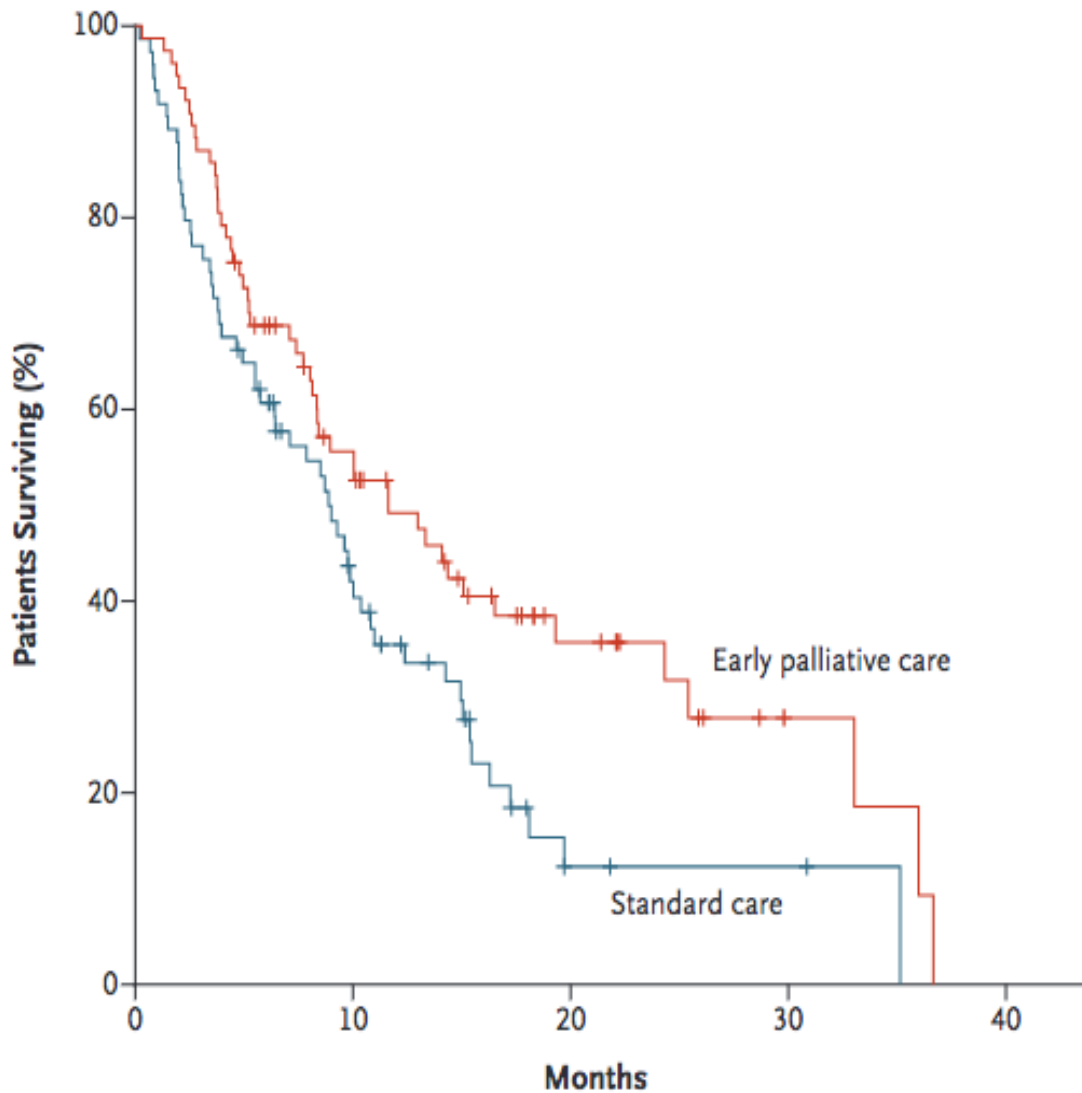


Figure 5. Kaplan-Meier survival estimates based on cancer patients in study. The median survival was 11.6 months for the palliative care group and 8.9 months for the standard care group. The Kaplan-Meier estimator is a statistical method used to predict the percentage of patients surviving for an amount of time following a diagnosis. Palliative care group (N = 77); Standard care group (N = 74). Taken from (Temel et al., 2010).

These findings demonstrate that palliative care when presented early in the treatment of NSCLC may benefit not only psychological health and QOL but also length of life compared with those patients receiving standard care without palliative support.

According to Temel and colleagues (2010), one potential reason for this observation was that previous research suggests that depression and low QOL are associated with shorter life expectancy in patients with cancer. Figure 6 shows the changes in QOL scores for both study groups.

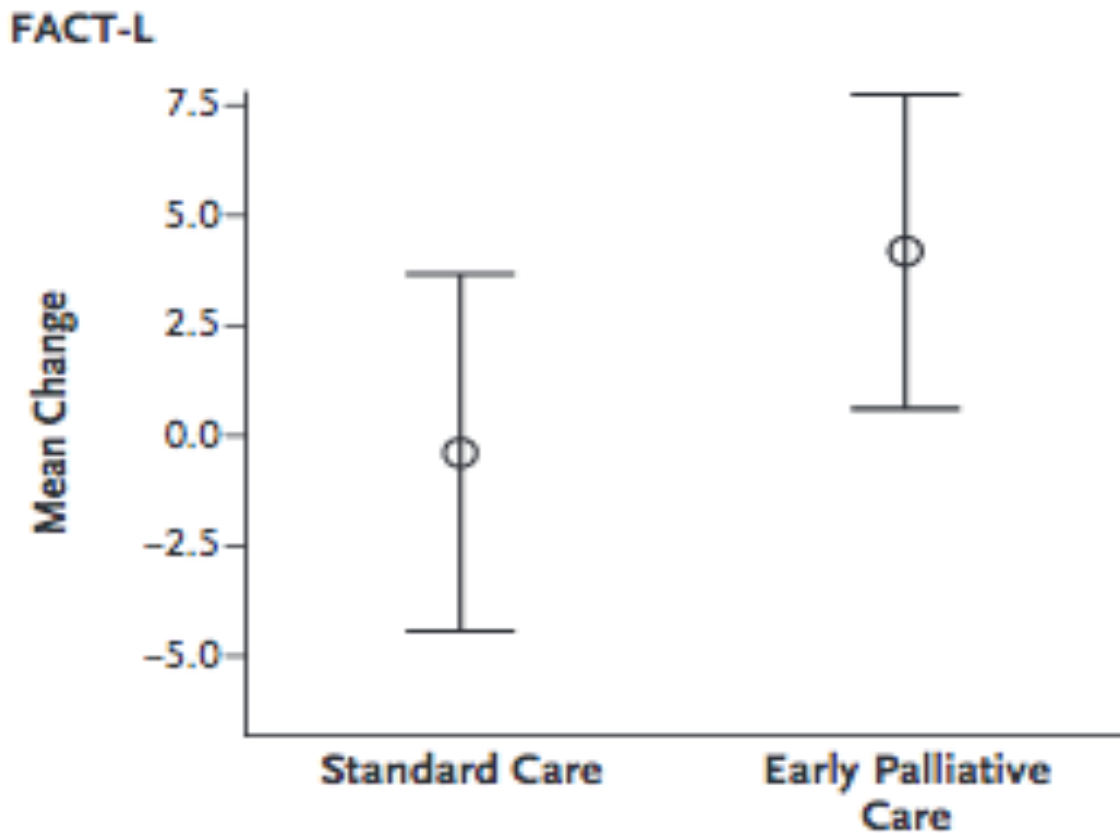


Figure 6. Changes in QOL scores for cancer patients in standard care versus palliative care. The mean change in QOL assessment scores from baseline to study completion at 12 weeks was calculated using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. Higher scores correlate with improved QOL. Error bars signify 95% confidence intervals. QOL = quality of life; Palliative care group (N = 77); Standard care group (N = 74). Taken from (Temel et al., 2010).

One similar study examining advanced NSCLC patients determined QOL to be a primary prognostic factor for overall survival time (Movsas et al., 2009). Specifically, patients

with QOL scores above the mean showed a 70% lower death rate than those patients scoring below the mean. In addition, with each 10-point increase in QOL score, there was a 10% reduction in risk of death (Movsas et al., 2009). Further examination of lung cancer patients determined that palliative intervention was successful in lowering anxiety and depression levels during curative treatment (Delibegovic & Sinanovic, 2013). Psychological and physical symptoms associated with cancer treatment can have a negative impact on QOL. However, adding palliative care to standard inpatient cancer treatment to lower psychological stress associated with a smaller decrease in overall QOL (El-Jawahri et al., 2016). End-of-life care is beneficial not only for the inpatient setting but also for outpatients. Dying at home as opposed to in the hospital can lower the psychological burden for patients. About 50% of individuals prefer to die at home, but only about a third of patients fulfill this desire (Wheatley & Baker, 2007). Outpatient palliative care can raise the likelihood of dying at home and reduce symptom affliction for those with cancer (Gomes, Calanzani, Curiale, McCrone, & Higginson, 2013).

The incidence of anxiety and depression is not limited to lung cancer but found in various other types of cancers. Breast cancer in women has been associated with a variety of psychological disorders, including depression and anxiety (Lueboonthavatchai, 2007). Having negative family relationships and lacking problem and conflict resolution skills, along with symptoms of pain and fatigue, are risk factors for anxiety and depression in breast cancer patients (Lueboonthavatchai, 2007). The roles of palliative care in aiding family dynamics, communication skills, and pain management could potentially protect against these predictors of mental health morbidities among cancer patients.

Researchers in the Czech Republic used the Hospital Anxiety and Depression Scale (HADS) to determine the levels of anxiety and depression in a group of 225 advanced cancer patients receiving palliative care (Bužgová, Jarošová, & Hajnová, 2015).

Depression was found in 47.6% of the participants, and anxiety was present in 33.9%, with both values exceeding that of the general public (Bužgová et al., 2015). After analysis and comparison with QOL measurements, it was shown that patients suffering from greater anxiety and depression also experienced a statistically significant reduction in quality of life (Bužgová et al., 2015). This could have resulted from a decline in emotional and physical functioning, which would include an increase in symptoms such as nausea and vomiting.

It is difficult to isolate anxiety and depression and their impact on QOL because psychological symptoms can lead to physical symptoms, and vice versa. However, a cross-sectional study done at The University of Manchester (Manchester, U.K.) found that anxiety and depression were associated with decline in social, cognitive, and physical functioning, independent of pain level and severity of illness (Smith, Gomm, & Dickens, 2003). As a result, it would be consistent with the goals of palliative care to address psychological comorbidities in the hope of improving the life of terminally ill patients.

Unfortunately, there is a deficiency in randomized controlled studies examining the impact of palliative care on QOL in patients with terminal illness. However, a randomized controlled trial of 322 patients with advanced cancer was initiated to determine the impact of adding nursing-led palliative care to typical care (Bakitas et al.,

2009). Experienced palliative care nurses implemented Project ENABLE (Educate, Nurture, Advise, Before Life Ends) early in the course of curative treatment for various cancer types (Bakitas et al., 2009). The intervention consisted of four preliminary education sessions which focused on problem solving, communication, social support, pain management, and advanced care planning (Bakitas et al., 2009). Advanced practice nurses were then responsible for monthly telephone follow-ups with patient and caregivers to address emotional, physical, social, and spiritual problems as they arose throughout the course of treatment (Bakitas et al., 2009). The aim of such intervention was to empower patients to communicate with caregivers and physicians about their goals of care, values, and desired treatments to ensure optimal care (Bakitas et al., 2009). Focus on end-of-life (EOL) communication and patient-centered care has shown to improve quality of life, avoid aggressive cancer treatment, and maximize use of hospice care (Wright et al., 2008). Upon analysis of the clinical trial results, it was determined that patients in the palliative intervention group had higher QOL and less depression; however, they had limited reduction in symptom intensity scores when compared with the usual care group (Bakitas et al., 2009). Figures 6 and 7 illustrate the improvement in QOL and depressive symptoms among the palliative intervention group.

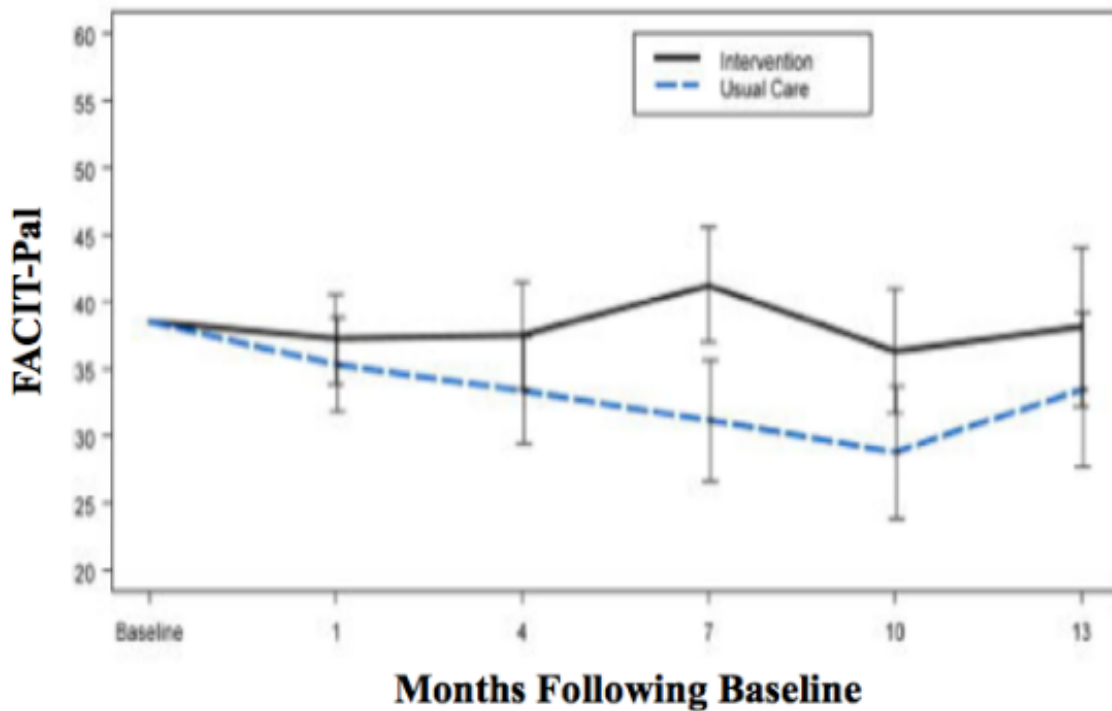


Figure 7. QOL assessment scores in usual care versus palliative intervention groups for cancer patients over 13 months. QOL assessments were measured using the Functional Assessment of Chronic Illness Therapy-Palliative (FACIT-Pal) scale. Higher scores represent better QOL. Error bars signify 95% confidence intervals. QOL = quality of life; N = 322. Taken from (Bakitas et al., 2009).

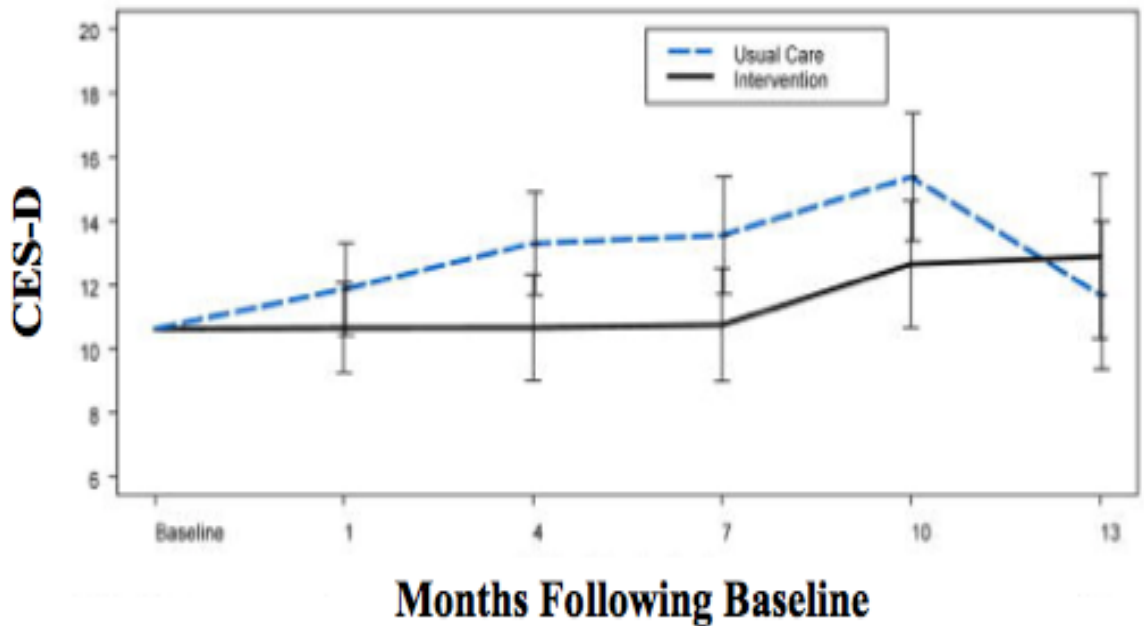


Figure 8. Depression assessment scores in usual care versus palliative intervention groups for cancer patients over 13 months. Assessments were measured using the Center for Epidemiological Studies-Depression (CES-D) scale. Higher scores represent worse depression. Error bars signify 95% confidence intervals. N = 322. Taken from (Bakitas et al., 2009).

Contrary to the study hypothesis, there was no significant difference in use of medical resources because both groups had similar times spent in the hospital as well as trips to the emergency room (Bakitas et al., 2009). The study notes several limitations, including a lack of diversity in the patient population and the presence of geographical constraints, which required a majority of interventions to be implemented by phone (Bakitas et al., 2009). It is possible that traditional in-person consultation could have provided greater relief to patients, and this aspect should be examined further as more controlled studies are needed to replicate results. Despite study limitations, the impact of palliative care on survival time was similar to recent research examining early palliative care intervention

in the oncology setting. Figure 9 shows the Kaplan-Meier survival graph for participants in the palliative care and usual care groups.

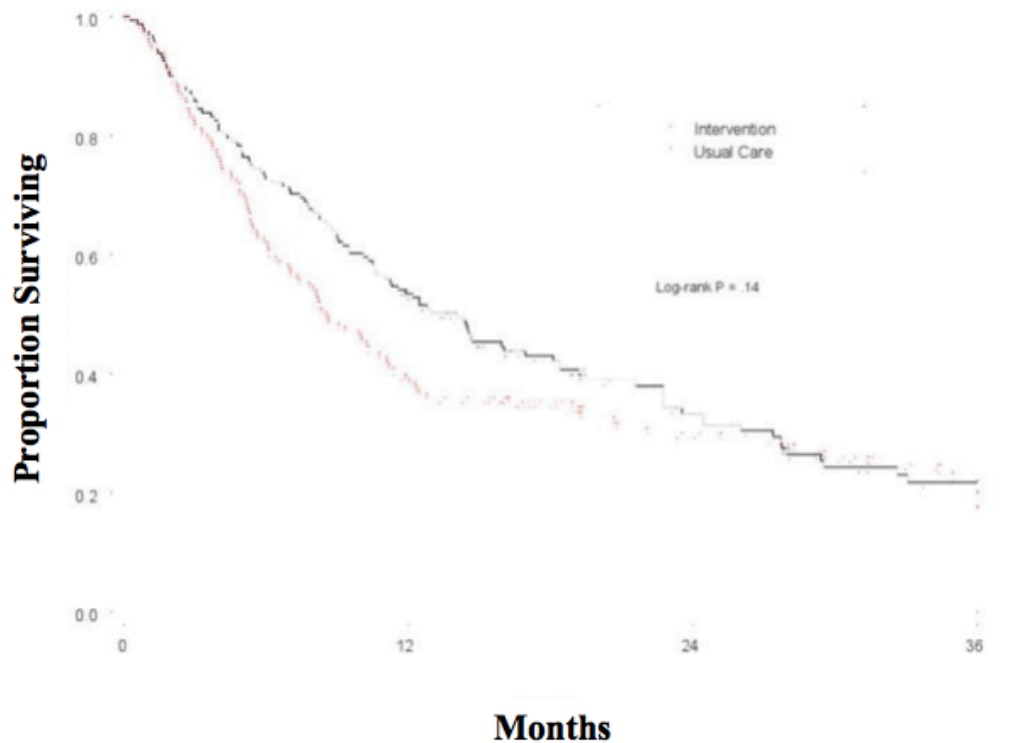


Figure 9. Kaplan-Meier estimates of survival in usual care versus palliative intervention groups for cancer patients over 36 months. The top line (black) shows palliative care correlating with median 14-month survival, while the bottom line (red) shows usual care patients surviving a median of 8.5 months. The Kaplan-Meier estimator is a statistical method used to predict the percentage of patients surviving for an amount of time following a diagnosis. N = 322. Taken from (Bakitas et al., 2009).

The results in Figure 9 show a modest increase in survival time for those receiving palliative care. More important, those with palliative intervention had improved QOL and less depressive symptoms. Although the results are encouraging, there is a need for replication across diverse populations to determine a direct connection between QOL, depressive symptoms, and survival time.

Support for Oncology and Palliative Care Providers

Oncology and palliative care providers require psychological support to manage the stress of frequently losing patients to terminal illness. The stress of working in such close proximity to death can manifest as suicide, substance abuse, depression, anxiety, fatigue, and decreased mental health and overall QOL (Shanafelt & Dyrbye, 2012). Burnout syndrome is a common consequence of physicians experiencing overwhelming distress from their work, especially when they are not receiving support to manage these issues (Shanafelt & Dyrbye, 2012). Other common causes include lack of autonomy, increasing productivity targets, malpractice suits, delivering bad news, and administrative tasks, which lead to poor work-life balance (Shanafelt & Dyrbye, 2012). Burnout syndrome is a form of emotional exhaustion where work loses its meaning and sense of purpose. The result has negative consequences for patient care, including declining professionalism, more medical errors, and lower patient satisfaction with care (Shanafelt & Dyrbye, 2012).

In 2015 a survey of 1357 palliative care providers found that 62% experienced burnout (Kamal et al., 2016). Physicians working in various oncology-related specialties showed a burnout prevalence of roughly 28%-38%, somewhat lower than other specialties in internal medicine, which approach near 50% (Shanafelt & Dyrbye, 2012). Despite the fact that oncology physicians were less likely to experience burnout and more likely to re-choose their career path, they still had an increased risk of experiencing symptoms of depression when compared with other internal medicine physicians (Shanafelt & Dyrbye, 2012). Various studies on palliative care teams have shown significant association between burnout and compassion fatigue (Levy et al., 2009).

In order for palliative care and oncology physicians to provide the best quality of care to their patients, there needs to be a focus on physician mental health. Although mental health affects the lives of patients and families, it should be kept in mind that physicians need similar psychological support to prevent burnout and ensure optimal patient care.

Spirituality and Mental Health

Medicine and religion do not always overlap, and at times they conflict with one another causing ethical dilemmas to patient care. However, religion and spirituality take on greater significance and relevance during end-of-life care. Studies have exhibited spirituality to be a protector against psychological distress among terminal patients.

Despite some limitations, a cross-sectional study examined the specific impact of spirituality on psychological and physical symptoms of terminal patients receiving palliative care (Kandasamy, Chaturvedi, & Desai, 2011). Data indicated that spiritual well-being (Sp WB) was not only a predictor of improved physical symptoms but also a factor of negative correlation with symptoms of anxiety and depression (Kandasamy, Chaturvedi, & Desai, 2011). A survey-based study examined the correlation between unmet spiritual concerns and quality of life for cancer patients receiving palliative radiotherapy (Winkelman et al., 2011). The results indicated that patients with unmet spiritual crises had reduced quality of life (Winkelman et al., 2011). Another study interviewing 343 patients with cancer showed that addressing spiritual crises can improve QOL, avoid unnecessary treatments, and increase utilization of hospice care (Balboni et al., 2010). Patients indicated spiritual needs were important aspects to their care and

desired for spirituality to be addressed by their physicians (Winkelman et al., 2011).

However, only a minority of physicians believed that it is their responsibility to address spiritual concerns; therefore, it is important to utilize hospital or community chaplaincy services to meet the spiritual requirements of patients at EOL (Kelley & Morrison, 2015).

Coping Strategy

Depression can be associated with a feeling of despair and hopelessness (Assari & Lankarani, 2016). In the case of patients with terminal cancer, this hopelessness may then lead to a subsequent reduction in QOL and survival. A study of 85 individuals with advanced cancer examined hopelessness, anxiety, and depression among the group prior to and 30 days after their first visit with a palliative care physician (Sorato & Osório, 2015). It was found that depression, anxiety, hopelessness, and QOL scores remained the same before and after palliative care involvement (Sorato & Osório, 2015). These results could reflect the importance of integrating palliative care early and more frequently in the course of disease for maximal benefit. Because this group was comprised of advanced cancer patients, there may be less of an impact of palliative care when no curative treatment is available. Upon further study analysis, there was found to be a correlation between levels of anxiety, depression, and hopelessness with various coping strategies (Sorato & Osório, 2015). Coping mechanisms such as positive reappraisal, pursuing social support, planful problem-solving, and confrontation coping were protectors against hopelessness and depression symptoms felt by patients (Sorato & Osório, 2015). In

contrast, escape-avoidance coping and lack of problem-solving showed positive correlation with anxiety (Sorato & Osório, 2015).

These results are consistent with other studies depicting that avoidance and denial reaction to negative stimulus can result in activation of the sympathetic nervous system and promote anxiety (Gross & Levenson, 1997). It is important for palliative care teams to promote a positive coping strategy to prevent maintenance of unwanted psychological symptoms and stress, which can negatively impact end-of-life care. The diagram in Figure 10 summarizes the causes of anxiety in patients with cancer and how coping strategy can lead to a cycle of maintaining symptoms.

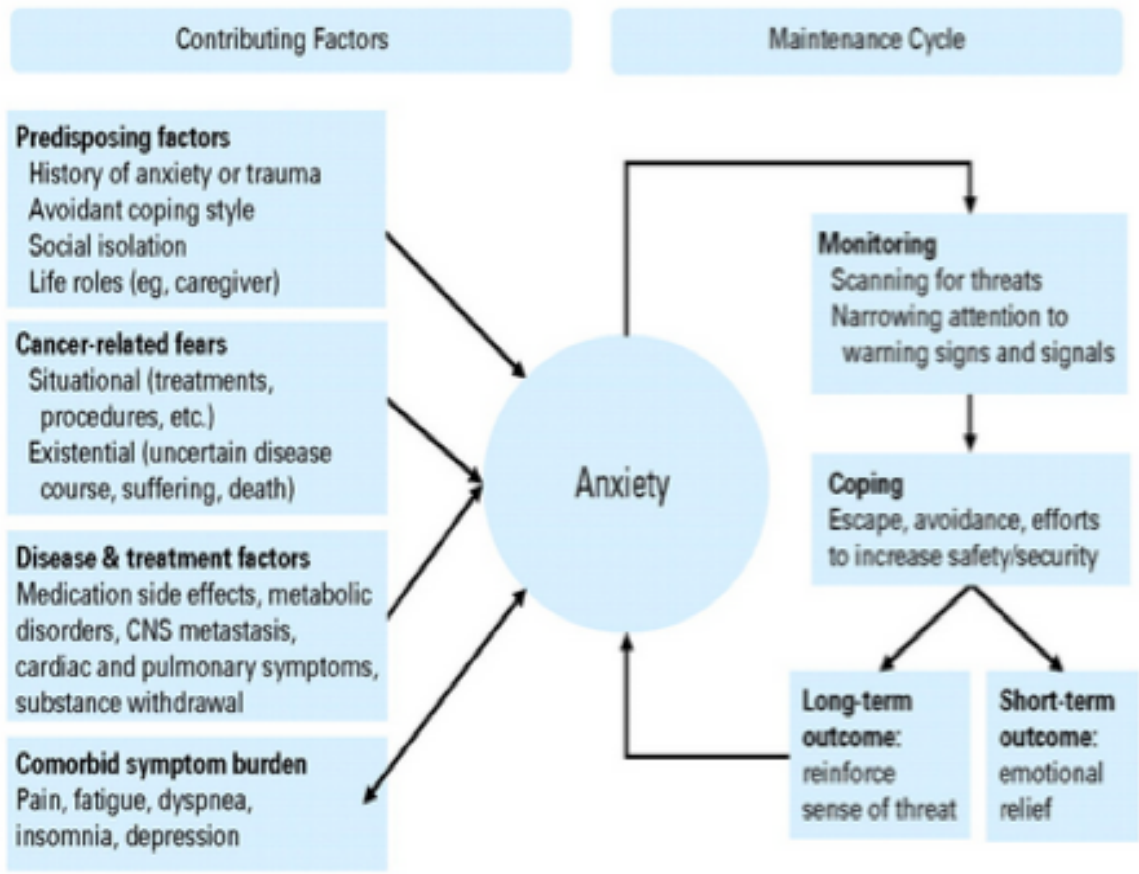


Figure 10. Etiologic factors contributing to and maintaining anxiety in cancer patients. An escape-avoidance coping strategy leads to short-term relief of symptoms but causes long-term consequences by reinforcing threats and maintaining the cycle of anxiety. CNS = central nervous system. Taken from (Traeger, Greer, Fernandez-Robles, Temel, & Pirl, 2012).

Avoidance and escape behavior are examples of maladaptive strategies and coping mechanism, which seek to circumvent stressors. Inevitably with any advanced disease, there are many stressors, such as grief, which would be better managed by positive reappraisal strategy. Positive reappraisal is a form of meaning-based coping characterized by active and adaptive strategies, which allow people to adjust effectively to adverse life events (Garland, Gaylord, & Park, 2009). Mindful-based therapy (MBT) and meditation are tools used to promote positive coping and lower anxiety. With more research, MBT

could potentially be utilized to help patients with advanced disease manage loss and come to peace with their circumstances (Piet, Würtzen, & Zachariae, 2012).

A study done in the United Kingdom examined the effect of depression-focused treatments on cancer patients with major depressive disorder (MDD) (Strong et al., 2008). Those patients receiving combined standard care with psychiatric intervention were provided with education on depression and coping strategies to manage feelings of helplessness with their physical condition (Strong et al., 2008). The utilization of collaborative care and management of depression by psychiatrists and oncology nurses in cancer clinics was shown to be a beneficial and cost effective model for managing depression in the oncology setting (Strong et al., 2008).

It is important to note that even though there is a strong association between coping strategy, QOL, and depression, there are questions about the feasibility of palliative intervention in supporting coping strategy. As cognitive decline progresses in terminal patients, there may be a lack of mental capacity to benefit from intervention focused on improving communication and coping strategy (van Laarhoven et al., 2011). For these reasons, it is again important to emphasize the application of palliative care early in the disease process when cognitive capacity is less likely to be compromised.

Clinical Features of Mental Illness

Symptoms of depression and anxiety are not a natural reaction to a terminal diagnosis (Barraclough, 1997). There is some evidence to support the under-diagnosis of psychological disorders in the palliative care setting as symptoms are attributed to a

natural response to disease and failing physical health (Barraclough, 1997). Other reasons for under-diagnosis include lack of communication from patients because of mental health stigma and lack of inquiry by physicians who may not have proper training (Barraclough, 1997). Anxiety and depression are most commonly caused by stress from the patient's illness and from losses associated with such dramatic changes in life circumstances. Common losses associated with a major medical diagnosis include (Barraclough, 1997):

- *Prognostic uncertainty; fear of death and the process of dying.*
- *Physical symptoms (pain, nausea).*
- *Undesirable side effects of medical and surgical treatments.*
- *Loss of functional capacity; loss of independence.*
- *Social and economic issues such as finance, work, and housing.*
- *Changes in relationships; concerns for dependents.*
- *Changes in body image; sexual dysfunction; infertility.*

Factors that put patients at high risk for anxiety and depression are as follows

(Barraclough, 1997):

- *Organic mental disorders.*
- *Poorly controlled physical symptoms.*
- *Poor relationships and communication between staff and patients.*
- *History of mood disorders or substance abuse.*
- *Personal characteristics such as pessimism, rigidity, and need for independence.*
- *Concurrent life events or social difficulty.*
- *Lack of support from family and friends.*

Symptoms of depression and anxiety are characterized in two main categories: somatic and psychological. Somatic symptoms have to do with the physical body and its physiologic response to mental disorders. Examples of somatic symptoms associated with depression include fatigue, sleep disturbance, change in appetite, slowed or impaired movement, and pain (Barraclough, 1997). Physical symptoms of anxiety vary widely and

include nervousness, palpitations, shortness of breath, difficulty sleeping, agitation, trembling, and nausea (Barraclough, 1997). The psychological symptoms of depression manifest themselves as low mood, lack of interest, indecisiveness, lack of concentration, feeling of guilt, and suicidal ideation (Barraclough, 1997). These symptoms may be difficult to diagnose in some patients, especially those receiving chemotherapy whose symptoms such as nausea can be side effects of treatment. Therefore, it may take several visits with a patient to identify emotional distress as clinically significant rather than an ordinary adjustment to disease and treatment (Barraclough, 1997).

It is crucial for palliative care teams to address the root cause of illness so that they can improve symptom management. There should be attention placed on psychological screening to rule out psychological causation of physical symptoms. In addition, psychological distress such as anxiety can have negative effects on treatment. Table 1 is a list of anxiety disorders and potential impact on delivery of cancer care.

Table 1. DSM-IV Anxiety Disorders and Clinical Manifestations in Patients with Cancer^a

Disorder	Summary of DSM-IV Diagnostic Criteria	Example Presentations in Cancer
Generalized anxiety disorder	<p>≥6 months of excessive anxiety/worry about multiple events/activities.</p> <p>Worry is difficult to control and is associated with symptoms such as restlessness, fatigue, poor concentration, irritability, tension, poor sleep.</p> <p>Disturbance is impairing and/or distressing.</p>	<p>Cancer-related worries shift from one topic to another, including both major and minor concerns.</p> <p>Difficulty focusing on other tasks because of apprehension or worry.</p>
Panic disorder	<p>Recurrent unexpected panic attacks.</p> <p>≥1 month of persistent worry about future panic or consequences of panic, or behavior change related to panic.</p>	<p>Avoidance of physical activity or self-care behaviors that might increase heart rate or shortness of breath.</p>

Table 1. DSM-IV Anxiety Disorders and Clinical Manifestations in Patients with Cancer^a (Continued)

Disorder	Summary of DSM-IV Diagnostic Criteria	Example Presentations in Cancer
Agoraphobia	<p>Fear of places/situations in which escape may be difficult or help for panic may not be available.</p> <p>Places/situations are avoided or endured with distress or fear of having a panic attack.</p>	<p>Marked difficulty in leaving home alone and/or traveling to oncology visits.</p>
Specific phobia	<p>Persistent fear of a specific object or situation.</p> <p>Exposure provokes immediate anxiety.</p> <p>Person acknowledges fear as excessive or unreasonable and impairing/distressing.</p>	<p>Strong vasovagal response to specific event such as blood draw.</p> <p>Panic attack in anticipation of specific medical procedure.</p>
Social anxiety disorder	<p>Persistent fear of social or performance situations.</p> <p>Exposure provokes anxiety or panic.</p> <p>Person acknowledges fear as excessive or unreasonable and impairing/distressing.</p>	<p>Avoidance of situations in which patient may be center of attention.</p> <p>Marked fear of embarrassment in front of medical staff.</p>
Obsessive-compulsive disorder	<p>Recurrent, intrusive thoughts/images, with persistent attempts to ignore or suppress them via a neutralizing thought or action.</p> <p>Repetitive, rigid behaviors that person is driven to perform to reduce distress/threat, although behaviors are not realistically connected to threat.</p> <p>Patient acknowledges disturbance as excessive or unreasonable and impairing/distressing.</p>	<p>Intrusive, distressing thoughts about medical contamination, with persistent behaviors (e.g., repetition of specific phrases) to neutralize threatening thoughts.</p> <p>Compulsive checking or arranging of medications.</p>
Acute stress disorder	<p>Experience of a traumatic event. Persistent and impairing symptoms in four domains ≤ 1 month after trauma:</p> <ul style="list-style-type: none"> - Dissociation (e.g., numbing, derealization) - Re-experiencing (e.g., intrusive thoughts) - Avoidance - Hyperarousal (e.g., tension, hypervigilance) <p>Patient acknowledges disturbance as impairing/distressing.</p>	<p>Derealization or lack of emotional responsiveness during receipt of a cancer diagnosis or news about worsening prognosis.</p> <p>Irritability, hypervigilance, and difficulty sleeping soon after a traumatizing cancer-related event.</p>

Table 1. DSM-IV Anxiety Disorders and Clinical Manifestations in Patients with Cancer^a (Continued)

Disorder	Summary of DSM-IV Diagnostic Criteria	Example Presentations in Cancer
Post-traumatic stress disorder	<p>Experience of a traumatic event. Persistent and impairing post-trauma symptoms in three domains for >1 month:</p> <ul style="list-style-type: none"> · Re-experiencing (e.g., intrusive thoughts) · Avoidance/numbing · Hyperarousal (e.g., tension, hypervigilance) <p>Patient acknowledges disturbance as impairing/distressing.</p>	<p>Avoidance of places or situations that trigger reminders of cancer-related events.</p> <p>Difficulty discussing cancer-related events with others.</p> <p>Marked physical and emotional distress during oncology clinic visits.</p>

^aThis table lists and defines various anxiety disorders according to the DSM-IV. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition. Anxiety disorders may cause barriers to curative treatment for cancer. Examples of clinical manifestations and their accompanied anxiety diagnosis are listed. Adapted from (Traeger et al., 2012).

Untreated psychological distress not only adds to patient suffering but also may interfere with curative-treatment measures. Addressing psychological problems such as anxiety and depression could prevent avoidance of curative and life-prolonging treatments available to patients with cancer.

Delirium in Palliative Care

Clinical presentation of delirium, or confusion, is particularly relevant to the palliative care setting. Delirium is the most frequent neuropsychiatric diagnosis among terminal cancer patients and is a typical cause for hospital admission (Centeno, Sanz, & Bruera,

2004). Furthermore, delirium can be a major cause and contributor to anxiety and depression among terminally ill patients. Symptoms of delirium include (Barraclough, 1997):

- *Clouding of consciousness (reduced awareness of environment).*
- *Impaired attention.*
- *Impaired memory, especially recent memory.*
- *Impaired abstract thinking and comprehension.*
- *Disorientation in time and place or person.*
- *Perceptual distortions (illusions, hallucinations).*
- *Transient delusions, usually paranoid.*
- *Psychomotor disturbance (agitation or underactivity).*
- *Disturbed sleep cycle, sleep walking, nightmares.*
- *Emotional disturbance (anxiety, depression, fear, irritability, euphoria, apathy).*

Delirium is caused by the direct effect of cancer on the central nervous system, cancer therapy or medication side effects, electrolyte imbalance, metabolic syndromes, infections, and other medical problems (Mehta & Roth, 2015). With worsening prognosis, the likelihood of the manifestation of delirium increases, with nearly 90% of terminal patients receiving a diagnosis at some point before death (Mehta & Roth, 2015). Early diagnosis may be complicated by certain presenting symptoms mirroring anxiety, depression, or other psychiatric problems (Mehta & Roth, 2015). As a result, delirium is often misdiagnosed and improperly treated early in its presentation (Centeno et al., 2004).

With the exception of patients suffering from terminal delirium, approximately half of the cases are reversible and responsive to therapeutic intervention. Cancer drugs like methotrexate, 5-fluorouracil, and interleukin-2 are associated with delirium, along with benzodiazepines and notably opiates (Mehta & Roth, 2015). Experts in the field of palliative care recognize that there is a paradox between the cause and effect of delirium

and the therapeutic medication. In a presentation, Dr. Diane Meier, a palliative care specialist at The Mount Sinai Hospital (New York, NY), remarked that although opioids are labeled as a cause of delirium in terminally ill patients, the primary predictor of delirium in this demographic is uncontrolled pain (Meier, 2012). Therefore, careful dosing of opioids is crucial to control pain and prevent pharmaceutical and pain-derived delirium. Non-pharmacological interventions are also of great importance in preventing delirium in the palliative care setting and include (Breitbart & Alici, 2012):

- *Avoiding polypharmacy.*
- *Promoting sleep.*
- *Monitoring dehydration and electrolyte levels.*
- *Monitoring nutrition intake.*
- *Providing visual and hearing aids to prevent sensory deficiencies.*
- *Encouraging mobility and minimizing physical restraints.*
- *Orienting the patient frequently to surroundings (e.g., placing familiar objects in the room).*
- *Encouraging cognitively stimulating activities.*

Although patient reorientation and other non-pharmacological activities are preferred first line interventions for delirium, the use of the antipsychotic haloperidol is considered the gold standard treatment. This medication, however, may require cardiology consultation to monitor prolongation in electrocardiography QT intervals (start of Q wave to end of T wave) (Breitbart & Alici, 2012). Proper management of delirium by palliative care teams is critical to protect against patient anxiety and depression. In addition, because delirium is distressing to family and caregivers, prevention can avert additional suffering.

Training, Managing Symptoms, and Prevention

Managing the care of patients with terminal illness is a sensitive process that requires delicate yet candid communication between the patient and the physician. Breaking bad

news to patients in an appropriate manner is an important skill for physicians, especially those in palliative care. Proper delivery of bad news can have therapeutic outcomes, whereas poor communication can add to the quantity of suffering. In an interview, Dr. Diane Meier described breaking bad news as a “procedure” that requires “proper training”, just like any other complex medical procedure (Meier, 2013). The six-step protocol SPIKES (S for setting, P for perception, I for invitation, K for knowledge, E for empathy, and S for summary/strategy) is an example of available training that can aid physicians in developing competency in this critical skill (Baile et al., 2000).

Many physicians feel underprepared on how to properly deliver bad news and provide palliative support because of limited training devoted to such skills in medical school (Block, 2002). Dr. Susan Block, a palliative care specialist at Dana-Farber Institute (Boston, MA), stated that it is not only a lack of “formal” curriculum, including education, faculty, and fellowship opportunities in palliative care, but it is also a lack of “informal” curriculum. The latter refers to the culture that students are trained in during medical school and beyond which contributes to deficiency in EOL care (Block, 2002). In his notable TEDTalk, Dr. B. J. Miller, a palliative specialist at University of California San Francisco (San Francisco, California), described how modern medical training fails in the face of EOL care (Miller, 2015). Dr. Miller commented, “healthcare was designed with diseases not people at its center, which is to say it was badly designed” (Miller, 2015). The disease model of care is successful in treating pathology and prolonging life; however, it may fail to recognize the individual needs of patients at EOL. Therefore,

additional training in a human-centered model of care could improve doctor-patient communication surrounding death and prevent greater suffering.

After delivering bad news, physicians must recognize the importance of allowing patients to voice their concerns and express their emotions. Physicians can then address the goals of care and develop a plan for patients to achieve the care they desire. Using the patients' goals of care is an ideal way for developing a treatment and intervention plan; therefore, solid communication is the foundation for palliative and end-of-life care (Kreher, 2016). Communication and centering care on the patients' goals allow doctors to develop optimum treatment regimens, avoid over-treatment and under-treatment, and improve quality of life (Bernacki, Block, & American College of Physicians High Value Care Task Force, 2014).

Listening to patients' verbal expression of their feelings and emotions is an important screening tool for psychological distress. A study examining 451 audio-recorded visits with an oncologist found that patients may use words such as "concerned," "scared," "worried," or "nervous" to hint that they are suffering from anxiety (Anderson et al., 2008). An empathetic response that acknowledges the patients' emotions and facilitates further discussion is important to invite disclosure of unresolved emotional distress (Anderson et al., 2008). Physicians who respond to emotional concerns with an active and empathetic approach are successful in lowering the anxiety and psychological distress of patients (Anderson et al., 2008).

When anxiety is mild to moderate in level, there may be some benefit to the patient from non-pharmaceutical interventions such as psychotherapy, behavioral training, music, and mindfulness therapies (Mehta & Roth, 2015). Pharmacologic therapies are used when non-pharmaceutical interventions fail and emotional distress is significant to impair daily life (Mehta & Roth, 2015). Typical pharmaceutical interventions, such as selective serotonin reuptake inhibitors (SSRIs), are used in the general population (Traeger et al., 2012). The downfall of this treatment approach in the EOL setting is that these medications may take weeks to show effects, and this is time that the patient may not have. When the prognosis is under 6 months, psychostimulants are appropriate to treat major depression (Kreher, 2016). Other interventions include benzodiazepines for acute anxiety attacks and panic symptoms; they may also help insomnia and nausea (Traeger et al., 2012). Mirtazapine has been used for its anxiolytic, weight gaining, and sedating properties, which can aid cancer patients suffering from anxiety, insomnia, and anorexia (Traeger et al., 2012). Presently, some researchers are evaluating the efficacy of using psychedelics to treat anxiety and depression for cancer patients at the end of life.

Key to Palliative Care: Communication

Listening to patients' concerns and goals about their care, together with utilizing solid communication skills, is a key effort made by palliative care physicians and teams. As the field of palliative care continues to expand rapidly, so does the research on communication skills and its impact on patient care. Physicians and providers in the palliative care setting may be confronted with scenarios that include "breaking bad news", discussing treatment options, prognoses, goals of care, and fears of patients and

their family members (Back, Arnold, & Tulsy, 2009). Training and educational programs have been developed to improve clinical skills and aptitude at addressing difficult conversations and communicating with patients. The six-step SPIKES protocol (Figure 11) has been successful in increasing providers' confidence in disclosing negative medical information, obtaining information from patients, providing support for patients, and collaborating to develop treatment plans that coincide with goals of care (Baile et al., 2000).



Figure 11. SPIKES 6-step protocol for breaking bad news to patients and families. The diagram illustrates the six steps involved in the SPIKES protocol. Step 1: Arrange for an appropriate private setting to make the patient and family feel comfortable and safe. Step 2: Ask open-ended questions to assess the patient's perception and understanding of the illness. Step 3: Gain invitation and permission from the patient to discuss diagnosis, prognosis, and treatment options in appropriate detail. Step 4: Deliver knowledge in an empathetic manner, and forewarn the patient that bad news is coming. Provide the patient with information in small chunks to avoid overwhelming the individual or causing demoralization. Step 5: Respond to the patient's emotions with empathy. Emotional reactions may vary greatly after receiving bad news and may include shock, anger, and denial. Physicians may observe the patient's response and offer support, or they may use exploratory questions to probe for what the patient is experiencing. Step 6: Provide the patient with a summary and strategy to move forward, lower anxiety, and reassure future support (Baile et al., 2000). Image taken from (Hausdorff, 2017).

Workshops at the University of Texas Cancer Center (Houston, TX) found that training with the SPIKES protocol increased the confidence of experienced oncologists, fellows, and medical students in “breaking bad news” (Baile et al., 2000). For some physicians, addressing death, or the “elephant in the room,” can be a difficult process leading to complications for patients and families. The reason that a physician may be reluctant to have such discussions usually revolves around a lack of certainty in the patient’s prognosis, and a fear that the patient will feel abandoned by the physician and become more depressed and hopeless (Quill, 2000). These concerns may be valid fears, and undoubtedly patients vary in their response and distress to hearing bad news. Despite this fact, evidence supports that failure to give a candid prognosis and overabundance of optimism can indeed cause greater pain and psychological distress in the long run (Quill, 2000).

The physician’s ability to have “difficult” conversations is important, especially in the oncology and palliative care setting where providers discuss advanced care planning with patients. From 2002 to 2008, a longitudinal cohort study examined how advanced care planning discussions affected treatment of advanced cancer patients at the end of life (Wright et al., 2008). The results of the 332 patients enrolled in the study showed that those who engaged in end-of-life discussions with their physicians had less aggressive treatment, better utilization of hospice, no increase in depression, and improved QOL (Wright et al., 2008). Increased utilization of hospice care decreased aggressive treatments such as ventilation and resuscitation, which are associated with low QOL and greater levels of depression in bereaved caregivers (Wright et al., 2008).

In 2000 the Journal of the American Medical Association (JAMA) used a cross-sectional, stratified random survey to determine factors that patients, family members, and providers thought were crucial areas of communication at EOL (Steinhauser et al., 2000). Topics that were rated as most important throughout all groups were pain/symptom management, planning for death, attaining a sense of conclusion, reviewing treatment preferences, and receiving treatment as a “whole person” (Steinhauser et al., 2000). Other items that patients specifically viewed as critical included being perceptually aware, preparing funeral arrangements, not burdening family members, assisting others, and coming to peace (Steinhauser et al., 2000).

Communication between patients and physicians can therefore address many of these factors and improve patient stress even in the absence of medical cure. The empirical evidence supports the deployment of particular communication skills to address patient concerns, lower anxiety and depression, and enhance QOL and satisfaction with care (Morrison & Meier, 2004). Having a “patient-centered” approach to discussions that highlight empathy, asking open-ended questions, reassuring patients’ emotional reactions, and simply maintaining eye contact are all correlated with satisfaction of care, particularly for those with poor prognosis (Dowsett et al., 2000). One of the benefits of communicating with patients is to determine clear goals of care in order to avoid over-treatment or under-treatment of disease, which can lead to more suffering. Experts in the field use open-ended questions such as “What are your fears?” and “What do you hope to

achieve?” as a means of probing for what the goals of the patient are and what treatment plan will achieve those goals (Morrison & Meier, 2004).

The role of the palliative care physician is to take a step back and see the larger picture, a task that is easier said than done for physicians who are trained in an education system focused on specificity and small details. The responsibility of a palliative care physician to prevent over-treatment may best be detailed by an example. In a paper written in the New England Journal of Medicine (NEJM), a patient scenario is presented where an individual suffering from end-stage dementia has difficulty swallowing (Morrison & Meier, 2004). The traditional medical approach would indicate placing a percutaneous endoscopic gastrostomy tube to help the patient receive adequate nutrition and prolong life (Morrison & Meier, 2004). However, because the procedure has side effects, including significant pain, and removes the enjoyment of tasting food, its palliative benefit on QOL is insignificant (Morrison & Meier, 2004). This case exemplifies the importance of communication and discussing advanced care planning with patients early in the course of disease when there is less likely to be significant cognitive impairment. Studies show that cancer patients suffering from significant uncontrolled pain are more likely to suffer from depression (Mehta & Roth, 2015). By preventing unnecessary painful procedures, physicians can avoid causing additional emotional distress in terminally ill patients.

Palliative Oncology

Oncologists play a major role in screening for psychological symptoms in cancer patients in settings where palliative care and psychiatric physicians are absent. A pilot study examining men with prostate cancer suggested that there is a crucial need for rapid screening tools in the oncology setting to ensure patients' distress needs are met in the face of increasing pressure to condense time spent with each patient (Roth et al., 1998). Cancer care has seen dramatic improvements in curative-treatment options as personalized medicine develops targeted therapies for certain pathologies. However, the psychological consequences of struggling with a cancer diagnosis are commonly overlooked and can intensify emotional problems like depression and anxiety (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). Furthermore, lack of attention to emotional issues can cause increased suffering, disruption of family life, and lower compliance with treatment plans (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). Figure 12 illustrates a model of psychological intervention in the palliative oncology setting.

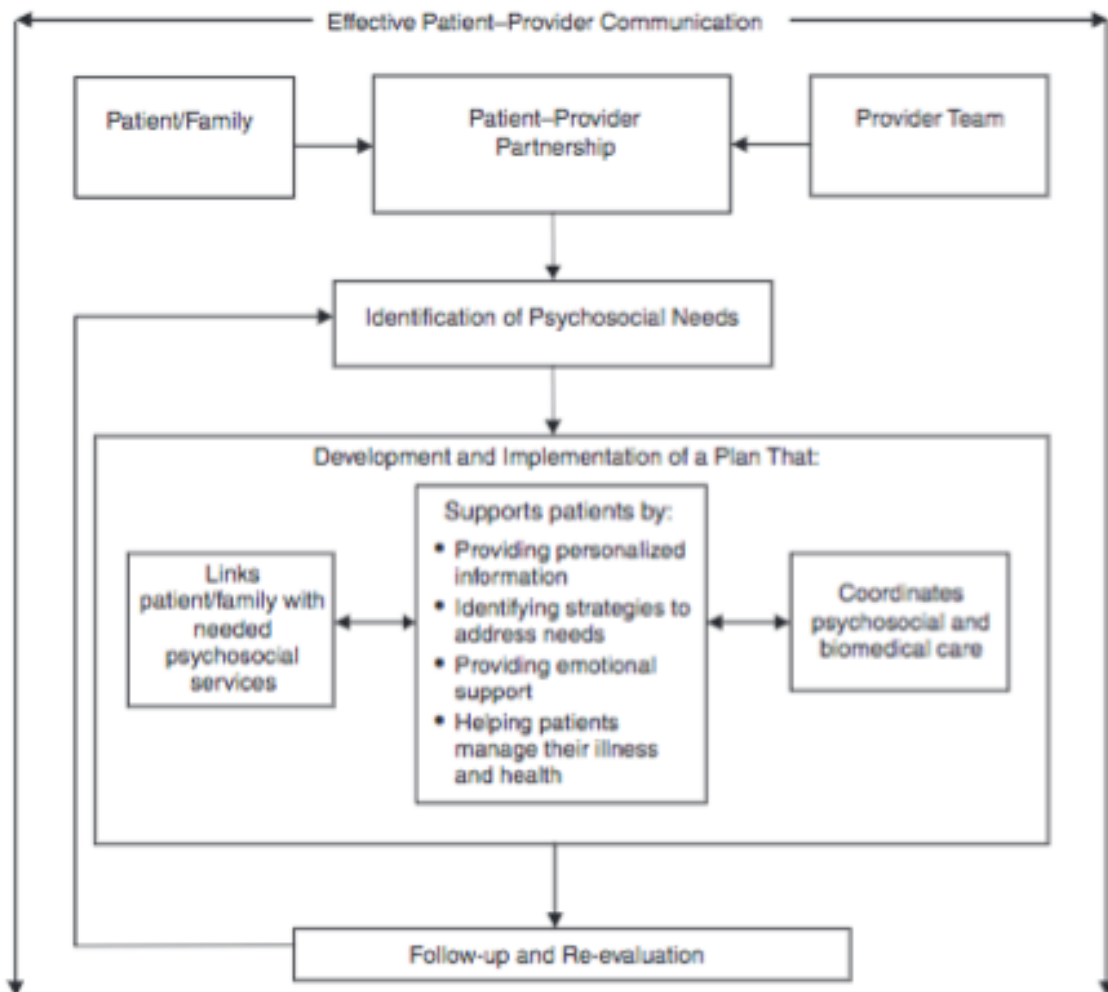


Figure 12. Intervention model for providing psychological care to cancer patients.

The diagram provides a model for effective doctor-patient communication. There must be coordination between the physician, medical staff, family, and patient in order to identify psychological needs and develop appropriate treatment plans. Taken from (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008).

Periodic follow-up and reevaluation of psychological needs are crucially important as patients' goals change with the course and progression of their disease.

Curative Treatment and Quality of Life

Does prolonging life through chemotherapy treatment lead to a better quality of life, or does it only prolong suffering? Although there are instances of positive outcomes for patients undergoing chemotherapy, some studies suggest that chemotherapy for advanced cancer has negative impact on QOL and minimal effect on survival.

Researchers in Australia sought to isolate the contribution of cytotoxic therapy to the five-year survival rates of cancer patients (Morgan, Ward, & Barton, 2004). After examining several studies, they determined that the contribution of cytotoxic treatment to five-year survival time was just over 2% in both Australia and the United States. (Morgan, Ward, & Barton, 2004). These findings illustrate the minimal impact of adjuvant cytotoxic chemotherapy for patients with cancer, and raise questions about whether the numerous side effects that impact QOL are worth minor survival gains.

A longitudinal cross-sectional study was performed in Iceland on patients with various cancers. This study examined QOL measurements at the onset of chemotherapy as well as the 3- and 6-month follow-ups. The analysis showed that there was an association between continuing chemotherapy and declining QOL; however, the overall QOL for the patients was better than anticipated (Saevarsdottir, Fridriksdottir, & Gunnarsdottir, 2010). Saevarsdottir and colleagues (2010) found that the areas of QOL most affected were sexual and other physical symptoms. There was also a correlation between levels of anxiety and depression and poor QOL, and this correlation remained consistent at all points in time throughout treatment (Saevarsdottir et al., 2010). Anxiety levels seemed to

be greatest among younger patients and, interestingly, greater in married men than in single men (Saevarsdottir et al., 2010). The latter result contradicts other studies that found anxiety to be lower in patients with more social support (Parker, Baile, de Moor, & Cohen, 2003). In addition, the levels of depression in the study peaked at the 3-month follow-up and declined after cessation of treatment (Saevarsdottir et al., 2010). Speculation was made that as physical side effects of chemotherapy begin to present themselves, depression begins to manifest (Saevarsdottir et al., 2010).

Prevalence and Biomarkers of Depression and Anxiety

A study published in the Journal of the American Medical Association (JAMA) investigated the prevalence of psychiatric disorders in 215 patients with cancer (Derogatis et al., 1983). The patients were assessed based on the criteria established in the DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Third Edition), which was the most updated diagnostic system at the time of the study (Derogatis et al., 1983). The results of the study determined that 47% of patients were capable of being diagnosed with various mental illnesses based on the DSM-III criteria (Derogatis et al., 1983). Anxiety and depression were the primary symptoms of roughly 85% of the patients who screened positive for mental illness (Derogatis et al., 1983). The study also found that the majority of the disorders that were diagnosed were treatable (Derogatis et al., 1983).

Other studies showed that there were generally lower rates of depression and anxiety than would be expected in the palliative and oncology setting; however, the frequency was

still significant, ranging from 30%-40% (Mitchell et al., 2011). In 2001 a study of a large sample of over 4,000 patients was undertaken to examine the prevalence of psychological distress in relation to cancer type and site of diagnosis (Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). The results determined that the complete prevalence of psychological distress among patients was 35.1% (Zabora, et al., 2001). Lung cancer patients displayed the highest levels of distress at 43.4% (Zabora et al., 2001). Zabora and colleagues recognized that these results were consistent with other studies that showed lung cancer patients were at risk for higher levels of distress (Faller, Bülzebruck, Drings, & Lang, 1999). Poor prognosis of lung cancer, combined with the commonly self-afflicted nature of the disease, caused patients to be particularly high-risk for experiencing significant psychiatric distress levels (Zabora et al., 2001). Other cancers with poor prognosis, including brain cancer and pancreatic cancer, exhibited levels of distress close to lung cancer, with pancreatic cancer patients displaying the greatest levels of anxiety and depression (Zabora et al., 2001). Patients suffering from cancer types with poor prognosis may identify with greater feelings of “doom” expressed by family, physicians, and other healthcare personnel (Zabora et al., 2001). The significance of this study was the finding that patients with certain types of cancer, particularly cancers with poor prognosis, are at risk for psychological distress (Zabora et al., 2001). Thus, these issues should be adequately screened for and addressed early on in treatment to avoid jeopardizing QOL and raising the burden of patients and family members.

The results from the Zabora et al. (2001) study are consistent with other analyses that showed higher prevalence of anxiety and depression among stomach, pancreatic, head-

neck, and lung cancers (Brintzenhofe-Szoc, Levin, Li, Kissane, & Zabora, 2009). The etiology of anxiety and depression among patients with these cancer sites raises questions about whether there may be a biological connection between cytokine release in specific cancers and psychological distress (Brintzenhofe-Szoc et al., 2009). The connection between immune response, cytokine release, and depression is a growing area of research that adds to the theory of serotonin deregulation as the central cause of depression.

Studies have shown that patients who display higher levels of inflammation during the course of chronic illness have higher rates of depression (Yirmiya et al., 2000). Research demonstrated a connection between depression and cancer patients who exhibited a high level of circulating proinflammatory cytokines (Felger & Lotrich, 2013). Additional data showed that higher-than-normal levels of interleukin-6 (IL-6), an inflammatory cytokine secreted by macrophages and T-cells, were correlated with major depression in patients suffering from cancer (Musselman et al., 2001). It is hypothesized that IL-6 may disrupt the hypothalamic-pituitary-adrenal (HPA) axis, causing increased release of stress hormones and disruption in feedback inhibition of cytokine production (Musselman et al., 2001). Elevated cytokine levels have been linked to “sickness behavior,” which presents as symptoms of fatigue, anhedonia, decreased psychomotor activity, and other symptoms that overlap with depression (Musselman et al., 2001). It is unclear whether higher cytokines levels are a cause or consequence of cancer disease process; nonetheless, patients of specific cancer sites associated with high cytokine levels may be at risk for greater prevalence of mood disorders (Musselman et al., 2001).

Cytokines such as IL-6 could be used as a biomarker to screen for cancer patients at risk of developing a mood disorder (Jehn et al., 2006). The diagram in Figure 13 summarizes the mechanism of cytokine action and the effect of neurotransmitter-release systems in the brain. Much of the information depicted in Figure 13 is not within the scope of this study; however, the diagram illustrates the complex relationship between inflammatory cytokines, such as IL-6, and the effect on neurotransmitter release, degradation, and reuptake in central nervous system neurons.

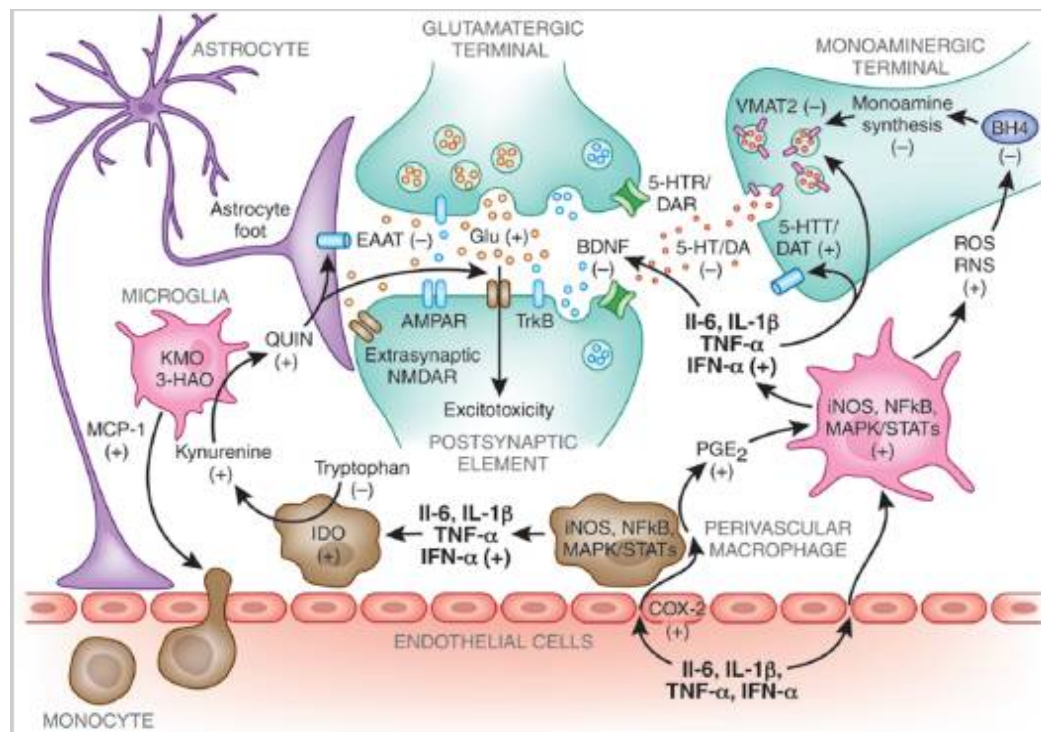


Figure 13. Inflammatory cytokine effect on neurotransmitter systems and neurocircuitry. The diagram shows an overview of plausible mechanisms of action on monoamine, glutamate, and brain-derived neurotrophic factor (BDNF) neurotransmitter systems. The modification of such systems is believed to impact mood and behavior. Circulating inflammatory cytokines (IL-6, IL-1 β , TNF- α , IFN- α) access the central nervous system where they recruit a variety of local inflammatory cells (COX-2, PGE₂). The result is a disruption of enzymes, precursors, and neurotransmitter transport channels. Figure terms: 3-HAO, 3-hydroxyanthranilic acid oxygenase; 5-HT, serotonin; 5-HTT, serotonin transporter; AMPAR, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor; BH₄, tetrahydrobiopterin; BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; DAT, dopamine transporter; glu, glutamate;

EAAT, excitatory amino acid transporter; IDO, indoleamine 2,3 dioxygenase; IFN, interferon; iNOS, inducible nitric oxide synthase; IL, interleukin; KAT II, kynurenine aminotransferase II; KMO, kynurenine 3-monooxygenase; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemotactic protein-1; NMDAR, N-methyl-D-aspartic acid receptor; NF-kB, nuclear factor-kappa B; PGE2, prostaglandin E2; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TH, tyrosine hydroxylase; TNF, tumor necrosis factor; TrkB, tyrosine kinase receptor B; VMAT2, vesicular monoamine transporter 2. Taken from (Felger & Lotrich, 2013).

In addition to inflammatory markers, studies have found age to be a predictor of patients at risk for anxiety and depression. In an examination of 736 men with prostate cancer, it was determined that older patients had less prevalence of anxiety and distress but greater symptoms of depression (Nelson et al., 2009). A longitudinal study of 500 patients of varying cancer sites found that 21% had significant anxiety and 13% significant depression according to the Hospital Anxiety and Depression Scale (HADS) (Weiss Wiesel et al., 2015). Upon further analysis, age was inversely correlated with anxiety levels but showed no relation to depression (Weiss Wiesel et al., 2015). Depression was significantly associated with lower social support, increased comorbid conditions, and higher stages of cancer (Weiss Wiesel et al., 2015). The results mostly align with other studies that found old age to be a “protector” against psychological distress in cancer patients (Parker et al., 2003). Some researchers point out that the psychological well-being of older persons is protected by their improved emotional control, ability to adapt to life changes, and capacity to adjust goals accordingly (Nelson et al., 2009).

Palliative Care Relevance and Challenges

Within the next 20 years, approximately one-fourth of the U.S. population will be over 65 years of age (Bluthmann, Mariotto, & Rowland, 2016). Palliative care is not exclusively for elder and geriatric patients, although the majority of individuals suffering from

chronic or terminal illness are older. These patients suffering from chronic illness, especially those of older generations are likely to have several comorbid conditions. The role of palliative care is to bridge the gap between two traditional goals of medical training and care. The primary goal in the training of most practitioners is to cure illness and prolong the life of the patient, and the second goal is to provide relief from suffering when there is no longer a cure (Morrison & Meier, 2004). This philosophy is partially a result of healthcare and payment programs like Medicare that reimburse life-prolonging treatment. Hospice and care focused on relief of suffering are only reimbursed after the suspension of life-sustaining treatments (Christakis & Escarce, 1996). The separation of these two goals of care comes at a cost to patients' QOL when they are suffering from terminal illness (Morrison & Meier, 2004). As studies have shown, patients benefit from care focused on relief of suffering in combination with curative-treatment measures (Morrison & Meier, 2004).

Because there are pressing issues in regard to the aging population and the higher incidence of cancer in the United States, palliative care is increasingly being recognized as necessary. In 2008, the Institute of Medicine (IOM) published guidelines for adding and implementing psychological support into the biomedical treatment of cancer, based on the determination that it was a critical factor in delivering quality care (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). Other organizations are following this trend. According to the American College of Surgeons Commission on Cancer, by 2015 it was required that

cancer treatment centers screen all patients for psychological stress to maximize treatment outcomes (Mehta & Roth, 2015).

However, the skills needed by palliative care physicians are relatively new and rarely taught in traditional medical school training. A report on the status of medical education in EOL care was published more than a decade ago (Sullivan, Lakoma, & Block, 2003). The results of the approximately 2,000 participants ranging from medical students to residents and faculty concluded that less than 18% received formal EOL training and about 50% felt unprepared to help assist the psychological needs of patients and families (Sullivan, et al., 2003). Nevertheless, 90% of the students and residents regarded the physician's duty to aid and manage patients at EOL as an important responsibility (Sullivan et al., 2003).

Bereavement Counseling for Family and Caregivers

Family members of patients with cancer are also at risk for suffering psychological distress (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). The psychological suffering of patients' family members and caregivers can cause greater distress in patients and should be addressed to avoid negative impact on care outcomes (Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008).

Studies on partners of women with breast cancer showed that they experienced similar anxiety and depression to the patients receiving treatment and that their relationship was

interdependent (Segrin, Badger, Dorros, Meek, & Lopez, 2007). This study and others also suggest that low mental health quality of caregivers at the time of diagnosis corresponds with decreased patient mental health and declining physical health in both patients and caregivers (Shaffer, Kim, & Carver, 2016). Therefore, aiding family members in distress may improve mental and physical health of both patients and their families (Shaffer et al., 2016).

New Research on Treating Anxiety and Depression at EOL

A new and somewhat controversial area of research, which targets anxiety and depression in the EOL setting, has recently seen resurgence. In the 1960s and 1970s, clinical research examining the use of hallucinogens among cancer patients showed improvements in anxiety, depression, fear of dying, and QOL (Grob, Goodman, Richards, & Kurland, 1973; Kast, 1966). However, the passage of the Controlled Substances Act of the 1970s classified psychedelics as Schedule I substances, and further research on their use in the EOL setting was suspended (Ross et al., 2016). In 2011 researchers at the University of California, Los Angeles (UCLA) began reexamining the use of psychedelics to treat advanced-stage cancer-related psychological distress and anxiety. Data showed an improvement in the patient's anxiety and established that a moderate dose of psilocybin was safe with no significant adverse events (Grob et al., 2011). The impact of psychedelics on spiritual well-being, anxiety, and depression in the EOL setting has gained increased attention in the field of palliative care. Current research in palliative care shows that enhanced spiritual well-being among cancer patients is associated with improved psychological distress and better QOL (Breitbart et al., 2000). As a result, there

is an interest among those in the palliative care setting to have access to a therapy that addresses spiritual and existential crises at EOL.

In 2016 researchers at New York University (NYU) enrolled 29 patients suffering from significant cancer-related anxiety and depression in a double-blind, placebo-controlled study examining the impact of a single dose of psilocybin, or psychedelic mushrooms (Ross et al., 2016). The results showed remarkable promise as participants experienced an acute and prolonged anxiolytic and antidepressant response to a single dose (Ross et al., 2016). Sustained improvements in anxiety and depression among the intervention group were reflected in a reduction of demoralization and hopelessness, an increase in spiritual well-being, an improvement in QOL, and an enriched outlook toward dying (Ross et al., 2016). Clinically significant improvements in these domains were persistent for 60%-80% of patients at 6 months after the single treatment session (Ross et al., 2016).

The results of Ross et al. (2016) correspond to other studies showing psilocybin therapy as effective in lowering anxiety concerning death, improving depressive mood, and increasing optimism and overall QOL in patients suffering from advanced cancer (Griffiths et al., 2016). Although there were no significant adverse events in these studies, further research needs to be conducted on a larger and more diverse sample to validate results, safety, and generalizability. The clinically significant impact of a single-dose medication is novel in the field of psychiatry in which most existing pharmacologic therapies require continual dosing with delayed effects (Ross et al., 2016). The future usage of combined psychotherapy and psychedelics is a fascinating potential tool for

palliative care physicians struggling to manage existential crises, anxiety, and depression at EOL.

DISCUSSION/CONCLUSION

The literature data examined in this study show that there is a convincing benefit to cancer patients receiving palliative care. The optimal benefits were found in clinical studies in which palliative care was initiated early in the course of a diagnosis in combination with curative-treatment measures. Some studies suggest that palliative intervention is effective in extending life while simultaneously improving patient psyche and quality of life (QOL). These data imply a link between declining survival time, low QOL, and increased depression. Therefore, researchers hypothesize that the central focus of palliative care is to improve patient QOL and address psychological distress, which may explain the increase in patient survival time.

In addition, the palliative care model of care seems to improve doctor-patient communication to avoid unnecessary and aggressive end-of-life care and to increase utilization of hospice care. Prompt utilization of hospice care is another hypothesis that is suggested for the increased survival time observed in some patient populations. The focus of hospice on managing symptoms and providing comfort could potentially contribute to improvements in length of life and QOL.

Although the data show promising benefits to patient care, there remains a need for replication and refinement of current research studies. Studies that focus specifically on the connection between improvements in depression and anxiety and their impact on survival and QOL would help address limitations in current research. In addition, future studies should test specific mechanisms of palliative intervention that account for

improvements in patients' mood, survival, and well-being. The ability to isolate specific palliative intervention techniques would allow development of a more universal model of care that could be replicated and studied across various disciplines. Developing a model of palliative care to apply to patients with cancer and other chronic illnesses is an ever-pressing issue in medicine.

The aging U.S. population is creating a higher incidence of patients who suffer terminal disease; however, the growth in palliative care is reflective of the needs of this patient population. Although there is a current shortage of palliative care physicians, the growth of this field is undeniable. In the last two decades, palliative care programs have become nearly universal at large hospitals and institutions where the majority of chronically ill patients receive treatment. The rapid evolution of palliative care is an important first step in further research and advancement in patient care. With more time, it is the hope of many in the medical field that a universal model of care may be refined to address physical and psychological suffering at the end of life (EOL).

Unfortunately, examination of current research shows that patients suffering from terminal cancer are at high risk for developing psychiatric comorbidities like anxiety and depression. Patients at higher risk are those in the younger demographic, those lacking in social support, and those displaying counterproductive coping strategy. In addition, patients with aggressive cancer, poor prognosis, increased pain, and elevated inflammatory markers may be at a greater risk of suffering anxiety and depression. Data suggest that the prevalence of anxiety and depression among patients with advanced

cancer is higher than for the general public and can range from one-third to nearly one-half of patients. The consequences of this situation can be measured in studies linking mood disorders to lower quality of life and worse survival time among cancer patients. Furthermore, psychiatric conditions present obstacles to physicians and curative-treatment measures that may affect survival time. Patients with untreated clinical anxiety and depression may avoid treatment and doctor's appointments, contributing to worse outcomes. Looking beyond survival time, there is a risk that cancer patients who are suffering from anxiety and depression are unable to enjoy their lives and the remaining time before death. For these reasons, it would be beneficial to pay close attention to the psychological distress of all cancer patients, particularly those who may be at high risk.

When anxiety and depression arise in patients diagnosed with cancer, there are several treatment and management options. For palliative care providers, the use of non-pharmacologic methods may possess both direct and indirect benefits to the patients' moods. For instance, research mentions the advantage of supporting positive coping strategy, meditation, reorienting, and assistance for bereaved family members. Current studies show that improvement in spirituality is another noteworthy non-pharmacologic area of intervention for palliative care patients.

Studies linking spiritual well-being to enriched QOL and survival have led to the resurgence in past areas of controversial research. Clinical trials have begun examining the usage of Schedule I psychedelic drugs to improve anxiety, depression, spiritual well-being, and QOL among those dying from cancer. The novelty of such treatments is that

they have thus far shown immediate and sustained benefits to patients after a single dose. The lack of adverse events among these current studies makes this a promising area of further study and intriguing potential therapy for patients in the future. Meanwhile, the precise administration of current pharmacologic therapies is necessary in the palliative care setting. Proper pharmaceutical management of physical pain can prevent delirium, anxiety, and depression in terminally ill patients.

Based on this in-depth review of current literature, it seems that advanced cancer patients are at high risk for suffering anxiety and depression. Unfortunately, the psychological distress associated with anxiety and depression is likely to lower patient QOL, decrease treatment compliance, and negatively impact survival. The recognition of such problems is reflected in the current increase in palliative care programs and research targeting psychological distress at EOL. Palliative intervention seems to mitigate the level of suffering endured by cancer patients and to elevate their mental health. It is hoped that the field of palliative care may continue to grow and make new discoveries in an effort to improve how patients live and die with chronic disease.

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