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### The Role of Antidepressants in a Malignancy Patient with Palliative Care: A Systematic Literature Review

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#### ABSTRACT

**Background:** Depression is a common complication in malignancy patients, and can worsen their quality of life and prognosis. Palliative care aims to improve the quality of life of patients with life-limiting illnesses, and antidepressants are often used in this context. **Methods:** This systematic review was conducted to evaluate the effectiveness of antidepressants in malignancy patients with palliative care. A literature search was conducted in three databases: PubMed, Cochrane, and ScienceDirect. Search terms included "Antidepressants," "Malignancies," and "Palliatives." **Results:** Two studies met inclusion criteria: First study: Randomized controlled clinical trial evaluating the effectiveness of mirtazapine compared with escitalopram in malignant patients with depression. The results showed that mirtazapine was more effective in improving quality of life and reducing depressive symptoms compared with escitalopram. Second study: a study evaluating the effectiveness of antidepressants in elderly malignancy patients with depression. The results suggest that antidepressants may be effective in reducing depressive symptoms and improving quality of life, but further research is needed to confirm their effectiveness and safety. **Conclusion:** Available evidence suggests that antidepressants may be effective in treating depression in malignancy patients with palliative care. However, further research is needed to identify the most effective and safe antidepressants for this patient population.

#### 1. Introduction

In 2018, approximately 18.1 million people worldwide were diagnosed with cancer, and 9.6 million of them died from the disease. These numbers are expected to double by 2040, with the maximum increase occurring in low- to middle-income countries, which account for more than two-thirds of the world's cancer cases. The most common types of cancer diagnosed in different countries are lung and female breast cancer which account for 11.6% of all cases, followed by colorectal cancer (10.2%).<sup>1</sup> Cholangiocarcinoma accounts for approximately 3% of gastrointestinal malignancies and is the second most common primary liver tumor and accounts for approximately 10-15% of all hepatobiliary

malignancies. As with most cancers, its incidence increases with age, with the most common age group being 50 to 70 years. Men are slightly more likely to be diagnosed with cholangiocarcinoma than women, possibly due to primary sclerosing cholangitis being more common in men.<sup>2</sup>

The development of screening examinations and therapies for malignancy patients has not kept pace with social support for malignancy patients, especially in developing countries. Evidence has shown that support from close family members has a positive effect on patients' physical health and mental well-being, as well as their ability to adapt their living conditions to chronic illness and associated symptoms including pain, sleep difficulties, distress, and

depression.<sup>3</sup> Several studies reveal that in breast cancer depression is one of the important concerns that is strongly associated with physical deficits, disease severity, poor health conditions, poor performance and reduced survival.<sup>4,5</sup>

Pilevarzadeh et al (2019) reported that the global prevalence of depression in breast cancer patients is 32.2%. In fact, based on the results of various studies, the prevalence rate is reported between 9.3 to 56%. Moreover, if breast cancer occurs together with depression, patients will experience more severe pain, extreme fatigue, decreased life expectancy, and decreased quality of life. Moreover, a recent meta-analysis, confirmed that cancer patients with depressive symptoms have a 25% higher mortality rate.<sup>6,7</sup> The high incidence of depression in malignancies can affect the patient's condition including increasing mortality, so the importance of comprehensive patient management in order to improve the quality of life, reduce symptoms, and survival rates of cancer patients. Patients with malignancies often feel great physical and psychological stress that can affect patients to make decisions and patient management plans, so there is a need for palliative care in cancer patient care. However, until now in the guidelines for the management of malignancies both nationally and internationally, there are still no sources that mention palliative care in patients with malignancies.

## 2. Methods

The clinical questions were determined based on the population, intervention, comparison, and outcome (PICO) of the study. The clinical questions of this study are: Do antidepressants reduce complaints in malignancy patients with palliative care? P : Malignancy patients with palliative care ; I : antidepressants ; C : placebo ; O : Clinical manifestations of improvement. Literature search based on inclusion and exclusion criteria. Inclusion criteria were 1) malignancy patients with palliative care; 2) antidepressant administration; 3) relevant keywords in the last 5 years (Malignancy) AND

(Palliative) and (Antidepressant); 3) prospective study, systematic review/meta-analysis, randomized clinical trials (RCT); 4) articles that were not written in English or did not have a full manuscript were excluded.

A systematic literature search was conducted from October 20-27, 2023, using AND Booleans in three databases: PubMed, Cochrane, and Science Direct. The literature search strategy is shown in table 1. Titles/abstracts and MeSH terms were searched according to the study design and clinical question with keywords including "Antidepressant", "Malignancy", and "Palliative". Two studies were critically reviewed using the Oxford Center of Evidence-based medicine (CEBM) critical appraisal tools for randomized controlled trials by the authors. The review assessed the validity, importance, and applicability of the studies.

Table 1 presents the results of a literature search on antidepressant use in malignancy patients with palliative care in three major scientific databases: PubMed, Cochrane, and ScienceDirect. The search keywords used were a combination of "Antidepressant", "Malignancy", and "Palliative". PubMed: This database yielded 7 articles. PubMed is a major resource for biomedical and health research, so these 7 articles potentially represent the most recent and high-quality research. Cochrane: This database focuses on systematic reviews and meta-analyses. The search results yielded 3 articles, which can provide an overview of the effectiveness and safety of antidepressants in this patient population based on a synthesis of existing research. ScienceDirect: This database yielded 44 articles. ScienceDirect has broader coverage than PubMed and Cochrane, so its greater number of results can cover a wider range of research types, such as clinical trials, observational studies, and reviews. A search of these three databases indicated that there is sufficient literature on the use of antidepressants in malignancy patients on palliative care. The largest number of results are from ScienceDirect, but PubMed and Cochrane provide more focused and potentially high-quality resources.

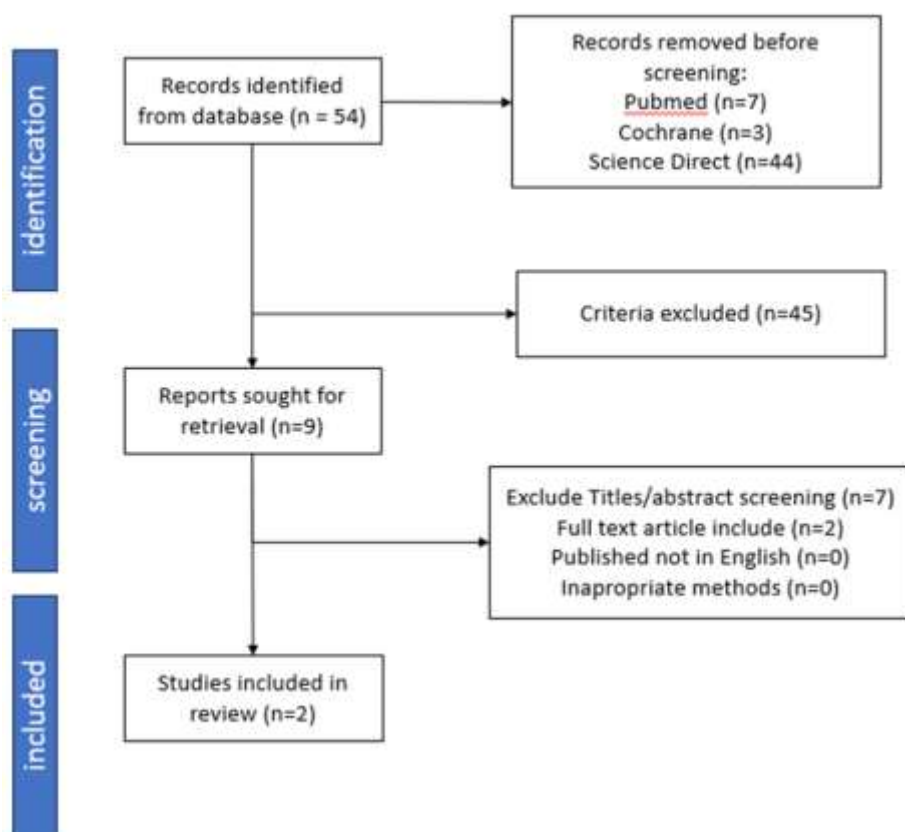


Figure 1. Prisma diagram.

Table 1. Literature search.

Database	Keywords in search	Hits
PubMed	(Antidepressant) AND (Malignancy) AND (Palliative)	7
Cochrane	(Antidepressant) AND (Malignancy) AND (Palliative)	3
Science Direct	(Antidepressant) AND (Malignancy) AND (Palliative)	44

### 3. Results

From the screening of titles and abstracts, 2 studies were obtained that met the criteria. Then the study will be excluded if it does not have the

appropriate outcome. Articles that meet the criteria and are analyzed in this literature are RCTs and systematic reviews so that they have a level of evidence.

Table 2. Validity criteria validity.

Study	PICO	Search strategy	Study design	Study quality assessment	High quality	Results in table/forest plot	Similarity of study results	Results	Level of evidence
Economos et al	+	+	+	-	+	+	-	<b>A</b>	2a
Rabin et al	+	+	+	-	+	-	+	<b>A</b>	1a

Table 3 presents two important studies that address the treatment of depression in malignancy patients. The first study, by Economos et al, showed that the antidepressant mirtazapine was effective in reducing depressive symptoms and other symptoms associated with cancer (poly-symptoms). The dose of mirtazapine needs to be adjusted according to the severity of the patient's symptoms, with an initial dose of 15mg/day and weekly evaluation to ensure effectiveness and safety. The second study, by Rabin et al, examined the cost-effectiveness of combining cognitive behavioral therapy (CBT) and antidepressants in malignancy patients. The results showed that the combination of CBT and

antidepressants was more cost-effective than administering antidepressants alone. However, it is important to note that brain tumors are a high risk factor for depression in malignant patients, and the choice of therapy needs to consider the patient's overall condition. These two studies provide important information about the treatment of depression in malignancy patients. The use of mirtazapine and a CBT-antidepressant combination can be an effective option to improve the patient's quality of life. However, it is important to consult a doctor to determine the most appropriate therapy according to the patient's individual condition and needs.

Table 3. Criteria of importance.

<b>Study</b>	<b>Outputs</b>	<b>Important research results</b>
Economos et al	Mirtazapine may decrease poly-symptomatology in patients with malignancy	Dose adjustments can be made according to the severity of the patient's symptoms or complaints, with an initial dose of 15mg/day and evaluated weekly.
Rabin et al	A combination of CBT and antidepressants improves the cost-effectiveness of services	Brain tumor is one of the predilections for high incidence of depression. There are various side effects of antidepressant administration.

Table 4 presents the study feasibility of two studies investigating the treatment of depression in malignancy patients. Assessment criteria include similar populations, the feasibility of the intervention, and whether the benefits outweigh the risks. Both studies (Economos et al and Rabin et al) both targeted malignant patients who experienced depression. This shows the similarity of the populations studied so that the study results can be compared and applied to a wider population (malignancy patients with depression). Both studies evaluated interventions that could be applied to patients with malignancies. Economos et al studied the use of mirtazapine, while Rabin et al studied the combination of CBT and antidepressants. Both interventions have the potential to be applied in clinical practice. Both studies show

that the interventions studied have potential benefits that outweigh the risks. Economos et al demonstrated the effectiveness of mirtazapine in reducing symptoms, while Rabin et al demonstrated the cost-effectiveness of a combination of CBT and antidepressants. Of course, a thorough evaluation of risks and benefits is still needed in clinical practice, but these two studies provide positive indications. Based on the assessment of the table, both studies (Economos et al and Rabin et al) had similar populations, applicable interventions, and potential benefits that outweighed the risks. This suggests that both studies are worthy of consideration and may contribute to the development of effective depression treatments in malignancy patients.

Table 4. Implementation criteria.

Study	Population similarity	Interventions can be made	Benefits outweigh disadvantages
Economos et al	+	+	+
Rabin et al	+	+	+

Table 5 compares two studies investigating the use of antidepressants to treat depression in malignancy patients. Economos et al used a mixed-methods randomized controlled clinical trial protocol, which is a robust research approach with a control group and randomization to assess the effectiveness of mirtazapine. Instead, Rabin et al used a systematic review, which analyzes existing research to provide an overview of antidepressant use in this population. Economos et al compared the effectiveness of mirtazapine with escitalopram, both of which are antidepressants. Rabin et al generally discussed the use of antidepressants without comparing specific types. Both studies focused on patients with malignancies and depression. However, Economos et al did not limit age, whereas Rabin et al focused on elderly patients. Economos et al showed promising results for mirtazapine in

improving quality of life, controlling symptoms, and reducing the risk of complications in polysymptomatic (experiencing many symptoms) patients. In contrast, Rabin et al highlighted the lack of guidelines for antidepressant therapy and the debate about its effectiveness in malignancy patients. However, they also mentioned the potential benefits of antidepressants in reducing the side effects of chemotherapy. These two studies provide valuable information about the use of antidepressants to treat depression in malignancy patients. Economos et al provided promising initial evidence for mirtazapine, while Rabin et al highlighted the need for further research and development of appropriate therapeutic guidelines. The combination of these two research approaches may help advance the treatment of depression in this vulnerable patient population.

Table 5. Study characteristics.

Articles	Study design	Intervention	Population	Outcome
Economos et al	Mixed-method Randomized control trial protocol	Administration of mirtazapim compared with escitalopram and evaluated for 56 days	Subjects over 18 years of age with malignancy and depression	Mirtazapine administration in polysymptomatology patients with malignancy can improve quality of life, control symptoms, and reduce the risk of other complications.
Rabin et al	<i>Systematic review</i>	Administration of antidepressants	Elderly patients with malignancy and depression	There are still no guidelines for antidepressant therapy in malignancy patients with depression. The efficacy of antidepressant use is still debated, but it may reduce the negative effects of chemotherapy, such as fatigue, sleep disturbances, weight loss, etc.

#### 4. Discussion

Fluoxetine is an antidepressant that has been used in treating various diseases, including its use in patients with malignancies. Fluoxetine is a selective serotonin reuptake inhibitor antidepressant that works by inhibiting presynaptic serotonin reuptake and increasing serotonin availability and activity at the synapse. Various other classes of antidepressants that can also be used include serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and antidepressant atypicals. So far, the use of antidepressants has been associated with depressive conditions in patients who are diagnosed based on DSM-V criteria which require five or more criteria that include depressed mood or loss of interest that is not due to grief and persists for more than 2 months and is associated with real functional impairment. However, over time depression can be indicated through various other screening methods such as The Hamilton Depression Rating Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), The Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS), each of which has its own diagnostic power.<sup>8</sup>

Cancer patients have a higher risk of becoming depressed than the general population, and the quality of survival rates among patients with cancer and comorbid anxiety or depression are significantly lower compared to the general population. However, clinically, depression in cancer patients tends to be under-recognized, as in this case the search for depressive symptoms such as anorexia, weight loss, fatigue, and insomnia is more often associated with somatic disease effects of cancer than depression. Palliative care in patients with malignancy is still not found in various national and international cancer management guidelines. Chochinov (1997) conducted a study of palliative care inpatients and found that a single question, "Are you feeling down, depressed or hopeless most of the time over the last 2 weeks?" identified patients with 100 percent sensitivity and specificity and a positive predictive value of one in screening palliative patients for depression.

Unfortunately, a follow-up study using a single mood question in another palliative care population showed a sensitivity of about 55 percent and specificity of 75 percent. Despite the difference in results, this suggests that screening for depression in palliative care patients is easy enough to do that it could become a must-do test, especially in patients with malignancy.<sup>9</sup>

Palliative care in patients with malignancy is important to improve the quality of life as well as the readiness of patients and families in dealing with their illness. Patients with malignancies can have long-term complications such as decreased appetite, weakness, nausea and vomiting and various other complaints. Economos (2022) mentioned that in patients with malignancy, various complications can occur or known as poly-symptomatology and assessed the use of mirtazapine as an antidepressant to overcome it. Mirtazapine has  $\alpha$ -2 adrenergic activity that increases noradrenergic and serotonergic central neurotransmitters, causing short-term effects on depression and other acute symptoms. In addition to this  $\alpha$ -2 adrenergic activity, mirtazapine also connects to 5HT<sub>3</sub> receptors and H<sub>1</sub> receptors. This activity is thought to influence the receptors on the effects on appetite, sleep disturbance, pruritus, emesis, shortness of breath and several other symptoms so as to increase the cost effectiveness of the hospital.<sup>9,10</sup>

Palliative care is a comprehensive approach that focuses on improving the quality of life of patients with life-threatening illnesses, including patients with malignancies. This approach aims to relieve the physical and emotional symptoms associated with the disease, as well as providing psychosocial and spiritual support to patients and their families. Symptoms of malignancy, such as pain, fatigue, nausea and vomiting, and anxiety, can significantly impact a patient's quality of life. Palliative care can help manage these symptoms and improve the patient's ability to carry out daily activities. Palliative care helps patients and their families understand and prepare for illness. This can help reduce anxiety and depression, as well as improve communication and shared decision-making. Palliative care provides

emotional and spiritual support for patients and their families. A palliative care team can help patients and their families deal with a variety of problems that arise during the course of the disease. Pain is a common symptom in malignancy patients and can significantly impact their quality of life. Palliative care can help manage pain in a variety of ways, such as medications, physical therapy, and acupuncture therapy. Apart from pain, palliative care can also help manage various other symptoms associated with malignancy, such as fatigue, nausea and vomiting, constipation, shortness of breath, and insomnia. Palliative care provides psychosocial support for patients and their families, which can help them to cope with stress, anxiety, depression, and other problems associated with the disease. Palliative care also provides spiritual support for patients and their families, which can help them to find meaning and purpose in their lives. Patients with malignant diseases can experience various long-term complications.<sup>11-14</sup>

Decreased appetite can lead to weight loss and weakness, which can worsen the patient's quality of life. Fatigue is a common symptom in malignancy patients and can significantly impact their ability to carry out daily activities. Nausea and vomiting can be caused by various factors, such as cancer treatment, drug side effects, and intestinal blockages. This can cause dehydration and malnutrition. Constipation is a common side effect of some cancer medications and can be made worse by lack of activity and dehydration. Shortness of breath can be caused by various factors, such as fluid buildup in the lungs (pleural effusion), airway obstruction, and anemia. Insomnia is a common sleep problem in malignancy patients and can be caused by a variety of factors, such as pain, anxiety, and medication side effects. Mirtazapine is an antidepressant that is classified as a tetracyclic antidepressant (TCA). This drug has high effectiveness in managing depression in malignancy patients. In addition to its effectiveness in managing depression, mirtazapine also has several other beneficial effects for malignancy patients. Mirtazapine can increase appetite through its antagonistic effect on histamine

H1 receptors. Mirtazapine can improve sleep quality through its agonist effect on alpha-2 adrenergic receptors. Mirtazapine can reduce nausea and vomiting through its antagonistic effect on 5-HT3 receptors. Mirtazapine can reduce itching through its antagonistic effect on histamine H1 receptors.<sup>15-17</sup>

Depression is a common complication in malignancy patients, with a prevalence reaching 60%. This results in reduced quality of life, worsening physical and emotional symptoms, and even shortening life expectancy. Palliative care, which focuses on improving the quality of life of patients with life-threatening illnesses, often includes the use of antidepressants to manage depression in malignancy patients. Although antidepressants have proven effective in reducing depressive symptoms in this population, their use does not involve considering side effects and choosing the right type of antidepressant. Patients at high risk of agitation, delirium, or falls require closer monitoring while taking antidepressants. Multiple studies have demonstrated the effectiveness of antidepressants in managing depression in malignancy patients. A meta-analysis involving 23 studies with 1,523 patients found that antidepressants significantly reduced depression scores with a mean effect size of -0.62. This suggests that antidepressants can help relieve symptoms of depression and improve the quality of life of malignancy patients. Several studies have also shown the benefits of antidepressants in improving the quality of life of malignant patients. In one study, patients who received antidepressants experienced improved physical, emotional, social, and spiritual functioning compared to those who did not receive antidepressants.<sup>17-19</sup>

The mechanism of action of antidepressants in malignant patients is not fully understood. It is thought that antidepressants work by increasing levels of certain neurotransmitters in the brain, such as serotonin, norepinephrine, and dopamine. These neurotransmitters play an important role in regulating mood, motivation, and cognition. In malignancy patients, levels of these neurotransmitters are often

disturbed due to the disease and its treatment. Antidepressants help restore the balance of these neurotransmitters, thereby alleviating the symptoms of depression. The choice of antidepressants for malignancy patients should be individualized based on the patient's profile, including age, type of malignancy, medical comorbidities, history of medication use, and patient preferences. The two classes of antidepressants most frequently used in malignancy patients are: 1. Tricyclic antidepressants (TCAs): TCAs such as amitriptyline and imipramine have been shown to be effective in managing depression in malignancy patients. However, TCAs have significant anticholinergic side effects, such as dry mouth, constipation, and blurred vision. 2. Selective serotonin reuptake inhibitors (SSRIs): SSRIs such as fluoxetine, citalopram, and sertraline are generally preferred over TCAs because they have a safer side effect profile. SSRIs rarely cause anticholinergic side effects and tend to be better tolerated by patients. Antidepressants can interact with other drugs the patient is taking, such as chemotherapy drugs or analgesics. It is important to consult a doctor or pharmacist to ensure the safety of using antidepressants together with other medications. The patient's liver and kidney function may affect the metabolism of antidepressants. Doctors need to adjust the dose of antidepressants based on the patient's organ function. If the patient has experienced side effects with a particular antidepressant in the past, it is best to avoid using that antidepressant. Although antidepressants are generally safe, some side effects can occur in malignant patients. Antidepressants may cause agitation, especially in patients with a history of anxiety or mania. Antidepressants may worsen delirium in vulnerable patients, such as elderly patients or patients with dementia. Antidepressants may increase the risk of falls, especially in elderly patients or patients with balance disorders. Nausea and vomiting are common side effects of antidepressants, especially early in treatment. Dizziness and drowsiness may occur in some patients, especially at the beginning of treatment. Constipation

is a common side effect of TCAs. Dry mouth is a common side effect of TCAs.<sup>18-20</sup>

## 5. Conclusion

Depression screening in palliative care patients with malignancy was conducted. Administration of antidepressants in palliative care patients with malignancy was shown to reduce poly-symptomatology and increase hospital cost-effectiveness.

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