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Pharmacotherapy of depression in palliative patients

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Abstract

Introduction: Depression often affects people suffering from serious illnesses, including oncological and palliative patients. It reduces their quality of life and worsens their prognosis. This is why it is so important to properly treat depression in palliative patients.

Material and Methods: The information provided was collected as a result of analysis of various articles and textbooks on development, diagnosis and treatment, as well as prevention of depression in terminally ill patients using Google Scholar and PubMed databases.

Results: The results show that the most common drug in therapy for palliative patients with depression are the sluggish serotonin reuptake inhibitors (SSRIs). SSRIs inhibit serotonin transporter reducing serotonin reuptake. This raises the level of neurotransmitter - serotonin - in the synaptic cleft. They are well tolerated and have fewer side effects than older antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors). Tricyclic antidepressants may relieve neuropathic pain and they are also beneficial for patients with insomnia. Mirtazapine in addition to antidepressant effects also causes increasing appetite,

reducing nausea and sedative effect. In cancer-diagnosed patients particular attention should be paid to side effects such as nausea and vomiting that may occur in patients undergoing radiotherapy and chemotherapy using SSRIs or TCAs. SSRI therapy have a good safety profile and also interacts less frequently, while atypical antipsychotics may reduce the discomforts of taking chemotherapy. An alternative method of treating depression is the use of psychostimulants such as methylphenidate. Another way to treat depression is psychotherapy.

Conclusions: There are several options for treating depression in palliative patients. It is important to pay attention to the side effects of prescribed medicines. Nevertheless, the best results are obtained by combining pharmacotherapy with psychotherapy.

Key words: depression, palliative patients, sluggish serotonin reuptake inhibitors, SSRI, tricyclic antidepressants, TCA

Introduction

Depression is a disease with development resulting in a destructive effect on the entire body. The mentioned illness can affect people of all ages. However, those who suffer from serious diseases, including oncological and palliative patients, are particularly at risk. Patients with cancer and depression more often suffer physical symptoms. They experience worsening quality of life and more often have suicidal thoughts or a desire for accelerated death than cancer patients who do not have depression [1, 3].

Depression is not only associated with reduced quality of life and patients with depression have a worse prognosis, which is linked to shorter life expectancy, increased disability, longer hospitalization episodes. According to different accounts from 3.7% to 58% of palliative care patients suffer depression. The mentioned disease is therefore a common problem in terminal care, but often remains undiagnosed. Additionally, almost 80% of psychological disorders in severely ill patients are skipped in treatment. That is why, the treatment of these patients is commonly based only on the alleviation of physical symptoms, and mental disorders are overlooked [3].

One of the most important drawbacks of depression therapy in palliative treatment is very difficult diagnosis of this disorder among these patients. Numerous somatic symptoms that are included in the diagnostic criteria for major depression are simultaneously known as indications of advanced disease. The diagnosis must therefore be focused on psychological symptoms (hopelessness, worthlessness, unjustified guilt). Moreover, similar symptoms make it difficult to distinguish between real depression and sadness that accompanies the right illness. On the other hand, clinicians should also consider the diagnosis of other diseases that may also show a decreased mood (for example: hypothyroidism or Parkinson's disease) [2, 3, 4].

The most common drug in therapy for palliative patients with depression are the sluggish serotonin reuptake inhibitors (SSRIs). SSRIs increase the level of neurotransmitter - serotonin - in the synaptic cleft, because it limits its reabsorption to the presynaptic cell. Unfortunately, the application of these drugs is also connected with numerous side effects. The attending physician should consider the harmful adverse effects of pharmacotherapy, adverse drug interactions and treatment-related problems that are inextricably linked to cancer therapy [1, 5].

Psychotherapy, another modality for depression treatment in palliative patients, has no risk of side effects or drug interactions. The mentioned therapy is particularly useful for older patients who are already taking medicines for hypertension, diabetes and many more. Additionally, psychosocial sins can cause or worsen depressive episodes, so it is important to eliminate them. Moreover it may be very advantageous to treat depression in combination therapy, that is, using psychotherapy and medication [1].

Connection between terminal phase of the disease and depression

Treatment of patients suffering from progressive diseases, with a limited life span, is often based on the treatment of physical symptoms. That is why psychiatric disorders are often overlooked and therefore 60-80% cases of depression are untreated. Some studies based on cancer patients reported prevalence of depression between 10 and 50%, the symptoms occur three times more often in the last 3 months before death than 1 year before [11].

Individual emotional and behavioral reactivity patterns play a role in the development of major depressive disorders. Depression is a common condition in people receiving palliative care and it is not only associated with reduced quality of live [6, 11]. Those patients have poorer prognosis, poor treatment adherence, increased disability, longer inpatient episodes and shorter life expectancy [6, 8].

In palliative care, a quick detection and diagnosis of depression is necessary to implement the appropriate treatment. Weakness and pain accompanying the disease, may cause difficulties and delay in diagnosis [6]. Similar symptoms make it difficult to distinguish depression from appropriate sadness in palliative care patients. There are also no diagnostic tests or biomarkers to facilitate the diagnosis [8]. Moreover, in order not to delay the implementation of appropriate treatment, clinicians should consider alternative diagnostics for other diseases that may be presented in a similar way, like dementia, hypothyroidism or Parkinson's disease. Therefore, it is important to carefully observe the palliative patient and be aware of non-verbal signs which may indicate depression, such as slumped posture, flat affect and reduced emotional reactivity [6].

The suffering of palliative patients due to depression also applies to their caregivers, which reduces their quality of life and the risk of accelerating death [8]. Some studies show that fewer depressive symptoms and longer terminal patients' survival are associated with palliative care services [7].

Family caregivers play an important role in palliative care, because at the end of life most patients in the terminal phase want to be cared for at home. In the case of palliative care patients at home, who are more tense and depressed at the end of their lives, the greater burden on family caregivers was observed. Care of a palliative patient, including psychological support and practical help, affects caregivers physically, socially and emotionally. They have to deal with fear or loss, they often lack sleep and therefore they feel tired and exhausted. Some studies showed that depression of the caregiver develops with the patient's depression and is more common in family caregivers than in a non-caregiving population [10]. It is likely that depression correlates with the severity of the disease, which causes depression symptoms to worsen as the disease progresses [9].

SSRI as the first-line drugs

Selective serotonin reuptake inhibitors (SSRIs) are usually chosen as first-line drugs in palliative care. It has been shown that in patients whose life expectancy is several months, these medicines are helpful and effective [12]. SSRIs include fluoxetine, fluvoxamine, setraline, paroxetine, citalopram and escitalopram. These drugs vary in strength and specificity of action on the serotonin transporter. Some of them, apart from inhibiting the serotonin transporter have additional pharmacological effects. They have different effects on hepatic enzyme CYP-450 which is important when the dosing and combination with other drugs [13, 14].

It can take up to 4 to 6 weeks before their full clinical effect is seen [17]. They are well tolerated and have fewer side effects than older antidepressants like tricyclic antidepressants and monoamine oxidase inhibitors [12]. The most common side effects of SSRIs are nausea, decreased appetite, weight loss, sleep disorders and sexual dysfunction. The most serious complication is the serotoninergic syndrome (disturbances of consciousness, psychomotor stimulation, myoclonus, hyperthermia, sweating, chills, diarrhea, convulsions). Symptoms from the heart and circulatory system are rare compared to tricyclic antidepressants [15, 17, 19].

Fluoxetine is characterized by a very long duration of action, metabolites can work up to 14 days. It has potent inhibitory effects on hepatic enzymes especially CYP2D6 and CYP3A4. The starting dose is 5-10 mg/day, the dose can be increased to 60 mg/day. May have an impact on weight loss. [12, 13, 16, 17]. Fluvoxamine is a strong inhibitor of serotonin re-uptake. It is also a sigma receptor agonist, it may have a sedative effect. The half-life is 15 hours. It inhibits enzymes CYP1A2 and CYP2C1 [16]. Paroxetine due to many interactions and stronger anticholinergic side effects is not recommended. There are also some reports of serious disorders liver function [13, 14, 16].

Sertraline, citalopram and escitalopram are characterized by a lower risk of enzyme inhibition. Sertraline is generally well tolerated. The half-life is 26 hours. The starting dose is 25 mg/day. Therapeutic daily dose is 50-200 mg [12, 14, 16]. Citalopram practically does not work on other transporters and receptors except for the serotoninergic transporter. It weakly inhibits CYP-450. It is used in doses 10-60 mg /day. Escitalopram is the (S)-stereoisomer of citalopram. Is the most selective of the available serotonin reuptake inhibitors. It has a faster duration of action than citalopram. The effectiveness of escitalopram in a dose 10-20 mg /day is comparable to a dose of 20-60 mg/day citalopram. This allows the recognition of escitalopram as a drug with a more favorable ratio of efficacy to tolerance [12, 18].

New antidepressants

There is no direct evidence from palliative care population indicating one group of antidepressants as the predominant one [23]. Based on several clinical trials, tricyclic antidepressants, mirtazapine and mianserin may replace SSRIs.

Meta-analysis of 25 studies shows that as well SSRIs as TCAs were more efficacious than placebo, but before nine weeks of therapy the effect was statistically significant only for TCAs [20]. The anticholinergic effect that occurs during the use of TCA may be troublesome for geriatric patients and may include: constipation, dry mouth, urinary retention, orthostatic hypotension and tachycardia [24].

There is a lack of reliable data presenting the quality-of-life outcomes of TCAs, mirtazapine or mianserin therapy. In the referenced meta-analysis only 4 studies reported these outcomes. Although in all cases great improvement in measures of life quality was observed, different scales to assess these outcomes make results not readily comparable. Aside of efficacy and acceptability, other issues, dependent on the specific patient may impact upon choice of a drug. Among the palliative care population sedation and increased appetite, which are caused by mirtazapine, often are beneficial. Tricyclic antidepressants, such as amitriptyline, may relieve neuropathic pain. If a patient is already on a low dose of amitriptyline for neuropathic pain, it may be beneficial to increase this dose, rather than introduce another antidepressant [20].

According to a study by Lauren Rayner and co. [21] mirtazapine, sertraline and citalopram are considered to be a reasonable selection for use in palliative care patients. During TCAs therapy there is a greater risk in overdose than SSRIs, but they are potential second-line medicines, especially for a specific group of patients. In addition to their neuropathic pain reducing effect, this antidepressants may also be beneficial for patients with insomnia. Additional mirtazapine effects, except increasing appetite, are: early onset of action, reducing nausea and sedative effect what make it a reasonable therapy to try in an individual who is distressed by insomnia and weight loss [21]. Another very important advantage is the fact, that this medication has few significant drug interactions [22].

Antidepressants in cancer-diagnosed patients

Depression in people diagnosed with cancer can be treated as a complication or a direct effect of fighting against life-threatening disease. It may result from many factors, among which attention should be paid to the fight against chronic pain, fear of death, chronic stress related to the disease, metabolic, endocrine and immunological changes resulting from the disease itself as well as its treatment [25, 26].

A systematic analysis of 9 studies assessing the effectiveness of antidepressant therapy in cancer-diagnosed patients conducted by F. Matcham et al. in 2015 proved the lack of conclusive evidence confirming the effectiveness of antidepressants compared to placebo during 6-12 weeks of therapy. In addition, based on the analysis, it has not been possible to indicate which of the groups of medications used in the treatment of depression accepted by the patients showed a more favorable profile of effectiveness and tolerance [25].

Therapy using commonly used drugs belonging to tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is only supported by limited evidence [27]. Particular attention should be paid to side effects such as nausea and vomiting that may occur in patients undergoing radiotherapy and chemotherapy using SSRIs or TCAs [28]. However, available studies indicate that SSRI therapy such as escitalopram, citalopram, and setraline have a good safety profile and also interact less frequently, while atypical antipsychotics such as quetiapine and olanzapine may reduce the discomforts of taking chemotherapy [28].

In the case of oncological patients, drugs interactions are particularly important because anti-cancer drugs are mostly characterized by a narrow therapeutic range, so any change in their concentration in the blood due to drug interactions may lead to therapeutic failure - for example, patients with breast cancer treated with tamoxifen. In this group, antidepressants that are also an inhibitor of CYP2D6 should be avoided because inhibition of this enzyme results in the decrease of concentration of endoxifene (the active metabolite of tamoxifen), thus increasing the risk of relapse [29, 30].

In the case of the patients with cancer or in terminal phase, anti-depression treatment is different. It is better to avoid typical antidepressants due to therapy based on regression of symptoms. In such cases, the alternative seems to be ketamine, also used in pain therapy, due to the NMDA receptor involved in the pathophysiology of chronic pain [26, 31]. However, to confirm the effectiveness of ketamine as an antidepressant in terminal cancer-diagnosed patients, multi-center randomized clinical trials are required.

Among other alternative treatments of depression, terminally ill patients also use psychostimulants such as methylphenidate. In 1996, Jonathan Olin and Prakash Masand carried out a study to analyze the history of the disease of oncological patients with depression treated with dextroamphetamine or methylphenidate. An improvement was noted after only 2 days of treatment, 83% of patients showed some improvement in depressive symptoms, while 73% of all patients showed a significant or moderate improvement. There were no differences in efficacy between the used drugs. Based on this study, conclusions were drawn that it is a safe and effective therapy. However, it should be noted that in the case of psychostimulants, the physiological tolerance increases rapidly, which in turn is associated with increasing the dose of the drug [26, 32].

Pharmacotherapy vs psychological therapy

The prevalence of depression is particularly high in elderly patients [33]. There are several ways of treating depression including antidepressant medications and different types of psychotherapy. The treatment may also combine psychotherapy and pharmacotherapy. They both have their advantages and disadvantages.

Pharmacotherapy may be based on a variety of drugs which mechanisms mainly impact the concentration of neurotransmitters in central nervous system. SSRIs are the first-line treatment and the most often choice [34]. In the past, older classes of antidepressants were used, such as: tricyclic antidepressants and monoamine oxidase inhibitors. The usage of SSRIs is constantly increasing and older agents are replaced by them [34]. Studies have proven that SSRIs are as effective as older antidepressants with the only exception of amitriptyline which has stronger effect. Moreover, they are more tolerable in comparison to TCAs [37]. What is most important, SSRIs cause less antimuscarinic side effects but more gastrointestinal ones. Newer agents such as SSRIs cause fewer side effects in comparison to older ones. Despite many advantages pharmacotherapy may fail in patients who are not willing to undergo such treatment or are susceptible to side effects or interactions between drugs [34].

There are many psychotherapies of depression and the most common of them is cognitive behaviour therapy. Psychotherapy has its advantages – there is no risk of side effects, or drug-drug interactions [34]. It is important for older, geriatric patients who suffer from other conditions, for instance diabetes mellitus [35], other general diseases and are prone to drug interactions. Considering that psychosocial stressors may cause or worsen depressive episodes, psychotherapy may help develop abilities of interpersonal interactions, dealing with stressors, and improve social supports [34]. The disadvantage of psychotherapy alone may be its late response. Moreover, patients may meet many structural obstacles – higher costs of psychotherapeutic treatments, lack of qualified therapists, transportation barriers [36].

Metaanalysis from 2017 showed that pharmacotherapy and psychotherapy have equal effects – that is the improvement of functioning and better quality of life [37]. The combination of pharmacotherapy and psychotherapy gives significant effects in comparison to each method of treatment alone. Nevertheless, each therapy alone is also efficacious for treating depression [37]. Another study indicated that the result of treatment may vary in a significant way depending on the choice of antidepressant or psychotherapy [38].

Discussion

In the first part of results there was described connection between terminal phase of the disease and depression. It is worth mentioning that the occurrence of depression in the group of end-of-life patients is estimated at approximately 20 to over 50%, moreover it especially affects patients with advanced metastatic processes also the ones with neck, head and pancreatic tumors [39, 40]. According to the statistics besides cancers the most common somatic diseases accompanying depression are: Parkinson's disease (51%), pain syndromes (50%), brain stroke (23-35%), Alzheimer's disease (11%) [41].

Furthermore, there was a part about SSRI (selective serotonin reuptake inhibitor) used as the first-line drugs in depression in palliative care. Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitaloporam were mentioned in this part of work. In section about antidepressants in cancer-diagnosed patients an author mentioned about TCAs (tricyclic antidepressants). Additionally, in neuropathic pain associated with tumors some antidepressants for example duloxetine, venflaxine and tricyclic antidepressants are commonly used. All of the mentioned drugs in last sentenced are classified as SNRIs (serotonin-norepinephrine reuptake inhibitors). In the treatment of neuropathic pain daily dose 100 mg is not exceeded, moreover in the group of patients older than 65 years daily dose greater than 75 mg is not recommended [42, 43].

Last but not least, beside dementia, depression is the most common mental disorder in elder people. According to various authors, the incidence of depression among people over 65 years life is 2.4-11.3%, while psychotic depression is 1-3,7% of the elderly population [44, 45]. It is often unrecognized and untreated disorder, and its symptoms are treated as part of the natural aging process or the consequence of somatic illness. Patients with depression are frequently terminally ill. As proven, mortality in the elderly population with depression is greater than in the population of people without depression [46].

Conclusions

Depression is a common disease that can affect everyone, but palliative patients at more at risk. Because of chronic disease that cause pain, sleepless nights, days spend at a hospital and a lack of will to live those patients often develop depression. Unfortunately, psychological issues are underestimated and only physical symptoms are treated.

Depression can be hard to diagnose in palliative patients, but it should always be taken into consideration. They often suffer from malignant cancer, their life is expected to be shorter and its quality is lower because of the disability and constant negative thoughts. It is important to think about other diseases with similar symptoms like hypothyroidism or neurological issues. Thorough observation and talking to the patient is crucial. What is interesting is that caregivers also have higher risk of depression because of their work with palliative patients.

The basic of pharmacotherapy are SSRI, like sertraline or fluoxetine. They are effective, safe and so commonly used as first-line drugs. Like every medicine they can cause side effects, like nausea or insomnia, though they are believed to be much less harmful to the cardiovascular system than tricyclic antidepressants. Doctors should remember about serotoninergic syndrome when prescribing other drugs to the patient taking SSRI that may affect serotonine levels.

TCA can be more effective in palliative patients than SSRI, although they lead to anticholinergic side effects that can negatively influence elderly ones so the dose should be controlled. Amitryptyline can be good in reducing neuropathic pain. Different kind of drug – mirtazapine- can be helpful in insomnia and lack of appetite cases. New antidepressants can be useful when SSRI do not give expected effects.

Depression often appears in cancer-diagnosed patients but is underrated because doctors do not want to focus on it. Studies did not prove enough efficiency of SSRI or TCA in those group of people, but they may be helpful in some cases. Attention should be paid to interactions between antidepressants and ongoing treatment to not cause negative effects. Atypical antipsychotics like ketamine seem to have a potential, but more research is needed. Methylphenidate can also be effective in oncological patients with depression.

Pharmacotherapy can be efficient in treating depression in terminally ill patients, but there is always a risk of side effects and interactions. Psychotherapy is completely safe and resultful but more time is needed for response. Cognitive behavior therapy is the most common and helps patients deal with their negative thoughts. Medication and psychotherapy used in combination give significant results.

Treatment of depression in palliative patients is an essential but overlooked issue. It is still being investigated and more research about new antidepressants and psychological therapies to improve terminally ill patients' quality of life is made to develop the subject.

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