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New treatment strategies for bipolar disorder in the elderly

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Abstract

Introduction and objective: The purpose of this paper is to systematically review articles and new research in the context of bipolar geriatric patients.

Materials and methods: PubMed searches were completed using the key terms bipolar disorder, bipolar elderly, bipolar depression, bipolar elderly treatment and review articles. In addition, references in these resources were searched. Search dates: 2010 to 2022.

Description of the state of knowledge: Mental disorders in the context of the elderly concern all depressive disorders. A problem with other disorders such as bipolar disorder is also increasingly recognized. In the elderly, it is quite rare in the general cross-section of society, but it may have a higher percentage, e.g. in nursing homes and care institutions. This review article shows both the difference and the similarities in the course of this disease in older and younger patients. The most important and common aspect for both age groups is psychotherapy with parallel pharmacological treatment. The greatest difficulty in pharmacotherapy in the elderly is polypharmacy and numerous drug interactions, as well as different pharmacodynamics and pharmacokinetics of the drugs used compared to younger patients. Attention should also be paid to the differentiation of bipolar disorder from different types of dementia and other cognitive disorders. Therefore, one should strive to carefully assess the patient's need for a given treatment, establish appropriate periodic monitoring of treatment, and assess the risk of taking or not intervening. This article also aims to review new research and drugs that seem promising, while the individualized and interdisciplinary approach to a geriatric patient with BD is the most important finding of this review.

Summary: Bipolar disorder in older people, compared to the younger population, should be treated pharmacologically in combination with psychotherapy. The elderly patient population requires a multidisciplinary approach due to the number of drugs used in a large number of diseases.

Key words: Bipolar disorder, depression, mania, elderly, treatment, psychotherapy, drugs

Introduction

Bipolar disorder is a mood disorder characterized by episodes of elevated mood, depression, and euthymia [1,2]. Elderly people with bipolar disorder are more likely to coexist with cognitive dysfunction [3]. As you age, your risk of developing bipolar disorder for the first time decreases. The prevalence in people over 65 is from 0.05 to 0.5% compared to 8.9% in people between 18 and 24 years of age. [2] Currently, people with bipolar disorder in the elderly account for 25% of all patients. Due to the aging of the population, it is estimated that this number will increase to 50% in the next 10 years. [3] The clinical picture of the disease in elderly patients is different from that in younger patients. [1] It should also be remembered that due to the multiple morbidity and the amount of medications taken, it is difficult to predict patients' response to treatment according to standard regimens, and therefore special care should be taken when treating patients with bipolar disorder in the elderly [2].

Material and methods

An unsystematic review of the scientific literature was carried out according to the following keywords: bipolar disorder, elderly people, bipolar elderly, bipolar depression, bipolar elderly treatment and review articles. The PubMed database was searched and 31 articles published up to 2022 were analyzed. Review, quantitative and qualitative studies were included in the analysis. The criteria for qualifying the records for the review were: the title, the content of the abstract and the topic related to the treatment of bipolar disorder in the elderly.

The course of the disease in the elderly

The cut-off age between old adult bipolar disorder (OABD) and adult- age bipolar disorder varies, but it appears that ≥ 60 years of age is usually accepted. Taking into account the onset of the disease two main groups of elderly patients with bipolar disorder can be distinguished: LOBD- "late onset" and EOBD- "early onset" patients with a longer clinical history of this disorder. Numerous differences between those groups are described. Bipolar disorder type II is observed more frequently in LOBD than EOBD patients. Patients with an early- onset disease are more likely to have a positive family clinical history, and in later- onset patients, bipolar disorder more often coexists with somatic disorders, cognitive and neurological impairment [4]. EOBD is more closely related to genetic predisposition and seems to have a worse prognosis than LOBD [11]. Due to the sensitivity to certain drugs, patients with LOBD are at risk of developing secondary mania, i.e. a manic episode caused by a somatic, metabolic or pharmacological factors. Euthymic patients with LOBD show a greater severity of cognitive impairment than euthymic patients with EOBD, and therefore it is believed that they may be more predisposed to the development of dementia [4]. Patients with EOBD more often show severe, psychotic symptoms in manic episodes. Rapid cycling, substance abuse and anxiety are also more common in this group [10]. Irritable behaviours, resistance to treatment and alcohol use are more characteristic in LOBD [4].

In elderly patients, compared to younger people with bipolar disorder, the clinical picture is dominated by depression, while psychotic episodes are less frequent. In some patients with OABD, the disease continues to progress and the risk of relapse increases with each episode of mood disorder. However generally the recurrence leading to hospitalization is less common in older age [5]. Some of the conducted studies have shown that with each subsequent episode, the time between episodes of the disease decreased [7].

In a randomized study of 184 participants with bipolar disorder of different age groups, the severity of psychiatric symptoms, self-stigma and functional status were assessed. Elderly patients showed a lower incidence of coexistence of anxiety disorders, depressive symptoms, substance abuse and self- stigma than younger patients. The degree of cooperation with clinicians and compliance with their recommendations turned out to be similar in older and younger subjects [6].

BP coexists with somatic diseases in as many as 20-80% of patients, this problem particularly affects the elderly. Most often, bipolar disorder is accompanied by metabolic diseases as well as respiratory and cardiovascular disorders. Psychiatric patients, especially the elderly, constitute a group at risk of developing somatic diseases, including liver diseases. This phenomenon contributes to the development of the problem of polypharmacy and, consequently, the difficulties in conducting effective therapy of bipolar disorder. Due to these factors, elderly patients with BP require a multidisciplinary approach and periodic assessment of used medications [9]. In psychopharmacological treatment, it is important to take into account changes in pharmacokinetics and pharmacodynamics related to age [7].

The risk of suicide is about 20 times higher in people with BD than in general population. Bipolar disorder is associated with the highest suicide rates out of other psychiatric disorders [8]. Among patients with bipolar disorder, those under the age of 35 have the highest risk of committing suicide [5]. It has been found that in the elderly, suicidal thoughts are often preceded by sleep disturbances, depressive symptoms, impairment of cognitive function and the discontinuation of treatment by the patient. The observations indicate that there is an

inverse correlation between the duration of the disease and suicidal ideation, and in younger patients with BD, the early age of onset is considered a risk factor for suicide. This may be due to the fact that older patients have accepted their diagnosis over time and developed effective ways to deal with its consequences [8].

New treatment programs

The multitude of forms that bipolar disorder can take makes the treatment very specific. The guidelines have changed over the years and do not yet provide a uniform answer to the question of what drug will be the best for the treatment of bipolar disorder [15]. Lithium, anticonvulsants, antipsychotics, antidepressants and benzodiazepines as well as electroconvulsive therapy have been shown to be effective [13].

The mainstay of treatment of bipolar disorder are mood stabilizers, otherwise known as mood stabilizing drugs. It is a heterogeneous group of substances with a diverse chemical structure, mechanism of action, properties and profile of side effects. Although the discovery of lithium by John Cade in 1949 was a milestone in the treatment of bipolar disorder, the mechanism of action is still not fully understood [12].

The use of lithium (usually at a dose of 0.75–1 g of lithium carbonate per day) allows some patients to achieve exceptionally good response and long-term remission. Thus, lithium therapy is most often recommended when there is a balance between the poles of the disease [13,4]. In the studies, lithium delayed the time to intervention for any mania or hypomania episode. Moreover, the purposefulness of using lithium is also supported by the evidence that lithium reduces the risk of suicide and the risk of cognitive deterioration [13].

Classic mood stabilizers include valproic acid and carbamazepine. Valproates increase the levels of gamma-aminobutyric acid (GABA), the brain's main inhibitory neurotransmitter. Thanks to this property, they can be used in mixed states and in diseases with the course of "rapid cycling" [12,15]. Valproic acid is often used in the elderly. Fairly good tolerance is one of the reasons for the frequent use of the substance. Valproic acid is not metabolized by the cytochrome C system, but by glucuronidation and β -oxidation, which is beneficial in elderly patients due to a lower risk of drug interactions [7]. Carbamazepine blocks voltage-gated sodium channels, so it inhibits the release of glutamic acid, the main excitatory neurotransmitter in the central nervous system. In addition to stabilizing the mood, it effectively reduces the level of irritability and impulsiveness. Carbamazepine may be beneficial for people with non-classical or atypical features of bipolar disorder [13].

Second-generation drugs include lamotrigine and second-generation antipsychotics. It is believed that lamotrigine has a marked antidepressant potential in bipolar disorder, while its effect on manic symptoms is slight [12]. There is ample evidence that lamotrigine is effective in preventing relapses, especially depressive ones, in stabilized patients. Some studies suggest efficacy in acute bipolar depression, but the results are inconsistent. There is little evidence to support its efficacy in acute mania, unipolar depression or rapidly recurrent bipolar disorder, and therefore it has a somewhat limited spectrum of action [19]. In various studies, lamotrigine shortened the time to relapse of a depressive episode [7]. Second-generation antipsychotic drugs normalize and stabilize the mood, which means that in addition to preventing disease relapses, they have an anti-manic effect and reduce the severity of depressive symptoms in bipolar disorder, because in addition to antagonizing D2 receptors, they also block serotonin receptors [12]. Moreover, antipsychotic drugs have a beneficial effect on motor restlessness, irritability or agitation [7]. Antipsychotic drugs are effective in the acute treatment of mania. However, it is important to bear in mind that their effectiveness in treating depression is variable. So far, the clearest evidence in this regard concerns quetiapine [16]. Among the new drugs worth noting is cariprazine, which is a partial dopamine D2 / D3 agonist, preferring D3 receptors. It is classified as an antipsychotic drug. Cariprazine at a dose of 3-12 mg / day is effective in the treatment of acute manic and mixed episodes. In contrast, in the case of depression in the course of bipolar disorder, the efficacy of cariprazine seems to be effective in monotherapy at a dose of 1.5-3 mg / day. Cariprazine gives high hopes because it is well tolerated by patients in both manic and depressive episodes [18].

Despite their widespread use, antidepressants still leave uncertainty and controversy regarding their use in the treatment of depressive episodes in bipolar disorder [16]. Antidepressants may bring short-term benefits in patients with bipolar disorder, but may increase the risk of mania in the long term [7].

Among people with bipolar disorder, electroconvulsive therapy remains the ultimate treatment when there is a need to quickly improve their health or even save lives. Electroconvulsive therapy is especially effective in people with bipolar disorder who are at immediate risk of suicide or homicide. It is also recommended in a catatonic or treatment-resistant psychotic state. It has been reported that this therapy is effective in about 80% of BD cases [13].

Recently, the importance of inflammation, oxidative stress and mitochondrial dysfunction in the progression of bipolar disorder has been recognized. However, a small study with a mitochondrial modulator and an antioxidant substance, coenzyme Q10, in depressed geriatric patients with BD showed no significant reduction [4]. New measures targeting alternative neurotransmitter pathways and inflammatory processes appear to be promising potential treatment options for bipolar depression in the future. Thus, inter alia, lurasidone and cariprazine suggest that patients' symptoms can be effectively treated without endangering their physical health [14].

Research shows a positive effect of psychotherapy on the condition of patients with bipolar disorder. The aim is to improve the ability to cope with stress, pay attention to biological rhythms and improve compliance with medical recommendations [17]. An additional benefit is the improvement of social relations, which is equally important for young patients and seniors. Cognitive behavioral therapy includes interventions in the case of relapses, cognitive interventions, behavioral methods in remission, interventions in the manic or hypomanic period [7,20].

Table 1.

Phase	Recommended treatment phase according to BAP (British Association for Psychopharmacology of 2016)	NICE recommendations (National Institute for Health and Clinical Excellence of 2014)
MANIA	DA antagonists, valproic acid, lithium	Olanzapine, risperidone, quetiapine, haloperidol
DEPRESSION	Lurazidone + lamotrigine - high degree of recommendation olanzapine + fluoxetine - average degree of recommendation	olanzapine + fluoxetine, lithium, valproate, lamotrigine, quetiapine, olanzapine
SUPPORTIVE CARE	lithium (mania, depression, suicide threat), partial antagonists DA agonists, valproate (mainly mania), lamotrigine (mainly depressions), psychoeducation	Lithium + valproate, quetiapine, olanzapine, or drugs that have managed the acute phase

Side effects of treatment

With age, there are changes in the pharmacokinetics and pharmacodynamics of drugs, which make treatment-related side effects more severe in older patients. Moreover, polypharmacy is a common phenomenon in the geriatric population, which in turn increases the risk of undesirable drug interactions.

As a result of the described changes, it is recommended that the target lithium level in elderly patients should be lower than in younger patients, ranging from 0.4 to 0.7 mEq/L [13,21]. Particular care should be taken when prescribing lithium to patients who are simultaneously taking loop and thiazide diuretics, calcium antagonists, ACEIs, ARBs or NSAIDs, because these drugs may intensify the toxic effects of lithium [13,4,22]. The initiation of lithium therapy should be preceded by an assessment of kidney, thyroid and heart function. Lithium is almost completely excreted by the kidneys, therefore its use is not recommended in patients with CrCl below 30 ml/min/1.73 m², and in patients with CrCl between 30 and 80 ml/min/1.73 m², caution should be exercised, starting with a low dose and gradually increasing it [22]. A study conducted in 2017 showed that the use of lithium in patients over 65 years of age is associated with an almost two-fold higher risk of developing chronic kidney disease [23]. For this reason, it is recommended that renal function is assessed every 3 months [22]. Lithium inhibits the synthesis and release of thyroid hormones, thus leading to hypothyroidism. Increased TSH levels promote thyrocyte proliferation and goiter formation. The appearance of hypothyroidism is an indication for levothyroxine supplementation, but it is not an absolute contraindication to the continuation of lithium treatment [24]. Diabetes insipidus is a common side effect of long-term lithium therapy, especially in elderly patients. It is characterized by polydipsia, polyuria, hypernatremia and low urine osmolality (≤ 300 mOsm/kg). Studies have shown that in patients over 65 years of age the symptoms may be non-specific or may not appear at all, therefore regular screening in this direction is recommended [25]. Due to the similarity of lithium to cations such as sodium and potassium, it influences the membrane potential of cardiomyocytes, thus leading to arrhythmias [24]. Other side effects during lithium therapy include gastrointestinal complaints, weight gain, leukocytosis, as well as skin changes in the form of acne, eczema, psoriasis or changes in the mucosa [22,26]. In older patients, neurological disorders such as cognitive dysfunctions, tremors, headaches and dizziness, delirium, memory problems occur relatively frequently, less often convulsions or coma may appear. In extreme cases, with serum lithium concentration above 3.5 mEq/L, death may occur [22,25].

Carbamazepine is a potent inducer of the hepatic enzymes CYP3A4 and CYP2D6. This results in numerous interactions with drugs metabolized by cytochrome P450, which include some anticonvulsants, antipsychotics and antidepressants [7]. Treatment with carbamazepine, especially in elderly patients, is associated with an increased risk of side effects from the nervous system, such as headache, dizziness, oculomotor disturbances, confusion and agitation. Rash, edema, hyponatremia and leukopenia may also appear, and in extreme cases, bone marrow suppression may occur in the form of agranulocytosis or aplastic anemia [26,7]. Better tolerated anticonvulsants are valproic acid and lamotrigine. A side effect of valproic acid use is thrombocytopenia, gastrointestinal complaints, excessive weight gain and gait disturbances [24,7]. A rare but potentially life-threatening complication may be hyperammonaemic encephalopathy, in the course of which an

increased concentration of ammonia in the blood, vomiting and a decrease in the Glasgow Scale score are observed [24,26]. Treatment with lamotrigine may cause skin lesions in the form of rashes or, less frequently, the appearance of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [22,24,26]. For this reason, it is necessary to initiate low-dose lamotrigine treatment with its gradual increase, especially in patients with renal insufficiency [22,14].

The use of atypical antipsychotics increases the risk of developing metabolic disorders in the form of weight gain, dyslipidemia, hyperglycemia, and death due to cardiovascular diseases [4,14]. Based on the studies, it was found that olanzapine and clozapine had the worst metabolic profile, while aripiprazole had the lowest risk of adverse metabolic changes [24,26]. When using atypical neuroleptics, extrapyramidal symptoms, such as tremors, parkinsonism, dystonias, akathisia or tardive dyskinesia are much less common compared to classic antipsychotics [22,24]. A rare but potentially fatal complication is neuroleptic malignant syndrome (NMS). The risk of its development is greatest during treatment initiation or when changing the dose, especially in elderly patients with polypharmacy and polypharmacy [26]. Particular caution should be exercised when using neuroleptics in patients with dementia, because an increased risk of death has been observed in this group of patients [7]. Regular ECG monitoring is also recommended during treatment, as these drugs may prolong the QT interval [24].

Complications of untreated bipolar disorder

Patients with BD show less willingness to cooperate with a physician than, for example, patients with schizophrenia, especially in states of mania or hypomania. This is related to more frequent questioning of the proposed therapy and discontinuation of drugs. [27]

A significant number of patients with bipolar disorder use drugs or alcohol instead of pharmacotherapy. Both depressed mood in depressive states and substance abuse are significantly associated with episodes of suicide attempts [28].

In people with untreated bipolar disorder, the risk of suicide is approximately six times higher than in those taking drug therapy. The suicide rate in BD is approximately 10-30 times higher than in the general population. This applies to both those undertaking treatment and those untreated. Unfortunately, most people deciding to attempt suicide belong to the untreated subgroup. The ratio of suicide attempts to suicides is also unfavorable, due to the fact that people struggling with BD are more effective in their actions. They undertake more radical and effective actions leading to death. Discontinuation of treatment largely contributes to the aggravation of mood disorders, which in turn is associated with more frequent occurrence of suicidal thoughts. [29]

An exacerbation of the disease may also occur in pregnant women who have stopped taking their medications. A study by Viguera et al. showed that 47% (16 out of 34) of women reported that pregnancy had a positive effect on the course of the disease and well-being, while 53% (18 out of 34) reported that pregnancy had a negative effect on their mood. [29]

Some studies support the effectiveness of maintenance treatment in pregnant women in stabilizing the mood, and the benefits for the mother are greater than the risk of a suicide attempt after stopping the medication. After abrupt discontinuation of drugs during pregnancy, the risk of depressive recurrence is significantly increased. [30]

Apart from the obvious risks of suicide attempts, other aspects of the lack of therapy should be mentioned - it is associated with a significant reduction in psychosocial functioning and changes in the functioning of the family. Mood disorders in episodes of mania, hypomania and depression can negatively affect relationships between people, sometimes even making it impossible to form relationships. In adult family life, the emotional instability of a partner or parent may have a destructive effect on the entire family, causing negative emotions towards the patient, repression, and, as a result, also a great feeling of guilt. Therefore, during therapy, both the patient and his family should be taken care of. [31]

Moreover, patients in manic episodes are more prone to risky sexual behavior. It is associated with a higher risk of contracting a sexually transmitted disease. Research by Ribeiro et. al indicated a higher incidence of HIV infection in patients suffering from bipolar disorder than in the general population. This may prove that bipolar disorder may be a risk factor for HIV infection [14].

Summary

The topic of mental disorders in the elderly is usually addressed in the context of depressive disorders, but the increasing prevalence of other mental disorders in the older age group, prompts an in-depth analysis of causes and treatment. The proportion of older people with BD is steadily increasing, as is the comorbidity and associated polypharmacy. [2, 3] In our review of the literature, we focused on assessing the nature of BD in elderly patients compared to younger patients and on analysing the appropriate treatment of the disease, taking into account the limitations of age, comorbidity and polypharmacy. However, it would be pertinent to mention that one of the most significant things seen in the available literature is the provision of psychotherapy in parallel to pharmacological treatment. [17] The benefits of such treatment are significant, particularly among older people, who are more likely than younger people to experience reduced psychosocial functioning and social

withdrawal. [31] Additionally, psychotherapy can help reduce the need for pharmacological treatment. [17] In the geriatric population, treatment increasingly requires a multidisciplinary approach, due to the use of many different drugs and age-related changes in pharmacokinetics and pharmacodynamics, which are associated with an increased incidence of adverse effects. [7] Careful assessment of the patient's need for a given treatment, establishment of appropriate periodic control of treatment, and assessment of the risk of taking or not taking an intervention should therefore be sought. More frequent relapses, increased risk of suicide attempts, social withdrawal, impaired family functioning and risky behaviour during episodes of mania and hypomania are among the main complications of no treatment or inadequate treatment of BD. [14, 29, 31] On the other hand, pharmacological treatment of BD in elderly patients is associated with a high risk of adverse effects from the drugs used. When treated with one of the most commonly used drugs, lithium, in geriatric patients, the risk of developing chronic kidney disease, diabetes, cardiac arrhythmias, neurological disorders and other somatic complaints is significantly increased. [22-26] Other drugs also have an increased risk of side effects due to the age of the patient. It is worth mentioning that a significant proportion of the drugs used to treat BD, may cause metabolic disorders, which in patients of the geriatric population, often characterised by multimorbidity, including overweight or obesity, dyslipidaemia and cardiovascular disease, is a significant risk factor for deterioration or death. [4] Among the new drugs under research, lurasidone and cariprazine are promising due to their lower exposure to side effects. [14]

In our observations, we would like to emphasise the important role of psychotherapy in the elderly, the need for a multidisciplinary approach in the treatment of BD, a detailed assessment of the risk of side effects of the most commonly used drugs, and an assessment of the risk of non-adherence to therapy, whether for reasons of inadequate treatment or patient non-adherence. An important role of the clinician is to work appropriately with the patient, paying attention to the patient's needs, capabilities and cooperation.

To conclude our review, we highlight the limited number of BD studies in the elderly and the need to improve this knowledge, given the ageing population and the increasing prevalence of BD in the geriatric population. More research is also needed on the adverse effects of BD treatment in the elderly. However, we consider the need for an individualised and interdisciplinary approach to the geriatric patient with BD as the most important conclusion of our study.

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