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Advances in Mood Disorder Pharmacotherapy: Evaluating New Antipsychotics and Mood Stabilizers for Bipolar Disorder and Schizophrenia

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This article provides a narrative review of recent developments in mood-stabilizing drugs, considering their mechanism of action, efficacy, safety, and therapeutic potential in the treatment of mood disorders, particularly bipolar disorder and schizophrenia. The review focuses on the mechanism and clinical aspects of second-generation antipsychotic medications; aripiprazole, classified as a third-generation antipsychotic medication; lamotrigine, as a representative of antiepileptic drugs; and lurasidone, a novel second-generation antipsychotic medication. Moreover, the article refers to one of the newest and most highly effective normothymic drugs, cariprazine. The potential of new mood stabilizer candidates lumateperone and brexpiprazole is also presented. Covered topics include the clinical efficacy of new drugs in reducing manic and depressive symptoms during acute episodes, as well as their role in preventing relapse. In addition, we analyzed the incidence of adverse effects of each drug. Many of the new drugs have strong potential to be beneficial and safe in cases of many comorbidities, as they do not cause many adverse effects and do not require high doses of use. The results underscore the importance of ongoing and future research to better understand the action and efficacy of these mood stabilizers and their implications in the treatment of mood disorders, aiming to achieve euthymia and improve the quality of life of affected patients.

In this article, we aim to review current drug treatments for the management of mood disorders, including bipolar disorder and schizophrenia.

Keywords: Affective Disorders, Psychotic • Antipsychotic Agents • Aripiprazole • Brexpiprazole • Lurasidone Hydrochloride • Risperidone

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Introduction

Mood stabilizers are mostly used as maintenance therapy to avoid relapse or as an acute phase treatment for bipolar illness [1]. Mood stabilizers are also frequently recommended in therapies for many other disorders, such as schizophrenia, schizotypal illness, and delusional disorders [2]. First-generation mood stabilizers are medications primarily used to manage mood disorders, such as bipolar disorder [3]. Unlike conventional antipsychotics, these drugs are designed to stabilize mood fluctuations and prevent manic and depressive episodes [1].

Mood disorders (affective disorders) are psychiatric disabilities in which there are long-term changes in mood, emotions that cause impaired social, emotional functioning of the individual [4]. These conditions are often associated with a high risk of suicide [5]. Affective disorders according to the International Classification of Mental and Behavioral Disorders include manic episodes, depressive episodes, bipolar affective disorder, recurrent depressive disorder, and persistent mood disorders [5]. During bipolar affective disorder, episodes of mania (bipolar type I) or hypomania (bipolar type II) and depressive episodes occur one after the other or are preceded by episodes of euthymia (normal mood episodes) [6]. In the United States, the prevalence of bipolar affective disorder is about 4% [6,7]. The treatment includes mood stabilizers, such as lithium, valproate, and carbamazepine, atypical antipsychotics, such as quetiapine and olanzapine, conventional antidepressants, such as selective serotonin reuptake inhibitors and bupropion, and psychotherapy [8].

Schizophrenia is a mental disorder with its characteristic positive symptoms including hallucinations and delusions, negative symptoms including abulia, allogia, and anhedonia, and cognitive dysfunction including memory deficits [9]. Negative symptoms are the dominant ones (affecting as many as 60% of affected patients) and are the symptoms that most impair daily functioning [10]. The prevalence of schizophrenia is about 0.3% to 0.7% [7]. The primary treatment for schizophrenia is first-, second- and third-generation antipsychotic drugs [11]. Despite their high efficacy, the many adverse effects of these drugs prompt further research into the still incompletely understood pathophysiology of schizophrenia and the search for new and better therapies for the condition [7].

Lithium is a prominent example of a first-generation mood stabilizer, and its effectiveness in managing bipolar disorder has been well-established [3]. While lithium can be beneficial, it can cause adverse reactions and requires careful monitoring to maintain therapeutic levels in the blood [1,3,12]. Additionally, it can induce certain adverse effects, such as weight gain, hand tremors, or kidney problems [1]. Other examples of first-generation mood stabilizers are valproate and carbamazepine, which also require constant monitoring of blood levels due to potential adverse effects [2].

Rybakowski has articulated a definition for mood stabilizers that includes the impact of the drug on bipolar affective disorder across acute and prolonged treatment periods [13]. The definition includes 3 criteria: demonstrating therapeutic efficacy on manic and/or depressive symptoms during acute episodes, preventing the recurrence of manic and/or depressive episodes, and ensuring that the drug neither induces nor exacerbates manic or depressive episodes or mixed states [13,14]. In addition, the medication should be used as monotherapy, and the duration of its administration should be at least 1 year [13,14]. According to the requirement that the medication must not worsen manic or depressive episodes, mood stabilizers do not include conventional antipsychotic drugs, which by their action can induce a depressive state and exacerbate recurrences, and antidepressants, which have a pro-maniacal effect [2,13]. In addition, other atypical antipsychotics do not meet the criterion for monotherapy and the time criterion [14].

Second-generation antipsychotic drugs, which include the innovative antiepileptic medicine lamotrigine and atypical antipsychotic drugs, such as clozapine, olanzapine, quetiapine, aripiprazole, and risperidone, on the other hand, are devoid of pro-depressant activity, and some of these drugs can even have antidepressant effects [14]. In addition, lurasidone is a newly introduced potential member of this class of antipsychotics, categorized as a third-generation antipsychotic [15].

In this article, we aim to review current drug treatments for the management of mood disorders, including bipolar disorder and schizophrenia.

Clozapine

Clozapine belongs to the group of atypical antipsychotics. It exhibits a mild blocking impact on the dopamine D1, D2, D3, and D5 receptors, while demonstrating a pronounced influence on the D4 receptor [16]. Furthermore, it displays robust binding to serotonin 5-HT2 and α1 receptors, along with affinity for muscarinic M and histamine H1 receptors. Clozapine is widely used in the treatment of psychiatric diseases [17]. It is used, among others, in psychosis in Parkinson disease and, mostly, in treatment-resistant schizophrenia [16,17]. The usual practice for initiating clozapine treatment involves starting in a hospital setting. Clinical guidelines and recommendations from manufacturers advise commencing with a daily dose of 12.5 to 25 mg and progressively raising the dosage to the target [17].

Currently, clozapine is not registered in Poland for the treatment of bipolar disorder, but available meta-analyses on this

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topic show that the effectiveness of clozapine in the treatment of bipolar disorder is similar to that of treatment with other antipsychotic drugs [18]. Clozapine can be effective and well tolerated in patients with severe mood disorders. A reduction in the frequency of readmissions among patients with mood disorders has also been demonstrated [19,20]. Moreover, numerous clinical studies have demonstrated the effectiveness of clozapine in reducing the risk of suicide, especially in patients with schizophrenia, but research on reducing suicide in patients with other mood disorders is needed [21].

Clozapine is safe and well tolerated when used properly. Adverse effects caused by clozapine include sedation, constipation, tachycardia, and arrhythmias, but the most severe adverse effects of this drug include agranulocytosis [19]. For this reason, it is important to perform regular complete blood count testing, and the lack of patient cooperation in the testing is an important argument against the use of clozapine. It seems essential to increase awareness among medical staff regarding the potential advantages and the associated risks and adverse effects by using clozapine.

Olanzapine

Olanzapine is a commonly recommended atypical antipsychotic drug. Its likely mode of operation involves inhibiting dopamine D2 and serotonin 5-HT2 receptors [22]. Olanzapine also exhibits affinity for additional receptors, including serotonin receptors and dopamine receptors D1-D5, along with muscarinic, 1-adrenergic, and histamine H1 receptors [22,23].

Olanzapine is a mood-stabilizing drug that has antimanic effects. For this reason, in Poland, olanzapine is registered for the treatment of schizophrenia and moderate and severe manic episodes, and for the prevention of relapses of bipolar disorder. Olanzapine is usually used in doses of 10 to 20 mg/day. One study showed that olanzapine reduced the relapse rate of bipolar disorder, compared with placebo. For those taking olanzapine, the average time without disease activity until relapse was 174 days, and for placebo, it was 22 days. Furthermore, the incidence of relapse was significantly lower in the olanzapine group (46.7%) vs placebo (80.1%) [23]. Comparable findings were observed in a research study by Tohen et al. Patients treated with olanzapine showed higher rates of response (65% vs 43%, respectively) and euthymia (61% vs 36%, respectively) than did those who received a placebo [24]. In the comparison of the efficacy of olanzapine therapy with lithium, findings revealed that olanzapine is more effective in preventing the recurrence of manic and mixed episodes in individuals who had previously achieved stabilization through concurrent treatment with olanzapine and lithium [3]. Recurrence of bipolar disorder symptoms occurred in 30.0% of patients treated with olanzapine and in 38.8% of patients treated with lithium [3]. In addition, the latest research on olanzapine concerns the possible effectiveness of the drug in preventing relapses in the postpartum period as an alternative to classic mood stabilizers [25]. In addressing a treatment-resistant depressive episode in bipolar disorder, olanzapine proves beneficial, particularly when used in combination with fluoxetine [26,27].

The main factor limiting the use of olanzapine is the frequent adverse effects, which primarily include significant weight gain; therefore, it will not be recommended in many patients with metabolic syndrome [27]. Furthermore, additional adverse effects include drowsiness, elevated prolactin levels, dizziness, and reduced libido. It is crucial to conduct regular monitoring of blood glucose and lipid levels as well.

Quetiapine

Quetiapine is a second-generation antipsychotic drug. The primary reason for the antipsychotic impact is the inhibition of dopaminergic and serotonergic 5-HT2 receptors [28]. Quetiapine exhibits the strongest affinity for histamine H1 receptors and α1-adrenergic receptors, notable affinity for serotonin 5-HT2, α2-adrenergic, and dopaminergic D2 receptors, and, to a lesser degree, D1 and 5-HT1A receptors [28]. Additionally, it demonstrates modest binding to benzodiazepine and M1 cholinergic receptors. Quetiapine is used for the treatment of schizophrenia, including the prevention of relapse in patients with stable schizophrenia who are receiving sustained-release maintenance therapy [29]. The indication for use is the treatment of moderate and severe manic episodes and severe depressive episodes in the course of bipolar disorder. Quetiapine is effective in maintaining euthymia in patients with bipolar disorder, compared with placebo [28,29].

One study assessed the effectiveness of quetiapine in the long-term treatment of bipolar disorder in relation to classic mood stabilizers. Quetiapine was administered as monotherapy and in combination, with quetiapine with lithium or sodium valproate [29]. Combination treatment of quetiapine with lithium or sodium valproate was more effective in maintaining euthymia, with results showing 80% for quetiapine in combination with lithium and 78.3% for quetiapine in combination with sodium valproate, while quetiapine alone was 29.3%, lithium was 46.2%, and sodium valproate was 32.9% [29]. This means that combining these drugs could be beneficial in making treatment options for patients. A study by Young et al compared the effectiveness of quetiapine with that of lithium in the treatment of a depressive episode in bipolar disorder [30]. Quetiapine doses were 300 and 600 mg/day, and lithium doses were from 600 to 1800 mg. The greatest effect was demonstrated in patients taking a higher dose of quetiapine [30].

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The Montgomery-Åsberg Depression Rating Scale (MADRS) showed a change in the initial result in the eighth week of the study by -16.1 for the 600 mg dose, -15.3 for the 300 mg dose, -13.6 for lithium, and -11.8 for placebo [30]. Quetiapine and lithium have similar effectiveness in the acute treatment and prevention of mania, while quetiapine may be more effective than lithium monotherapy in the acute treatment and prevention of depression in bipolar disorder [30].

The most common adverse effects of quetiapine are drowsiness, dizziness, and hypotension [28,32]. Quetiapine, like other atypical antipsychotics, also causes weight gain, can cause increases in plasma cholesterol levels (total cholesterol, LDL cholesterol, and HDL cholesterol), and is associated with an increased risk of developing hypertriglyceridemia; therefore, it is crucial to use the lowest effective dose of quetiapine [32]. These parameters should be assessed at the beginning of treatment and changes should be regularly monitored during treatment [32].

Risperidone

Risperidone, in its mechanism of action, has high affinity for serotonin 5-HT2, dopamine D2, adrenergic-α1 (and weaker to α2), and histamine H1 receptors [33]. It has no affinity for cholinergic or β-adrenergic receptors [33]. In Poland, risperidone is registered for treatment of schizophrenia, moderate to severe manic episodes in bipolar disorder, and in the short-term treatment of aggression in children from 5 years of age and adolescents in the course of behavioral disorders and aggression in people with dementia syndrome [34]. Due to its mechanism, risperidone has antipsychotic and antimanic effects. Compared with classical antipsychotic drugs, it has a lower risk of adverse effects, inhibits motor activities less strongly, and has a weaker cataleptic effect [34]. Risperidone is available as oral tablets and long-acting injections. In the injectable form, it is effective in patients who do not cooperate in the maintenance treatment of schizophrenia [35].

One study assessed the effectiveness of long-acting risperidone injections in people with bipolar disorder [35]. Patients were divided into 2 groups, with one group receiving an injection of risperidone every 2 weeks and previous oral medications (antidepressants, mood stabilizers, or anxiolytics), and the other group receiving oral medications and, instead of risperidone injection, a placebo [35]. The study showed that the time to relapse was longer in patients receiving adjunctive risperidone injection than in patients receiving placebo. Relapse rates were 23.1% with adjunctive risperidone, compared with 45.8% with adjunctive placebo [35]. A number of studies indeed indicate its efficacy in the treatment of mania in bipolar disorder, compared with placebo, on the Young Mania Rating Scale (YMRS). Moreover, risperidone has demonstrated a rapid onset of action [36].

The mean effective mania-reducing doses of risperidone were 1 to 6 mg/day [37]. When it comes to comparing risperidone with novel antipsychotics, the effectiveness of risperidone is similar to that of olanzapine in treating mania in bipolar disorder [37]. In a study conducted by Haas et al, the effectiveness of risperidone in the treatment of mania in bipolar disorder was investigated in a pediatric population (children and adolescents aged 10-17 years) [38]. Risperidone was well tolerated and effective in improving the mental condition in this age group. Greatest improvement in the YMRS score was achieved with a risperidone dose of 0.5 to 2.5 mg, with an average change of -18.5 from the beginning of the study; whereas there was a change of -16.5 for a risperidone dose of 3 to 6 mg, and a change of -9.1 in patients receiving placebo [38].

The most common adverse effects associated with risperidone are somnolence, headache, and fatigue [34]. Like other atypical antipsychotics, risperidone causes weight gain [34,39]. Risperidone demonstrates a heightened propensity to induce hyperprolactinemia, consequently predisposing individuals to disturbances in various somatic functions, including lactation disorders, irregular menstruation, and fertility complications [39]. Consequently, risperidone therapy is not the optimal therapeutic approach for all patients [39].

Aripiprazole

Aripiprazole, in its mechanism of action, is a partial agonist of dopamine D2 and serotonin 5-HT1A receptors and an antagonist of serotonin 5-HT2A receptors [40]. Therefore, it is classified as a third-generation antipsychotic, because unlike other antipsychotics, aripiprazole exhibits partial agonism over dopamine receptors [40,41]. As a result, aripiprazole shows a dual action depending on the dopamine concentration in the area [41]. For positive symptoms, its action is based on blocking dopamine, and for negative symptoms on enhancing its transmission [41]. Aripiprazole is metabolized by the liver via cytochrome P450, mainly CYP 3A4 and 2D6 [40]. Importantly, the antipsychotics in this group act as ligands for the G-protein-coupled receptor [40]. As a result, aripiprazole exhibits functional selectivity, meaning that it can differentially stimulate intra-neuronal signal pathways. According to this idea, antagonists can function as reverse agonists and can also induce receptor down-regulation, a property typical of agonists [40,41].

Indications for the use of aripiprazole are schizophrenia and bipolar affective disorder in monotherapy of manic episodes or in combination therapy and as a medication to prevent new seizures [42]. In addition, it can be used in combination with

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antidepressants and for autistic disorders. The recommended starting dose is 10 or 15 mg per day, with a maintenance dose of 15 mg per day, given once a day at a fixed time, regardless of meals [42]. For the treatment of manic episodes, a higher dose can also be effective, but the maximum daily dose is 30 mg. Apart from hypersensitivity to a component of the preparation, there are no contraindications to the use of aripiprazole [41,42]. Possible adverse effects include restlessness, tremors, extrapyramidal symptoms, dizziness, blurred vision, headache, and nausea [40,43]. However, the drug is generally well tolerated. Akathisia and tremor appear with incidences of 10% to 11% or less [43]. Very rarely, weight gain and metabolic or endocrine disorders, such as hyperprolactinemia, are observed [42,43]. Clinical studies have shown no significant effect of aripiprazole on liver dysfunction [43].

In a randomized double-blind study conducted by Keck et al among patients with acute bipolar I mania, the efficacy of aripiprazole at a dose of 15 to 30 mg/day was compared with that of placebo and lithium for 3 weeks [44]. There was a significantly greater improvement after aripiprazole than placebo in the mean final YMRS score (improvement after aripiprazole of -4.3 vs after placebo of -2.8) [44]. When comparing aripiprazole with lithium, the efficacy of both was similar. The response rate after 3 weeks in the aripiprazole group was 46.8%, while that of lithium was 45.8% [44]. Similar findings were obtained in another double-blind study, in which the significant improvement after aripiprazole and lithium was maintained for the subsequent 40 weeks of the extended study: after 52 weeks, the YMRS score from baseline was -22.5 for the lithium group and -26.4 for the aripiprazole group [45].

A long-acting formulation of aripiprazole (AOM 400) has also been available for more than 10 years [46]. It is registered for adult patients with schizophrenia who have achieved sufficient disease stabilization during treatment with oral aripiprazole. It is administered once per month, and the recommended starting dose is 400 mg [46]. In a number of multicenter simplex and double-blind studies, the long-acting formulation was shown to be a safe and effective therapeutic option in schizophrenia, but also in maintenance therapy for bipolar affective disorder [46]. The type and frequency of adverse effects of extended-release aripiprazole were found to be similar to those of the oral formulation [46,47]. One prospective study documented that 6-month treatment with this medication did not adversely affect the metabolic profile of patients, resulted in normalization of prolactin levels (from 43.0 to 14.7 ng/mL), and allowed the reduction of the doses of other antipsychotics taken in combination therapy [47].

A new long-acting formulation of aripiprazole for injection every 2 months at a dose of 960 mg (Ari 2MRTU 960) is also available [12]. It is currently being studied for its efficacy in the treatment of schizophrenia and bipolar I disorder. One randomized study in a 32-week efficacy and safety evaluation found that the incidence of adverse events was similar between Ari 2MRTU 960 (71.2%) and AOM 400 (70.9%), with the most common adverse event being weight gain (22.7% with Ari 2MRTU 960) [12]. Efficacy assessed on the MADRS scale showed no significant differences between the 2 formulations (-3.5 in the Ari 2MRTU 960 group vs -3.3 in the AOM 400 group), while results in favor of AOM 400 were shown on the YMRS (-1.9 vs -4.7) and Clinical Global Impressions-Bipolar (CGI-BP) (-0.2 vs -0.6) scales [12]. It is worth conducting further studies on the efficacy and safety of long-acting aripiprazole formulations in the described and other diseases.

Lamotrigine

Lamotrigine is an antiepileptic drug with antidepressant properties and is used to treat epilepsy, but it has also been approved by the Food and Drug Administration (FDA) for maintenance treatment and relapse prevention in people with bipolar disorder [48]. The antiepileptic effects of lamotrigine include inhibiting voltage-sensitive sodium channels, stabilizing presynaptic neuronal membranes, and inhibiting glutamate release [48]. Its mood-stabilizing mechanism of action, however, remains under investigation. Previous studies have shown that serotonergic, noradrenergic, and glutamatergic systems, as well as non-neurotransmitter pathways in inflammation and ongoing oxidative processes, can play a role in lamotrigine's antidepressant effects [49]. On the other hand, by affecting glutamatergic transmission, it can have an antimanic effect [49]. An important advantage of lamotrigine is its predictable pharmacokinetics; therefore, it does not require such frequent monitoring during treatment [48]. Lamotrigine shows much greater safety of use than lithium in the treatment of bipolar disorder, causing much less frequent or less severe adverse effects [48].

One systematic review summarized data on the use of lamotrigine in the maintenance treatment of bipolar disorder, comparing randomized trials with patient assessments using the YMRS, Hamilton Depression Rating Scale, and MADRS [48]. In all studies analyzed, lamotrigine doses were titrated starting at 25 mg [48-50]. Lamotrigine was shown to have a significant benefit over placebo. The estimated risk ratio of recurrence of manic symptoms after 1 year, as measured by the YMRS, was 0.67 in favor of lamotrigine, compared with placebo [50]. In contrast, its efficacy in the maintenance treatment of bipolar disease was comparable to that of lithium. However, an important issue was the observed increased risk factor for recurrence of a mania episode after 1 year with lamotrigine (the risk ratio for lamotrigine relative to lithium was 2.13) [48,50]. The evidence of lamotrigine's safety is the fact that it is recommended for

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the treatment of bipolar disorder during pregnancy, since, in studies, the risk of birth defects with its administration was significantly lower than that of other antiepileptic drugs [51].

Positive effects of lamotrigine on mood changes in depressive disorders and borderline personality disorder, reduction of chronic pain, or treatment of schizoaffective disorder are also described [52]. Among others, the literature presents cases of patients with recurrent brief depression who, with long-term treatment, did not respond to selective serotonin reuptake inhibitors and venlafaxine, while they responded to therapeutic doses of lamotrigine in a very favorable and safe manner [52]. One patient was resistant to treatment with different antidepressants, including several selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine, while the other responded only to valproate, but without any significant extent. Both patients initially received a dose of lamotrigine 25 mg, but the final dose was 125 mg [52]. One patient showed evident improvement after just 1 month, and the other, after 3 months, with maintenance at 8- and 10-month follow-ups on lamotrigine monotherapy in both patients [52].

The range of effective lamotrigine doses for affective disorders is 50 to 300 mg/day [53,54]. In Poland, lamotrigine is available in tablets with doses of 25, 50, 100, 200 mg and is recommended for the treatment of epilepsy and partial and generalized seizures [53]. It is recommended to increase the dose slowly, among other things, to reduce the incidence of severe rash or exfoliative dermatitis as one of the more common serious adverse effects (incidence 1: 500) [53,54].

One recent study reported results on the prescribing aspect of lamotrigine for bipolar disorder and depressive disorders [54]. A significant conclusion was that, due to the lack of data and therapeutic recommendations for the use of this drug in bipolar disorder, physicians encountered difficulties and uncertainties at the level of decision-making about prescribing the drug, monitoring it, and adjusting the dose [54]. Further research is therefore needed on the effectiveness of lamotrigine as a mood stabilizer.

Lurasidone

Lurasidone is one of the newer atypical antipsychotics. Functional tests have shown that it acts as an antagonist of D2 and 5-HT7 receptors and as a partial agonist of the 5-HT1A receptor subtype [15]. It also has a strong affinity for α2C norepinephrine receptors, acting as an antagonist [55]. The drug therefore exhibits antipsychotic and antidepressant or anti-anxiety effects, and importantly is associated with a lower risk of extrapyramidal and central nervous system depressant adverse effects [15]. It is metabolized primarily by the CYP3A4 isoenzyme [15].

The FDA has approved lurasidone, within the dose range of 20 to 120 mg/day, for treating acute bipolar depression, either in monotherapy or alongside lithium or valproate as adjunctive therapy [55]. A number of studies indicate its efficacy in the treatment of bipolar depression and as a relapse prevention drug in bipolar disorder [55]. In Poland, it is registered only for the treatment of schizophrenia in adults. The suggested initial dosage is 37 mg taken once per day, with no need for an initial dosage adjustment [15]. The product is effective in the dose range of 37 to 148 mg once daily [15].

In studies conducted to assess the long-term safety of lurasidone, patients were evaluated for 6 weeks, then for 6 months, and in follow-up studies for 12 months or 2 years [56-58]. In a 6-week double-blind study among patients with depressive episodes associated with bipolar I disorder, lurasidone was shown to significantly reduce MADRS and CGI-BP scores at a dose of 20 to 120 mg (mean improvement in both scales was 0.5-0.6) [56]. Importantly, no significant difference in the rate of adverse effects was noted depending on the drug dose [56]. Similar benefits and improvements in the mentioned scales were observed when lurasidone was used for 6 weeks as adjunctive treatment to lithium or valproic acid therapy [57]. Moreover, changes in body weight, lipid levels, and glycemia were virtually clinically insignificant during treatment [57].

In similar extended studies lasting 6 months, 12 months, or 2 years, utilizing doses ranging from 20 to 120 mg, further improvements were observed in MADRS and CGI-BP scores, as well as in measures of quality of life and functioning (Severity of Dependence Scale and Quality of Life Enjoyment and Satisfaction Questionnaire) [58]. In a Japanese study, the total MADRS scores decreased by an average of 2.0 points458]. In other study, the change by the 6 months of treatment was ±0.85 kg for body weight and -6.9 and -6.5 for MADRS scores [58]. Similar benefits were achieved with monotherapy and adjuvant treatment in the context of reducing depressive symptoms in patients with bipolar I type depression [57]. Depression severity was assessed on the CGI-BP scale, with an improvement of 0.61 in the 20 to 60 mg/day group, 0.50 in the 80 to 120 mg/day group, and 0.34 in the group with lithium or valproic acid adjunctive therapy [56,57]. For patients who did not achieve improvement prior to the extended study, after 6 months, improvement was achieved in 83% of patients receiving lurasidone monotherapy and in 73% of patients receiving adjunctive therapy [58].

The most common adverse events associated with lurasidone, as assessed in 1 clinical study, were akathisia (30.7%), nasopharyngitis (26.6%), nausea (12.1%), and somnolence

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(12.1%) [54,58]. Moreover, the need to discontinue therapy due to adverse events was very low; the study of monotherapy showed a frequency of 6.9% [58].

Current literature and clinical trial results indicate significant benefits of lurasidone in the treatment of schizophrenia and bipolar depression in the acute phase. The drug appears to be a safe therapeutic option within the range of doses used. Only the incidence of akathisia as an adverse effect seems to be more frequent. It is worth conducting further studies on the effectiveness of lurasidone in the long-term therapy of the described disorders, as well as in other disease entities.

Cariprazine

Cariprazine is a new atypical antipsychotic drug, whose mechanism of action involves interacting with dopamine and serotonin receptors, where it functions as a partial agonist at dopamine D2 and D3 receptors and serotonin 5-HT1A receptors, showing a higher affinity for D3 receptors [59,60]. Additionally, cariprazine acts as an antagonist at 5-HT2 and histamine H1 receptors and exhibits no affinity for muscarinic cholinergic receptors [59,61]. This partial agonism at D3 receptors in the limbic system helps address the negative symptoms of schizophrenia and provides an antidepressant effect, similar to the action of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors on serotonin 5-HT1A receptors [62,63]. Cariprazine is used to treat schizophrenia, bipolar disorder, and potentially autism, with emerging evidence suggesting it can have pro-cognitive effects [64,65]. Cariprazine was approved by the FDA in the United States in 2015, with a dose of 1.5 to 6 mg/day for schizophrenia and 3 to 6 mg/day for bipolar disorder in adults, and by the European authorities for schizophrenia in 2017 [63,66].

The most common adverse effects of cariprazine include akathisia, dyspepsia, vomiting, and somnolence [63,67]. It has a negligible impact on prolactin levels, making it a suitable option for patients with hyperprolactinemia [68]. Additionally, the low affinity of cariprazine for histamine H1, muscarinic M1, and α1 receptors indicates a reduced risk of sedation, hypotension, and metabolic adverse effects [67,68].

Lumateperone

Lumateperone (ITI-007) is a new antipsychotic medication for schizophrenia. Its mode of action involves the simultaneous modulation of glutamate, dopamine, and serotonin neurotransmission [69]. Lumateperone functions as a strong antagonist of the serotonin 5-HT2A receptor, a D1 receptor-dependent modulator, a presynaptic partial agonist and postsynaptic antagonist of the dopamine D2 receptor, and a serotonin reuptake inhibitor [69-71].

In 2019, lumateperone received FDA approval for the treatment of schizophrenia [72]. The use of lithium or valproate as an adjuvant therapy for depressive episodes in patients with bipolar I or II disorders was also added to the list of indications [73]. Lumateperone, under the name of Caplyta, is a medicine that comes in doses of 10.5, 21, and 42 mg [74]. For adults, a dose of 42 mg once daily is advised [73,74].

Results of a randomized, double-blind, placebo-controlled trial using ITI-007 (60 mg and 120 mg), placebo, and risperidone as monotherapy showed that 60 mg of ITI-007 reduced depressed and negative symptoms, whereas a dose of 120 mg and placebo did not differentiate [75]. However, low adverse event rates and a benign metabolic profile indicated by notably lower levels of prolactin, fasting glucose, cholesterol in general, and triglycerides than during the risperidone treatment, showed that both doses of ITI-007 were well tolerated [75]. Another study that looked at dosages of 40 and 60 mg found that both were well tolerated and did not significantly impact adverse effects when compared with placebo, nor did they influence cardiometabolic or endocrine conditions [69,76].

Typical adverse effects include drowsiness, tiredness, nausea, dizziness, dry mouth, nasal congestion, anxiety, restlessness, and weight gain [73,74]. Although lumateperone has not been connected to cases of clinically evident acute liver impairment, it is linked to a low rate of blood aminotransferase increases during therapy, due to its metabolism in the liver by CYP 3A4, 2C8, and 1A2 [73]. Lumateperone is a beneficial medication for those with schizophrenia who are not responding to treatment and for those who are at risk of metabolic problems [76].

Brexpiprazole

The structure and mode of action of brexpiprazole, a novel second-generation atypical antipsychotic medication, are comparable to those of aripiprazole. Brexpiprazole functions as a partial agonist of serotonin 5-HT1A receptors and a partial antagonist of D2 and serotonin 5-HT2A receptors [77,78]. The FDA approved the medication in 2015 for the treatment of schizophrenia and as an adjuvant therapy for major depressive disorders in the United States, and it is approved in Australia, Canada, the European Union, and Japan [79]. Brexpiprazole is advertised using its name Rxulti and is available in doses of 0.25, 0.5, 1, 2, 3, and 4 mg. For schizophrenia, a maintenance dose of 2 to 4 mg/day is typical [80]

In a single study, brexpiprazole 2 mg and 4 mg/day produced considerably greater improvements in the Positive and Negative

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Syndrome Scale scores following therapy than did a placebo [81,82]. In another study, patients with acute schizophrenia were treated with varying doses of aripiprazole of 10 to 20 mg/day and brexpiprazole 1 to 4 mg/day [83]. The effects of brexpiprazole on Positive and Negative Syndrome Scale scores after 6 weeks were similar to those of aripiprazole [83].

Frequent adverse reactions include akathisia, tremor, insomnia, blurred vision, exhaustion, headaches, nausea, and weight gain [84]. In short-term examinations, akathisia and weight gain were more commonly recorded with brexpiprazole than with placebo in individuals receiving up to 6 mg/day of the medication [85], and 5.6% of patients who took the medication for a year or longer saw a weight increase of at least 15 kg [85,86].

Future Directions

The future of drug treatments for mood disorders, particularly bipolar disorder and schizophrenia, holds significant promise with the ongoing research and development of novel therapeutic agents. Future directions in this field focus on several key areas. First, a deeper understanding of the pathophysiology and genetic underpinnings of mood disorders will enable the development of more targeted therapies, potentially leading to precision medicine approaches that tailor treatments to individual patients' biological profiles. Second, advancements in psychopharmacology are expected to yield new classes of medications with improved efficacy and safety profiles. This includes exploring the potential of recently introduced agents, such as lumateperone and brexpiprazole, and further refining the use of existing medications, such as cariprazine and lurasidone. Furthermore, holistic treatment approaches that combine pharmacotherapy with psychotherapy, lifestyle modifications, and social support systems are increasingly recognized as essential for achieving optimal outcomes. As research progresses, the continued collaboration between clinical practice and scientific inquiry will be crucial in advancing the management of mood disorders, ultimately improving patient outcomes and quality of life.

Conclusions

In conclusion, the evaluation of recent mood-stabilizing drugs underscores the need to develop pharmaceutical interventions for the treatment of mood disorders. Analysis of the existing literature indicates the high efficacy and safety of pioneering compounds in the treatment of manic and depressive symptoms during acute episodes, as well as in the prevention of relapse. Moreover, the priority given to mitigating adverse effects, particularly in avoiding exacerbation of manic or depressive episodes or induction of mixed states, underscores the crucial importance in the formulation and clinical use of these drugs. In the era of metabolic diseases, the low incidence of metabolic disorders during therapy with the drugs presented is an aspect that supports the significant benefits of this treatment. Continued research and clinical trials are necessary to further refine and expand our understanding of these innovative mood stabilizers, increase their therapeutic efficacy, and improve the condition of patients with mood disorders.

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