JOURNAL OF HEALTHCARE SCIENCES
Volume 4 Issue 10 2024, Article ID: JOHS2024000905
http://dx.doi.org/10.52533/JOHS.2024.41006
e-ISSN: 1658-8967

Review

A Review on Neuropharmacological Approaches to Treating Bipolar Disorder

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Received: 25 September 2024, Reviewed: 13 October 2024, Accepted: 14 October 2024, Published: 20 October 2024.

Abstract

Bipolar disorder (BD) is a severe mood disorder characterized by alternating episodes of mania and depression, with significant psychosocial impairment and an elevated risk of suicide. This review explores neuropharmacological treatments for BD, focusing on lithium, antipsychotics, antiepileptics, antidepressants and glutamatergic agents. Lithium, a cornerstone of BD treatment, offers robust efficacy in mood stabilization but has limitations due to side effects and a narrow therapeutic index. Antipsychotics, particularly atypical ones like olanzapine and quetiapine, are effective in managing mania and bipolar depression but can cause metabolic dysregulation. Antiepileptics, including valproate and lamotrigine, are used for mood stabilization, with lamotrigine particularly effective in bipolar depression. Antidepressants, while providing short-term benefits, carry risks of inducing mania and are best used cautiously. Emerging treatments like ketamine and memantine show promise in refractory cases but require further validation. Future research should focus on refining existing therapies, exploring novel agents and integrating personalized medicine approaches to enhance treatment efficacy and minimize adverse effects.

Keywords: *bipolar disorder, neuropharmacological treatments, lithium, antipsychotics, antiepileptics, antidepressants, glutamatergic agents, ketamine, memantine*

Introduction

Bipolar disorder (BD) is a mood disorder characterized by alternating episodes of elevated mood and prolonged periods of depression, along with asymptomatic or euthymic intervals. It is a serious medical condition associated with psychosocial impairment, heightened suicide risk, and significant comorbidity with other medical conditions, leading to reduced life expectancy (1). BD has a strong genetic component, with approximately 70% heritability and a 40-50% a correlation prevalence among in identical twins. Environmental factors such as childhood trauma and substance use can trigger the onset and influence the severity of the disease. While the exact cause of BD remains unclear, proposed mechanisms include deficits in neuronal/glial plasticity, monoaminergic activity, inflammatory responses, cellular metabolism, and mitochondrial function (2).

Bipolar disorder includes various subtypes, with Bipolar I disorder involving at least one manic episode, with or without a history of depression, and Bipolar II disorder involving one or more depressive episodes and at least one episode of hypomania, but no mania. Rapid-cycling BD is defined by experiencing four or more mood episodes depressive, manic, hypomanic, or mixed within a year (3). Recent epidemiological studies indicate that the various phenotypes within the bipolar spectrum affect about 5% of the population (4).

The progression of BD can become more complex over time, with shorter and fewer symptom-free intervals and a tendency toward a chronic, unremitting course. Subtypes such as rapid cycling are identified when patients experience at least four mood episodes within a year. Several factors influence the illness's severity, including a younger age of onset, the presence of psychotic features, persistent subthreshold symptoms, rapid cycling, the number of prior episodes, comorbidities and residual symptoms during euthymia (4).

More than 50% of patients with BD experience comorbidity with two or more psychiatric disorders, which is a predictor of poor outcomes (5, 6). The World Health Organization (WHO) identifies it as the fourth leading cause of neuropsychiatric disability in individuals aged 15–44 years. Bipolar disorder patients use more health resources than those with depression or chronic conditions (7). The most severe complication is suicide, with 25–50% of patients attempting it, with a prevalence of 32.4% for Bipolar I and 36.3% for Bipolar II (8). Suicidal behaviour is most common during depressive phases. Additional burdens include increased mortality from medical causes, substance abuse (primarily alcoholism), comorbidity with other psychiatric disorders, and chronic affective symptoms.

Pharmacological treatments are standard for managing acute manic or hypomanic episodes, requiring prompt intervention to prevent harm. Effective antimanic agents include antipsychotics, lithium, and certain anticonvulsants, as outlined in international guidelines such as those from Canadian Network for Mood and Anxiety Treatments (CANMAT) (9). However, these treatments often fall short in efficacy and are associated with adverse effects, including lethargy, cognitive impairment, mood changes, and metabolic imbalances (10). Addressing these unmet needs is crucial for improving mental health outcomes and managing physical comorbidities.

Methodology

This study is based on a comprehensive literature search conducted on 7 September 2024, in the Medline and Cochrane databases, utilizing the Medical Subjects Headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed neuropharmacological approaches for treating BD. There were no restrictions on date, language, participant age, or type of publication.

http://dx.doi.org/10.52533/JOHS.2024.41006

Discussion

The pathophysiology of BD involves inflammatory processes, with elevated levels of proinflammatory cytokines, such as interleukins and tumour necrosis factors, observed at various stages of the disorder. This suggests a significant role of inflammation in its development and progression (11). These cytokines can activate microglia, leading to excessive inflammation and neuronal damage during chronic BD episodes. Other implicated pathways include disturbances in neuronal-glial plasticity, monoaminergic signalling, cellular metabolism, mitochondrial function, endocannabinoid signalling, insulin regulation, oxidative stress, HPA axis changes, and circadian rhythm disruptions (10).

Managing BD involves two distinct phases: the initial treatment of an acute episode, which may lead to diagnosis, and long-term management aimed at preventing relapses. These phases require different treatment approaches and coordination between primary and secondary care (3).

Lithium

Since lithium discovery in 1949, lithium has become a cornerstone in psychopharmacology, often referred to as the aspirin of psychiatry. It is well-known not only for its antimanic and prophylactic effects but also for its antidepressant, anti-suicidal, and neuroprotective properties (12). Some argue that lithium functions as a psychiatric "cure-all," being the longest-used psychotropic medication in clinical settings. Lithium's role in BD treatment evolved from John Cade's discovery in 1949 to its recognition as maintenance therapy in 1968 (3).

Indications and efficacy

Lithium is primarily used for long-term relapse prevention in BD, although other medications have replaced it as the preferred antimanic agent. Lithium can be prescribed as an adjunct treatment for mania when two antipsychotics fail to manage symptoms (3). Lithium's efficacy as a maintenance therapy is well-established, with a network meta-analysis confirming it as the most effective treatment and supporting its continued first-line use (13). Strong evidence also supports lithium's anti-suicidal properties, with one meta-analysis showing an 82% reduction in suicide rates during lithium treatment (14).

Side effects and contraindications

Lithium is associated with various side effects, such as tremor, nausea, fatigue, increased appetite, elevated white blood cell count, polydipsia, and polyuria. Some side effects, like thirst and tremor, often subside within the first few weeks (15). However, lithium's narrow therapeutic index, three times its toxic concentration, is a significant concern, especially if therapeutic drug monitoring is not properly implemented. Blood lithium levels must be checked after the first week, after every dosage change, and weekly until stabilized, then every three months. Kidney function, body mass index (BMI), calcium, and thyroid tests are required every six months. Lithium must always be prescribed by brand name and salt form to ensure consistent bioavailability (3).

Lithium is associated with a range of potential contraindications, particularly due to its impact on renal function, electrolyte balance, and cardiac health. **(Table 1)** outlines the primary contraindications to lithium therapy, with details on the associated risks and complications that healthcare providers should consider when prescribing this medication (3).

Antipsychotics

The development of antipsychotics evolved from early phenothiazines to second-generation medications like clozapine, which reduced extrapyramidal side effects, improving BD management (3). Although the molecular mechanisms underlying BD are gradually being understood, there remains a significant gap between the neurobiological insights and the mechanisms by which antipsychotics operate. Atypical antipsychotics like clozapine manage mania by briefly antagonizing D2 receptors, reducing side effects (16). Their action on multiple receptors, including 5-HT2A and 5-HT2C, aids in mood regulation and treating depression (17).

http://dx.doi.org/10.52533/JOHS.2024.41006

Table 1. Key contraindications for lithium use in clinical practice (3)	
Contraindication	**Details**
Renal Impairment	Lithium is primarily excreted by the kidneys, making it contraindicated in patients with significant renal dysfunction.
Low Sodium Levels	Lithium is reabsorbed by the kidneys when sodium levels are low, leading to potential toxicity.
Diabetes Insipidus	Patients with diabetes insipidus cannot concentrate urine, making lithium use unsafe.
Untreated Hypothyroidism	While hypothyroidism can be managed with levothyroxine, untreated or untreatable hypothyroidism contraindicates lithium use.
Cardiac Rhythm Disorders	Lithium affects sodium and potassium regulation, leading to cardiac instability. It is contraindicated in patients with rhythm disorders such as Brugada syndrome.
Brugada Syndrome	Lithium can unmask or exacerbate Brugada syndrome, even at subtherapeutic doses, increasing the risk of ventricular arrhythmias.

The National Institute for Clinical Excellence (NICE) in the UK recommends the use of atypical antipsychotics for managing all facets of BD, including acute manic episodes, mixed episodes, depression, and maintenance treatment (3). According to these guidelines, first-line treatment options include either the typical antipsychotic haloperidol or one of three atypical drugs: olanzapine, quetiapine, or risperidone (18).

Both typical and atypical antipsychotics outperform placebo in treating mania, with atypical like olanzapine showing superior effects compared to lithium and less need for monitoring (19). Chlorpromazine and haloperidol also offer benefits, but haloperidol's higher adverse effect rate affects overall efficacy (20). For bipolar depression, quetiapine and olanzapine are effective, with the latter benefiting from combined use with SSRIs like fluoxetine for improved mood (21). Despite these advances, further research is needed to fully understand the efficacy of combination therapies in BD (22).

Atypical antipsychotics, while designed to reduce extrapyramidal symptoms, often lead to metabolic dysregulation, notably weight gain and truncal obesity, with olanzapine and clozapine being the worst offenders. Aripiprazole shows a lower risk of weight disturbances. These drugs can also prolong the corrected QT interval (QTc), posing risks for cardiac conduction issues, especially ziprasidone, which requires electrocardiogram (ECG) monitoring and caution when combined with other QT-prolonging drugs (3).

According to the guidelines, haloperidol, a typical antipsychotic, or any of the three atypical antipsychotics such as olanzapine, quetiapine, or risperidone are considered suitable first-line treatments **(Table 2)**.

Antiepileptics

The marketing of phenobarbital as an anti-seizure drug in the early 19th century hailed the beginning of a long era of antiepileptic drug discovery (23). Since then, the creation of the antiepileptic drug development program (ADD) has enabled several conventional therapies to come to the forefront of mainstay medical treatment. Modern-day antiepileptics were developed around the turn of the millennium with the aim of reducing the number of off-target effects and drug-drug interactions with prevalent medications. An example of this new class of antiepileptic includes lamotrigine, which, alongside the older anticonvulsant valproate, plays a crucial role in the management of BD (3).

http://dx.doi.org/10.52533/JOHS.2024.41006

Table 2. Overview of recommendations for antipsychotic use in bipolar disorder management (3)

Condition	Recommended Antipsychotic Treatment
Acute Mania and Mixed Episodes	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Depression	Quetiapine OR Olanzapine combined with Fluoxetine
Relapse Prevention (at least 4 weeks post-manic episode)	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Acute Mania While on Antidepressants	Discontinue antidepressants, then treat as for acute mania; Haloperidol OR Olanzapine OR Risperidone OR Quetiapine

Psychopharmacology

Sodium valproate and lamotrigine both modulate voltage-gated sodium channels to exert therapeutic effects. Valproate reduces neuronal firing and enhances GABA transmission (24), while lamotrigine stabilizes presynaptic neurons, decreasing excitatory neurotransmitter signaling (25). Both drugs are rapidly absorbed and widely bioavailable, with valproate also inducing long-term ion channel changes (3).

Indications and efficacy

As per the NICE guidelines for the management of BD, both lamotrigine and valproate are indicated as mood-stabilizing treatments to prevent future relapses. Valproate is further licensed as a third-line treatment for the management of mania where antipsychotics and lithium have shown poor efficacy or are contraindicated. Conversely, lamotrigine is also indicated as monotherapy for the management of bipolar depression and, unlike valproate, does not require regular blood tests to assess hepatic function (26).

There is considerable evidence to support the efficacy of both valproate and lamotrigine as mood-stabilizing agents. This effect is believed to be synergistic with antipsychotics, with a similar rate of adverse effects as antipsychotic monotherapy alone. Furthermore, work by McElroy and colleagues highlighted that orally loading valproate in acutely manic patients significantly improved overall outcomes. It is thought that this effect is due to a rapid reduction in the time taken to reach effective therapeutic concentration by administering high doses of the drug. Conversely, lamotrigine has been proven to be successful in the management of bipolar depressive states. Dose-dependent improvements in the Hamilton Rating Scale for Depression (HRSD) and Montgomery-Asberg Depression Rating Scale (MADRS) upon lamotrigine administration are well documented. This benefit is believed to be correlated with the magnitude of the depressive episode, as patients displaying a more severe phenotype showed a greater response to lamotrigine treatment (3).

Side effects and contraindications

Sodium valproate has an extensive side effect profile, with excessive weight gain being a significant cause of discontinuation, potentially related to insulin secretion and fatty acid metabolism. A rare but serious complication is hyperammonemia encephalopathy, treatable with L-carnitine. Additionally, valproate is contraindicated in pregnancy due to the risk of fetal malformations, severe hepatic failure and hematological malignancies. In contrast, lamotrigine does not cause significant weight changes but poses a risk of severe cutaneous reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). It is contraindicated in patients with Brugada syndrome and those with a family

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history of sudden death due to its impact on cardiac sodium channels at high doses (3).

Antidepressants

Antidepressant use in bipolar depression is controversial due to mixed evidence on short-term efficacy and a lack of long-term effectiveness against depressive recurrence (27). Concerns exist about mood-elevating agents potentially inducing manic episodes, particularly in bipolar I disorder patients, but evidence suggests such risks are lower than often believed (28). There is also no indication that antidepressants affect the risk of suicidal behaviour in bipolar patients, especially younger individuals (27).

Despite these issues, antidepressants may offer short-term benefits when used cautiously with mood-stabilizers and at low, gradually increased doses, especially for patients without agitation or hypomania. The risk of inducing mania varies by antidepressant type. Older tricyclics and venlafaxine are higher risk, while serotonin reuptake inhibitors (SRIs) and bupropion are lower risk. Bupropion's lower tolerance issues are partly due to its approval for low doses to minimize seizure risk (27).

A small trial found that adding bupropion to unsuccessful psychopharmacological regimens improved depressive symptoms by ≥50% in seven out of 11 patients without new mania or hypomania (29). Another study showed that low-dose bupropion added to aripiprazole and sodium valproate reduced cocaine abuse compared to a control group (30).

Despite the prevalence of unresolved depression in BD and extensive research on antidepressants in unipolar depression, there are few randomized controlled trials for antidepressants in BD. This may be due to concerns about inducing mania or hypomania, especially in bipolar I patients (27).

Glutamatergic Agents

Glutamate, the principal excitatory neurotransmitter in the brain, is involved in synaptic plasticity, learning, and memory. There is growing evidence suggesting that the glutamatergic system may contribute to the pathophysiology of BD. Various drugs target glutamatergic systems, with a focus on the N-methyl-D-aspartate (NMDA) receptor.

Ketamine, an NMDA antagonist, and hallucinogenic dissociative anaesthetic, affects monoamine transport and opioid receptors (27). Besides its anaesthetic effects, ketamine has rapid mood-enhancing properties, notably in depression (31). Two small double-blinded, randomized, crossover, placebo-controlled trials showed that intravenous ketamine significantly improved depressive symptoms in refractory bipolar depression, with 71% of subjects responding to single doses compared to 6% of controls (32). Another study also reported substantial depression relief and reduced suicidal ideation in severely depressed patients who had not responded to prior treatments (31). An uncontrolled trial of ketamine injections showed successful maintenance in two treatment-resistant bipolar patients over six months (33).

Memantine, an NMDA receptor antagonist used for Alzheimer's disease, has shown potential in treating bipolar disorder. Case reports and open-label trials, including a six-year mirror-image study, indicate beneficial effects for up to one to three years (27). A small randomized, placebo-controlled trial found that memantine added to lamotrigine led to superior early improvements in depression ratings, though not sustained beyond eight weeks (34).

Future directions

Future research should focus on refining neuropharmacological approaches for BD by addressing several key areas. First, exploring the mechanisms underlying the mixed efficacy of existing treatments and their side effects can guide the development of more targeted therapies with reduced adverse outcomes. This includes investigating novel glutamatergic agents like ketamine and memantine, which have shown promising results in treating refractory bipolar depression, to establish their long-term safety and effectiveness. Additionally, integrating personalized medicine approaches, such as genetic

http://dx.doi.org/10.52533/JOHS.2024.41006

and biomarker profiling, could enhance treatment precision by tailoring interventions to individual patient profiles. Finally, improving understanding of the neurobiological underpinnings of BD, including the role of inflammation and cellular metabolism, will be crucial for developing innovative therapeutic strategies and improving patient outcomes.

Conclusion

Neuropharmacological approaches to treating BD include established treatments such as lithium, antipsychotics, and antiepileptics, each with specific roles and limitations. Emerging therapies, including glutamatergic agents like ketamine, show promise for refractory cases. Ongoing research into their efficacy and safety, combined with advances in personalized medicine, is essential for improving patient outcomes.

Disclosures

Author Contributions

The author has reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Ethics Statement

Not applicable

Consent for publications

Not applicable

Data Availability

All data is provided within the manuscript.

Conflict of interest

The author declares no competing interest.

Funding

The author has declared that no financial support was received from any organization for the submitted work.

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