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Review

Pharmacological Strategies and Challenges in Treatment-Resistant Bipolar Depression

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Abstract

Bipolar disorder is a severe mental illness that is characterized by mixed, hypomanic/manic, and depressive episodes with periods of inter-episodic recovery. Three-quarters of the approximately 50% of follow-up weeks with therapy that have clinically significant residual morbidity are attributed to depressive aspects of the illness that have proven particularly challenging for successful treatment. Some patients do not react to treatment completely, and their long-term prognosis is marked by frequent relapses and persistent symptoms, which results in considerable disability and functional impairment. Failure to achieve prolonged symptomatic remission for 8 consecutive weeks after two different therapeutic strategies, at appropriate therapeutic doses, with at least two prescribed monotherapy treatments or at least one monotherapy and another combination treatment are marked as treatment-resistant bipolar depression. Only a few therapies have proven to be successful in treating treatment-resistant bipolar depression, which has been documented in around one-quarter of people with bipolar disorders. The most typical clinical method for the management of treatment-resistant bipolar patients involves a multidrug combination, for which lithium or valproate plus a second-generation antipsychotic is the optimal treatment. Ketamine, lurasidone, lamotrigine, risperidone, aripiprazole, valproate and their combinations are some of the effective pharmacological approaches for the management of treatment-resistant bipolar depression although more study is required, primarily concentrating on tailoring current therapies to maximize response and remission rates. The purpose of this research is to review the available information about pharmacological strategies and challenges in treatment-resistant bipolar depression.

Keywords: *bipolar, treatment, resistant, depression*

Introduction

Bipolar disorder is a long-term, complex mood illness that includes manic, hypomanic, and depressive episodes mixed together with strong subsyndromal symptoms that frequently appear in between major mood episodes. Initially, patients of bipolar disorder were present with depressive episodes which accounts for approximately 50% of the cases, making bipolar depression the most common cause of morbidity in those with the condition. Bipolar depression, which contributes to the majority of the time that people with the disease are ill even after receiving therapy, is a significant cause of long-term dysfunction, psychosocial impairment, and decreased productivity at work (1). Despite the use of available pharmacological and psychosocial treatments, bipolar disorder is associated with recurrent episodes of mania, hypomania, mixed manic-depressive states, or psychoses, as well as marked major depression and dysthymia, prominent anxiety symptoms, and high rates of suicide. accidents and mortality from co-occurring medical conditions. Three-quarters of the approximately 50% of follow-up weeks with therapy that have clinically significant residual morbidity are attributed to depressive aspects of the illness that have proven particularly challenging to treat successfully (2).

Given that each phase of bipolar disorder and depression requires a distinct strategy to treatment, managing it is likely the most difficult of all mental disorders. The establishment of treatment standards, which have been an increasingly significant component of medical reality over the past few decades, is likely to have a more positive impact on patients with such complicated mental diseases. This is especially true given how challenging it is to apply study findings to routine clinical practice as complicated and frequently contradictory research findings accumulate and are then incorporated in meta-analyses. According to the literature, depression, not mania, is the hardest phase to get over. If subsyndromal, the existence of persistent symptoms entails a higher likelihood of relapse, more impairment, and a worse prognosis. Therefore, the end goal of treatment should be complete remission and recovery. However, a sizeable minority of patients do not react to treatment completely, and their long-term prognosis is marked by frequent relapses and persistent symptoms, which results in considerable disability and functional impairment (3). Treatment resistant bipolar depression is characterized as the inability to achieve prolonged symptomatic remission for 8 consecutive weeks following two different treatment trials, at appropriate therapeutic doses, with at least two prescribed monotherapy treatments or at least one monotherapy treatment and another combination treatment (4).

Poor and inadequate response to acute manic or depressive episodes or to long-term preventive maintenance treatment plagues the treatment of bipolar disorder despite an impressive increase in drugs certified to be beneficial for the condition. Lithium, valproate, and second-generation antipsychotics are accepted first-line therapies for acute mania, and valproate and lithium are accepted first-line therapies for maintenance treatment. Evidence-based management and treatment of acute mania include carbamazepine and extended-release lamotrigine, olanzapine, and aripiprazole for maintenance therapy. Several more recent anticonvulsants, as well as an earlier anticonvulsant phenytoin, have showed some promise as effective maintenance therapy for mania that is resistant to treatment. Anticonvulsants vary in their effectiveness; thus, each medication must be assessed separately. The most typical clinical therapeutic approach for managing treatment-resistant bipolar patients involves combination of numerous medications for which lithium or valproate plus a second-generation antipsychotic is optimal treatment except in the case of severe mania. Other strategies that may work for people who are resistant to treatment include electroconvulsive therapy, clozapine, high-dose thyroid augmentation, and calcium channel blockers. Adjunctive psychotherapies have convincing effectiveness when employing a variety of methodologies, the majority of which pay close attention to education and the development of coping mechanisms (5). The purpose of this research is to review the available information about pharmacological strategies and challenges in treatment-resistant bipolar depression

Methodology

This study is based on a comprehensive literature search conducted on November 30, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible 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 the information about pharmacological strategies and challenges in treatment-resistant bipolar depression. There were no restrictions on date, language, participant age, or type of publication.

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Discussion

The treatment of major depressive disorder had been revolutionized by the monoaminergic antidepressants more than 50 years ago however, still about a third of depressed people experience treatment-resistant depression. As shown by increased disability, expense, human suffering, and suicide, these patients bear a disproportionately heavy burden of disease (6). Considerations of treatment resistance in bipolar depression are often influenced by concepts from the definition of treatment resistance in unipolar depression, which have been shown to be ineffective. In fact, the inclusion of an ad hoc criterion based on insensitivity to lithium and other mood stabilizers after reaching appropriate plasma levels appears to be an attempt to address the peculiarities of bipolar depression, but unfortunately fails to function. (7).

Bipolar depression patients who are treatment-resistant require careful management that takes into account both the possibility of iatrogenic mania and the potential for their depression to be life-threatening. The strategy to treating bipolar depression is mostly based on knowledge gained from treating unipolar depression because there is minimal data specifically related to its therapy. However, these two diseases differ significantly from one another. Patients with bipolar depression are more likely than those with unipolar disorder to benefit from mood-stabilizing medication's antidepressant effects and avoid its side effects. Response is improved by treating co-occurring anxiety and substance misuse. Although it can be mitigated, the risk of treating bipolar people still exists. Careful evaluation, prospective mood tracking, and efforts to go off antidepressants after an acceptable continuation term can all lead to better results (8).

Evidence from literature

Bipolar depression has a low rate of therapeutic approaches despite the high incidence and substantial burden of depressed morbidity. In addition, non-response in bipolar depression is extremely common and happens in 40% of patients after eight weeks of quetiapine therapy. Antidepressant non-response has become a requirement for the diagnosis of bipolar spectrum disorder due to how frequently it occurs. Although treatment-resistant bipolar depression is quite common, research is sparse and hindered by inconsistent and shifting classifications (9). Bipolar disorder is frequently treated with anticonvulsants. Due to the limited antidepressant benefits of the common mood stabilizers and the propensity of antidepressants to trigger mania or shorten cycle length, treating depression in bipolar disorder can be challenging. The novel anticonvulsant lamotrigine has few side effects and has the potential to stabilize and elevate mood. Its mode of action most likely entails preventing the excessive release of excitatory amino acids like glutamate. Antidepressant and mood-stabilizing properties of glutamatergic drugs (10).

Findings from a clinical trial showed that preliminary pairwise comparison analyses of open-label augmentation with lamotrigine, inositol, or risperidone depicted no changes. Lamotrigine may be more effective than risperidone and inositol for treating treatment-resistant bipolar depression, according to post hoc secondary studies. Lamotrigine had a recovery rate of 23.8%, while inositol and risperidone had recovery rates of 17.4% and 4.6%, respectively. In comparison to patients receiving inositol and risperidone, those getting lamotrigine had lower depression ratings, lower Clinical Global Impression severity scores, and higher Global Assessment of Functioning scores (11). Results of a study by Sharma et al. revealed that following the introduction of lamotrigine, patients were seen for an average of 19.4 months. In either monotherapy or in combination with a mood stabilizer, an atypical antipsychotic, or a sedative/hypnotic medication, the recommended daily dose of lamotrigine was 50–400 mg, 52% of patients showed very significant improvement, while 32% were deemed to have made significant progress. By itself or in combination with other psychotropic medications, lamotrigine was well tolerated and successful in the treatment of treatment-resistant bipolar II depression (12).

Inaba et al. stated that lamotrigine is generally safe with less side effect and is commonly used for the management of treatment-resistant bipolar depression. As per the current findings, lamotrigine re-challenge therapy for treatment-resistant bipolar depression may be an effective alternative treatment (13). Results of a study by ketter et al. revealed that Aripiprazole was administered to 30 patients for a mean length of 84±69 days at a mean final dose of 15.3±11.2 mg/day while they were also taking other psychotropic and non-psychotropic prescription drugs, 14 people stopped taking aripiprazole, including 17% due to ineffectiveness, 10% due to patient preference, and 20% due to side effects. Clinical Global Impression-Severity improved with aripiprazole, with 27% of patients responding, including 13% of remissions. The Global Assessment of Function, as well as ratings for depression

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and suicidal ideation, all improved. Aripiprazole was generally well tolerated, and neither the mean adverse impact ratings nor the mean weight significantly changed. In cases of treatment-resistant bipolar depression, aripiprazole showed promise and was generally well tolerated (14). Schaffer et al. revealed in their results that lurasidone is a safe and efficient supplementary drug for the complete spectrum of bipolar disorder patients who are treatment-resistant in an outpatient setting. For both acute and maintenance therapy of other significant bipolar disorder presentations, such as mixed and rapid-cycling symptoms, it appears to be effective, even at low doses. Last but not least, low doses however may reduce the chance of overactivation, which could lead to therapeutic failure (15).

Diaz et al. reported that the three drugs' recovery rates which ranged from 12.5% to 37.5% for inositol, 16.7% to 26.7% for lamotrigine and 7.7%-9.1% for risperidone, did not significantly differ from one another. Furthermore, the authors explained that according to a recent comprehensive review and meta-analysis of randomized controlled studies addressing treatment-resistant bipolar depressive therapy, ketamine was linked to a sizable response rate one day after infusion. Electroconvulsive therapy was simultaneously shown to be equally beneficial for both treatment-resistant bipolar depression and treatment-resistant unipolar depression. Additionally, some research findings suggested that the psychostimulant modafinil/armodafinil and the dopaminergic agonist pramipexole might be used to treat the depressed symptoms of people with treatment-resistant bipolar disorder (16). Similarly, the results of a clinical trial evaluating the effects of ketamine in treatment-resistant bipolar depression among 18 patients with a current depressive episode lasting at least four weeks, who had failed at least one adequate antidepressant trial and had not responded to valproate or lithium. for a minimum of four weeks at appropriate levels, 56% of those receiving ketamine were observed to respond, with only 13% showing remission 40 minutes after ketamine administration. After one day, response rates were 44% and remission rates were 31% (17).

Increases in dosage or the use of combination mood stabilizers, such as lithium and valproate, are common pharmacotherapeutic strategies for managing treatment resistance. In an effort to improve outcomes, medical professionals may also include other psychotropic medications in a patient's treatment plan, such as an atypical antipsychotic or an antidepressant. While some people may benefit from this, many people will still not experience clinical improvement, may not be able to tolerate treatment combinations or dose increases, or may get better before relapsing. Many people will exhibit reduced functioning and quality of life and continue to have severe mood instability over the long term even when standard medication is deemed appropriate for the alleviation of acute symptomatology (18, 19). Medical professionals face a considerate challenge in managing treatment-resistant bipolar depression because the condition has received little research and there is a lack of data to support each suggested treatment. The primary confounding element is the lack of a validated, systematic, and shared definition for treatment-resistant depression, leading to varied staging types and numbers of pharmaceutical trials failure to define diagnosis adopted by each study team. Different studies' definitions of response, remission, and recovery as well as the removal of patients with a high risk of therapy non-response are further complicating factors (20). Management of treatment-resistant bipolar depression still remains a challenge even today in modern era of medicine advocating direly for the further clinical research studies and trials for precisely addressing and developing therapeutic options for treatment- resistant bipolar depression as the available literature is quite limited in this aspect.

Conclusion

Despite new, emerging pharmacological and non-pharmacological treatments, managing treatment-resistant bipolar depression is a challenging task. It is a complex issue in clinical psychiatry. Due to the significant prevalence of treatment-resistant depression in patients with bipolar disorder and the limited number of therapies that are effective, it is obvious that new therapeutic approaches and a fresh paradigm for treating treatment-resistant bipolar depression are both necessary. Additionally, further research employing homogeneous patient samples and a precise definition of treatment resistance is urgently required.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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