

Maintenance Treatments of Lithium, Carbamazepine, and Adjunctive CBT in Bipolar Disorder: Review

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Abstract: Bipolar disorder is an acute mental health condition with high relapse rates. At the onset, it can affect the normal functioning of the individual life of patients. Although there are no curative treatments for it, many other treatments are available to reduce relapse rates and stabilise symptoms. This article reviewed previous experiments, meta-analyses, and literature reviews on the topic of pharmacotherapies and integrated therapies in treating bipolar disorder and their effects on recurrent rates. It focused on three treatments, which were lithium, carbamazepine, and adjunctive cognitive behavioural therapy, and aimed to assess their efficacy and tolerability in treating bipolar disorder. Lithium was found to show its anti-manic effect and anti-suicide effect, which remained the gold standard in treating bipolar disorder. Whereas, adverse effects should be carefully noted to avoid worsened long-term health conditions. It was shown that carbamazepine had a comparable effect to lithium and was a potential candidate for lithium. But it requires more research to further assess its effectiveness. Adjunctive CBT showed its efficacy in treating both manic and depressive episodes. While bipolar patients who had relatively more mood episodes may not benefit from it.

Keywords: Bipolar disorder, Lithium, Carbamazepine, Adjunctive CBT, Relapse

1. Introduction

Bipolar disorder, a severe and chronic mental health issue, is characterised by mood swings between two extreme episodes, which are mania or hypomania and depression. As a category, bipolar disorder encompasses three types, namely bipolar I disorder, bipolar II disorder and cyclothymic disorder. The factor that distinguishes and diagnoses these different types is the severity of symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), bipolar I disorder is the most serious type and can be diagnosed based on its manic episode, during which bipolar patients will feel high-spirited or irritable. They also gain some changes in behaviours, such as less need for sleep and increased activities or risky behaviours. While during depressive episodes, patients tend to have intense sadness and despair, or even suicidal ideations. In contrast, bipolar II disorder can be wrongly diagnosed as unipolar depression. Cyclothymic disorder involves milder symptoms of depressive episodes and hypomania [1].

According to the NHS website bipolar disorder is a common mental health disorder with no curative treatments and affects more than 1% of the world's population [2]. It can occur at any age but is more prevalent in late adolescence and early adulthood. People are equally likely to develop

bipolar disorder regardless of gender, race, or cultural background. However, there are several differences regarding the severity of symptoms and suicidal behaviours across gender. Diflorio and Jones found that women have higher risks of bipolar II disorder because of reproductive life events (e.g., childbirth) [3]. 26% of bipolar women showed episodes of bipolar disorder after their deliveries [4]. In addition, women had a higher frequency of attempted suicides, and they also had a higher number of suicide attempts than men [5]. It is worth noting that bipolar disorder has the highest suicide rate among psychiatric disorders. 20.9% of bipolar I disorder patients had at least one suicide attempt during their lifetime, and 25.2% of them had suicidal ideations [6, 7].

One notable feature of bipolar disorder is its recurrence, each time accompanied by dysfunctions in life. Moreover, these recurrent episodes are always associated with unwanted results. For example, bipolar patients may largely lose interest in their work during depressive episodes. Since the episodes can last for several weeks or even longer, they will lose their jobs due to inactivity. Nevertheless, the relapse rate is not uncontrollable. Although there are no treatments that can completely cure bipolar disorder, there do have many pharmacotherapies and psychotherapies which try to reduce the recurrences. Perlis and colleagues spotted a key fact here: among 58.4% of 1469 participants who recovered from bipolar disorder, 48.5% of them had recurrence during the 2-year follow-up study [8]. This suggests that patients can hardly fully recover from bipolar disorder, and therefore there is a necessity to have long-term treatments.

Since bipolar disorder is prone to relapse and requires long-term treatment, psychiatric medications are often used as standard treatment for most affective disorders, including bipolar disorder. Although they are not curative, they can stabilise symptoms and delay relapses. Three broad types of medication are commonly used to treat bipolar disorder, namely mood stabilisers, anticonvulsants and antipsychotics. These medications have little effect on depressive episodes and have shown efficacy in controlling manic episodes. However, it is important to note that the disadvantages of medication still exist in that patients may still suffer from frequent relapses after taking the medication, and they may have to suffer from adverse effects associated with medication.

In such cases, other treatments are recommended to be added to improve efficacy and reduce relapse rates in bipolar disorder. Adjunctive psychotherapies are now added to long-term treatments. Among many psychotherapies, cognitive behavioural therapy (CBT) shows its efficacy in helping patients identify and cope with their experiences of the onset of illness. However, the efficacy of CBT remains controversial, inconsistent results were obtained from different studies. Thus, this review chooses to focus on this widely effective therapy to assess its effects in treating bipolar disorder.

This review aims to evaluate the efficacy and tolerability of lithium and carbamazepine, together with adjunctive CBT in stabilising symptoms and reducing relapse rates of bipolar I disorder.

2. Treatments

2.1. Mood Stabiliser: Lithium

Mood stabilisers are known as a type of medication that is used to treat cyclic mood disorders (e.g., bipolar disorder). They are also sometimes called anti-manic drugs because of their efficacy in reducing symptoms of manic episodes [9]. Among these mood stabilisers, lithium plays an important role. It has been used for treating bipolar disorder for over 70 years and remains the gold standard [10]. The benefits of using lithium include its anti-manic and anti-suicide effects. However, its adverse effects, small therapeutic window and moderate effects in depressive episodes constitute its safety concerns.

As an anti-manic medication, lithium is proven to have high efficacy in reducing manic symptoms and mania relapses. Bowden found that patients who took lithium had significant improvements in manic symptoms, such as increased activity and motor hyperactivity, with effect sizes of 0.82 and

0.61 respectively [11]. While patients who received placebo treatments had effect sizes of 0.22 and 0.14. This demonstrated the exceptional effect of lithium in stabilising manic symptoms compared to a placebo. In addition, in terms of controlling mania recurrence rates, lithium also showed privilege in comparison with a placebo and some other anti-manic medications [10]. Geddes et al. found that lithium was better at reducing the relapse rate of manic episodes than valproate [12]. When compared to lamotrigine, Hashimoto and colleagues obtained a risk ratio of 2.13 (a risk ratio greater than 1 means lithium has higher efficacy and vice versa for lamotrigine) [13]. Indicating that lithium was more favourable. Similar results were reviewed by Cipriani et al. [14].

The anti-suicide effect of lithium plays a significant role in depressive episodes. The decreased lifespan of bipolar patients is associated with frequent suicides during the bipolar depression. The suicide rate of bipolar patients is 10-30 times higher than the general population, and approximately 20% of them commit suicide [15]. In fact, the mechanism by which lithium can reduce suicide rates remains unknown. However, Cipriani et al. suggested possible explanations [16]. They proposed that this effect can be due to the reduced recurrent depressive episodes, which indirectly reduce suicide rates. Moreover, they also found that lithium can decrease aggression and impulsivity, therefore, suppressing suicidal ideations.

However, contradicting the first explanation by Cipriani et al, lithium is not as effective in treating bipolar depression as it was in treating bipolar mania [16]. There is evidence that lithium has been shown to have comparable effects to placebo in bipolar depression treatments [17, 18]. Malhi et al. suggested that the possible reason for its moderate effects is that there is a significant time lag between taking the lithium and the onset of its effects, which makes patients find it inefficacious, and thus discontinue it [19].

When using lithium treatment, it is important to assess not only its effectiveness but also control its dosage and pay attention to its adverse effects. First, Lithium has a small therapeutic window, which means the difference between the minimum effective dose and the toxic dose is small. Nolen and colleagues proposed the standard serum level of lithium for bipolar treatment should be between 0.60-0.80 mmol/L [20]. and the dose can be adjusted depending on the individual conditions of bipolar patients (with a lower threshold of 0.40 mmol/L and an upper threshold of 1.00 mmol/L). Excessive lithium intake can result in a range of adverse effects, such as nausea, diarrhoea, polyuria, tremor and other even more serious symptoms [21]. Moreover, Honig et al. found that lithium can have side effects on cognitive functions (e.g., memory impairments and slow information processing) [22]. The mechanism of action of lithium remains unknown.

As a result of the adverse effects and concerns about long-term health, bipolar patients may choose to discontinue lithium treatment. The key point is that rapid discontinuation of lithium can result in a dramatic increase in relapse rate, which can be even higher than in untreated patients [23]. They also suggested that there was a 13-fold increased risk of fatal suicide after rapid discontinuation compared to during lithium treatment. While gradual discontinuation does not cause these results. Up to 30.7% of patients who discontinue lithium gradually experienced no relapse in the 2-year follow-up study, compared to only 4.9% in rapid discontinuation patients [24].

2.2. Anticonvulsant: Carbamazepine

According to the NHS website, carbamazepine is an anticonvulsant which is commonly used to treat epilepsy [25]. In recent years, it has been increasingly used as a mood stabilizer in the treatment of the bipolar disorder. Grunze and Grunze suggested that carbamazepine and lithium have similar effects, but lithium is more prominent, which indicates that carbamazepine is a qualified candidate for lithium [26]. When patients do not respond to lithium or they show serious adverse effects, carbamazepine can be the substitute for it. In this case, the reasons for using carbamazepine include its comparable effects to lithium on manic episodes and its medication adherence. While due to its

tolerability and less impressive effects than lithium, it is hardly the first choice for bipolar disorder treatments.

Compared to placebo, carbamazepine showed greatly more improvements in manic symptoms. Smith and colleagues acquired a huge mean difference of 5.82 in scores on the Young Manic Rating Scale (YMRS) between the placebo and the carbamazepine group [27]. And the placebo group obtained significantly higher scores in YMRS. Although carbamazepine showed its effects in stabilising manic symptoms, its role in controlling relapse rates remains unclear due to the lack of long-term controlled trials with placebo [26]. However, studies are comparing the effects of carbamazepine on mania relapse rates with lithium. It was found that within 2 years, only 27% of participants who received lithium had recurrences, and these relapses almost happened in the first three months. While 42% of the participants who received carbamazepine treatments experienced relapses, and they were evenly distributed over the 2 years [28]. This indicates the predominant role of lithium in treating bipolar disorder. While carbamazepine remains the second choice, more high-quality studies are warranted to assess the long-term effects of carbamazepine.

Based on available extant studies, it is known that the effect of carbamazepine in bipolar depression is comparable to a placebo, and is similar to lithium [29]. The odds ratio for carbamazepine of remission was 0.90, $p = 0.76$, (an odds ratio less than 1.00 means placebo has higher efficacy and vice versa for carbamazepine). While the odds ratio for lithium was 1.27, $p = 0.67$. These results are not significant, which shows that both carbamazepine and lithium are poor at affecting bipolar depression. Moreover, due to a lack of adequate studies addressing the efficacy of carbamazepine in treating bipolar depression, this review fails to provide further assessments of its role in this area.

2.3. Adjunctive CBT

CBT has been widely used as psychotherapy for many mental health problems, which aims to improve symptoms. It can be used either as a monotherapy or integrated with medications. However, in treating bipolar disorder, a greater reduction in relapse rates can be achieved when combining CBT and other pharmacotherapies [30]. The major steps of CBT, in this case, are cognitive reconstructing, behavioural activation and problem-solving [31]. Its effectiveness in stabilising symptoms and reducing relapse rates requires more studies, and some trials have concluded that the effects of CBT are related to the patient's demographic and clinical characteristics.

Perry and colleagues found CBT to be highly effective in treating bipolar mania [32]. They suggested that by helping patients learn to recognize prodromal symptoms of mania, together with prescribed medication, the relapse rate can be significantly reduced. However, other studies obtained different results. Scott et al. in their study found no significant difference between the effects of CBT and treatment as usual in reducing relapse rates [33]. By comparing the demographic and clinical features of patients, it can be found that all the participants in Perry's study had less than 30 times previous bipolar episodes, while in Scott's study, about 26% of participants experienced more than 30 times previous bipolar episodes. In addition, less than half of the people in Scott's experiment were living with a partner, compared to roughly 60% of those in Perry's experiment who were married or cohabiting. Thus, it can be concluded that companions and the number of previous bipolar episodes are two crucial factors leading to completely different study results. This conclusion is consistent with the one given by Scott et al., where CBT tends to benefit bipolar patients with comparatively fewer previous episodes [33].

In contrast to medication as monotherapy, a combination of CBT and medication showed high efficacy in treating bipolar depression. It was found to be associated with a low relapse rate and improvements in symptoms of depressive episodes with moderate effect sizes of 0.044 and 0.59 respectively (both indicated in favour of CBT). The reason for the high efficacy of CBT in treating

bipolar depression is most likely because it is a talking therapy, which can touch on the deep reasons for depression, rather than stimulating the body to respond as the medication does.

3. Conclusion

Bipolar disorder is a relatively common and chronic psychological disorder that not only deprives the person of a normal life but also leaves their family and friends to suffer with them. Although no cure has yet been developed, existing medication and psychological treatments have varying degrees of advantages. Lithium, for example, shows its high efficacy in stabilising manic symptoms and reducing manic relapse rates. Its unique effect in suppressing suicidal ideations also fills in for its ineffectiveness in bipolar depressive episodes. Moreover, although the newly prescribed carbamazepine is not as efficacious as lithium, it also presents its anti-manic effects. Since carbamazepine is a relatively new medication in bipolar disorder treatment, more long-term studies are warranted to further evaluate its effectiveness. What's more, when receiving medications, it is important to follow the regimen provided by therapists to ensure safety and long-term health. Regarding CBT, it has high efficacy in treating both manic and depressive episodes, while it is recommended that bipolar patients should receive CBT treatment as soon as possible to obtain its maximum benefits.

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