Advances in Research of Antidepressants in the Treatment of Bipolar Depression

Junchen GU, Xiong CHEN, Conghui WANG, Chunqi AI*

Mental Health Center, Shiyan Taihe Hospital (Hubei University of Medicine), Shiyan 442000, China

Abstract Drawing on recent evidence from large cohort studies and meta-analyses, this review summarizes advances in the use of antidepressants for bipolar depression. It focuses on the incidence and risk factors of drug-induced mania and compares the efficacy and safety profiles of various antidepressant classes. Available evidence indicates that the risk of antidepressant-associated mania may be lower than previously believed, and short-term efficacy has been partially supported. Nevertheless, long-term treatment strategies, risk-benefit assessments, and individualized prescribing require further validation through high-quality studies. This article aims to inform clinical decision-making and guide future research in the management of bipolar depression.

Key words Bipolar disorder, Bipolar depression, Antidepressants, Drug-induced mania, Mood stabilizers

1 Introduction

Bipolar disorder (BD) is a chronic psychiatric condition defined by recurrent episodes of depression alternating with mania or hypomania. According to epidemiological estimates, its lifetime prevalence is around 1%, accounting for a major source of global disease burden[1]. In clinical practice, given that manic or hypomanic episodes often entail significant social impairment and safety risks, treatment strategies typically emphasize control of the manic phase, making mood stabilizers the cornerstone of pharmacotherapy for bipolar disorder. However, multiple studies indicate that over the natural course of the illness, patients spend substantially more time in depressive episodes than in manic episodes, approximately 63% of the total illness duration[2]. Furthermore, depressive episodes have a more detrimental impact on cognitive function, social functioning, and overall quality of life[3].

Antidepressants are well-established as effective treatments for unipolar depression, but their role in bipolar depression remains a subject of debate. Currently, the only antidepressant regimens approved by the U. S. Food and Drug Administration (FDA) for bipolar depression are vortioxetine and the olanzapine-fluoxetine combination. Despite this, antidepressants are still widely used in clinical practice. For example, a study examining medication use in Germany, Austria, and Switzerland between 1997 and 2014 found that approximately 60% of patients with bipolar depression received ongoing antidepressant therapy[4]; in the United States, roughly 50% of BD patients were prescribed antidepressants[5]. These findings highlight a persistent gap between clinical practice and the available evidence base.

The controversy surrounding the use of antidepressants in the treatment of bipolar depression primarily centers on two aspects: first, antidepressants may induce drug-induced mania, and second, there is insufficient evidence to support their efficacy. Drug-induced mania generally refers to manic or hypomanic symptoms that occur within a certain period after the administration of antidepressants[6]. Although there is no unified definition regarding the time of onset, it is generally believed to occur within 4 to 12 weeks after antidepressant treatment[7-8]. This phenomenon was first reported in 1959 in studies of tricyclic antidepressants[9], and has since been observed across various types of antidepressants. In recent years, with improvements in research methodology and the expansion of sample sizes, studies on the efficacy and safety of antidepressants in bipolar depression have continued to deepen, and new evidence has gradually accumulated. This article reviews the relevant research progress, aiming to provide a reference for clinical practice and future research directions.

2 Incidence of antidepressant-associated drug-induced mania

Traditional views hold that patients with bipolar depression have a relatively high risk of developing drug-induced mania after receiving antidepressant treatment, with an estimated incidence of approximately 12.5% to 14%[10]. The risk varies significantly among different types of antidepressants. Tricyclic antidepressants are considered to carry the highest risk, with some studies reporting an incidence as high as 69% and a mean incidence of approximately 12.7%; the risk associated with venlafaxine is approximately 13% to 15%; while selective serotonin reuptake inhibitors (SSRIs) and bupropion have relatively lower risks, at approximately 7%[11].

However, recent large-sample studies have offered new perspectives challenging the above views. A study published in 2023 utilized data from the Danish National Health Registry, including 3 554 patients with bipolar disorder who were hospitalized for the first time and received antidepressant treatment. The results showed that manic episodes peaked in the three months prior to antidepressant treatment, whereas the incidence of mania decreased significantly (by 65%, $P < 0.01$) during the 6 to 9 months after treatment compared with the 6 months prior to treat-

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Junchen GU, master's degree, resident physician. * Corresponding author. Chunqi AI, master's degree, chief physician.

ment. When mood stabilizers were used concomitantly, the reduction reached 72% ($P<0.01$)[12].

A 2024 target trial emulation study by the same research team followed 979 patients hospitalized for their first episode of bipolar depression over one year, 358 of whom received antidepressants. Findings revealed that, irrespective of concomitant mood stabilizer use, the antidepressant-treated group did not show a significantly higher risk of manic conversion compared to those not receiving antidepressants ($HR=1.08$, 95% $CI=0.72-1.61$)[13].

Furthermore, a 24-week study involving 763 patients with bipolar disorder similarly found that antidepressant use was not associated with an increased risk of manic symptoms. A 2017 meta-analysis pooling 11 long-term studies (treatment duration > 4 months) reported no significant difference in the risk of antidepressant-induced mania compared with placebo[14].

3 Risk factors for drug-induced mania

A 2020 meta-analysis identified several key risk factors for drug-induced mania, including concomitant mood stabilizer use, the class of antidepressant, and a greater number of prior depressive episodes. In contrast, factors such as age at onset, sex, bipolar subtype, rapid cycling status, and prior manic episodes did not show statistically significant associations[15].

Genetic studies have produced mixed findings. Several reports suggest a possible link between the short allele (s allele) of the serotonin transporter gene (SLC6A4) polymorphism and drug-induced mania. However, genome-wide association studies (GWAS) have not consistently replicated this association. For instance, a GWAS involving 814 bipolar disorder patients of European ancestry found no loci significantly associated with drug-induced mania, with SLC6A4 not ranking among the top correlated genes[16].

Other research has revealed a positive correlation between a polygenic score for antidepressant response and the risk of antidepressant-induced mania. Additionally, slower metabolism mediated by cytochrome P450 (CYP) 2C19, which is an enzyme responsible for metabolizing multiple antidepressants, has been implicated in increased susceptibility to sertraline- and amitriptyline/clomipramine-induced mania, although the *CYP2C19* gene itself has not been directly linked to mania onset[17]. Collectively, these findings point to a multifactorial etiology underlying drug-induced mania.

4 Efficacy and safety of various antidepressants

For a long time, evidence on the efficacy of antidepressant monotherapy for bipolar depression has been limited and inconsistent. However, some recent studies suggest that its efficacy may be comparable to that in unipolar depression. A meta-analysis by Liu *et al.* showed that antidepressants significantly reduced the risk of new depressive episodes in patients with bipolar depression ($RR=0.64$, 95% CI: 0.49 – 0.83, $P=0.000\ 9$)[18]. Certain differences in efficacy and safety persist among different types of antidepressants.

4.1 Tricyclic antidepressants Tricyclic antidepressants are among the earliest antidepressants used in clinical settings. Prior research has consistently indicated that this class is associated with a substantially higher risk of drug-induced mania compared with SSRIs and SNRIs[19]. In addition, evidence supporting their efficacy in bipolar depression is limited. With their clinical use declining in recent years, research attention to tricyclic antidepressants has significantly decreased[20].

4.2 SSRIs and SNRIs SSRIs are currently the most widely prescribed class of antidepressants in clinical practice, and their safety profile in the treatment of bipolar depression is generally considered superior to that of tricyclic antidepressants. Studies have shown that fluoxetine and escitalopram have certain efficacy compared with placebo in short-term treatment[21-22]. A randomized double-blind controlled study also demonstrated that sertraline and lithium did not differ significantly in short-term efficacy for the treatment of bipolar II depression[23]. Venlafaxine was previously considered to carry a relatively high risk of manic conversion[24]; however, several randomized controlled trials have indicated that, in short-term treatment, it may alleviate depressive symptoms more rapidly than lithium, without a significant increase in the risk of mania[25-27].

4.3 Other new antidepressants Bupropion is generally considered to have a low risk of manic conversion, but high-quality evidence supporting its monotherapy in bipolar depression remains limited. A triple-blind randomized study found comparable efficacy between bupropion and venlafaxine in treating bipolar depression[28]; however, case reports have suggested that bupropion may still be associated with mania[29]. Among other newer antidepressants, a randomized controlled trial reported that in patients unresponsive to lurasidone, vortioxetine showed superior early treatment efficacy compared to valproate, though no significant differences were observed at 8 and 12 weeks. In particular, approximately 10% of patients in the vortioxetine group developed drug-induced mania[30] within 4 weeks. Furthermore, an open-label study suggested that adding agomelatine to a mood stabilizer may be effective and well-tolerated for bipolar depression, although 2 of 28 participants developed mania or hypomania within 6 weeks[31]. Some research further indicates that prolonged antidepressant use following remission of an acute bipolar depressive episode does not offer clear efficacy benefits and may instead elevate the risk of mania[32-33].

5 Conclusions and prospects

Recent large-sample studies and meta-analyses suggest that the actual incidence of antidepressant-induced mania may be lower than traditionally believed. Besides, evidence supporting the short-term efficacy of antidepressants in the treatment of bipolar depression has gradually accumulated. However, due to inconsistencies in existing research findings, the optimal strategy for antidepressant use in bipolar depression remains to be fully established. In addi-

tion, several limitations persist in the study of antidepressant-induced mania. First, the current definition of drug-induced mania is largely based on the emergence of manic symptoms within a certain period following antidepressant exposure. However, given the complex natural course of bipolar disorder, it is clinically challenging to definitively distinguish between medication-induced mania and the natural progression of the illness. Future research should therefore incorporate longer follow-up periods and more rigorously designed randomized controlled trials. Second, earlier studies often included tricyclic antidepressants, whereas newer antidepressants differ substantially in their pharmacological profiles and safety characteristics, which may contribute to inconsistencies across studies. Furthermore, patients with bipolar disorder exhibit significant heterogeneity, yet some studies have not adequately characterized patient subgroups, such as bipolar I versus bipolar II subtype, mood polarity, and mood trajectory. This limitation reduces the generalizability of findings. Future research should adopt more refined study designs and more detailed sample descriptions to better delineate the risks and benefits of antidepressant treatment across distinct patient subgroups.

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