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Review Article

No Evidence Support Quetiapine in Treatment of Adolescent Bipolar Depression

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Abstract

Quetiapine, an atypical antipsychotic with established efficacy in the treatment of schizophrenia, shows efficacy in the treatment of acute mania and depression associated with bipolar disorder. Quetiapine, either as monotherapy or in combination with lithium or divalproex sodium, is generally well tolerated and effective in reducing manic symptoms in adult and adolescent patients with acute bipolar mania, and is approved for use in adults for this indication. As monotherapy, the drug is also effective in reducing depressive symptoms in patients with bipolar depression. It is associated with a low incidence of Extrapyramidal Symptom (EPS)-related adverse events and low EPS ratings in bipolar disorder. Quetiapine thus shows potential in the treatment of bipolar depression, and represents a useful agent for the treatment of acute bipolar mania. But for children and adolescent, quetiapine show no difference to placebo. The both RCT and evidence-based medicine study indicate that quetiapine have no efficacy for children and adolescent bipolar depression.

Keywords: Quetipine; Bipolar depression; Children; Adolescent

Introduction

Quetiapine is considered one of the few atypical antipsychotic drugs for treating bipolar depression, therefore some guidelines include quetiapine, lurasidone, and caliprazine as atypical antipsychotic drugs for treating bipolar depression [1]. Unfortunately, it is not suitable to treatment for bipolar depression in children and adolescents, although it is very suitable to adult bipolar depression. Quetiapine is widely used in clinical practice for the treatment of bipolar depression in children and adolescents in present, but its efficacy is questionable. Therefore, there has been an increasing amount of research on the treatment of bipolar depression in children and adolescents with quetiapine, which has shown its effectiveness in a specific field.

Results from RCT Study

There are two clinical RCT studies cited on the treatment of depression in children and adolescents with quetiapine In 2009, a double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder, which was published in bipolar disorder was carried out by DelBello [2]. Thirty-two adolescents (ages 12-18 years) with a depressive episode associated with bipolar I disorder were randomized to eight weeks of double-blind treatment with quetiapine, 300-600 mg/day, or placebo. This two-site study was conducted from march 2006 through august 2007. The primary efficacy measure was change in Children's Depression Rating Scale-Revised Version (CDRS-R) scores from baseline to endpoint. Secondary efficacy measures included change in CDRS-R scores over the eight-week study period, changes from baseline to endpoint in Hamilton Anxiety Rating Scale (HAMA), Young Mania Rating Scale (YMRS), and clinical global Impression-Bipolar Version Severity (CGI-BP-S) scores, as well as response and remission rates. Safety and tolerability were assessed weekly. Results are following. There was no statistically significant treatment group difference in change in CDRS-R scores from baseline to endpoint ($p = 0.89$, effect size =-0.05, 95% confidence interval: -0.77-0.68), nor in the average rate of change over the eight weeks of the study ($p = 0.95$). Additionally, there were no statistically significant differences in response (placebo =67% versus quetiapine = 71%) or remission (placebo = 40% versus quetiapine = 35%) rates, or change in HAMA, YMRS, or CGI-BP-S scores (all $p > 0.7$) between treatment groups. Dizziness was more commonly reported in the quetiapine (41%) than in the placebo (7%) group ($p = 0.04$). Conclusions was that the results suggest that quetiapine monotherapy is no more effective than placebo for the treatment of depression in adolescents with bipolar disorder. However, limitations of the study, including the high placebo response rate, may have contributed to our findings and should be considered in the design of future investigations of pharmacological interventions for this population.

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In 2014, the efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial was also carried out by Findling, which was published in journal of child adolescent psychopharmacology. This multicenter, double-blind, randomized, placebo-controlled study investigated quetiapine XR (dose range, 150-300 mg/day) in pediatric outpatients with an American psychiatric association, diagnostic and statistical manual of mental disorders, 4th ed, Text Revision (DSM-IV-TR) diagnosis of bipolar I or bipolar II disorder (current or most recent episode depressed) treated for up to 8 weeks. The primary study outcome was mean change in Children's Depression Rating Scale-Revised (CDRS-R) total score. Secondary efficacy outcomes included CDRS-R-based response and remission rates. Of 193 patients randomized to treatment, 144 patients completed the study (75.3% of quetiapine XR group; 74.0% of placebo group). Least squares mean changes in CDRS-R total score at week 8 were: -29.6 (SE, 1.65) with quetiapine XR and -27.3 (SE, 1.60) with placebo, a between-treatment group difference of -2.29 (SE, 1.99; 95% CI, -6.22, 1.65; p=0.25; mixed-model for repeated measures analysis). Rates of response and remission did not differ significantly between treatment groups. The safety profile of quetiapine XR was broadly consistent with the profile reported previously in adult studies of quetiapine XR and pediatric studies of quetiapine Immediate-Release (IR). Potentially clinically significant elevations in clinical chemistry values included triglycerides (9.3%, quetiapine XR; 1.4%, placebo group) and thyroid stimulating hormone (4.7%, quetiapine XR; 0%, placebo group). An adverse event potentially related to diabetes mellitus occurred in 3.3% of the quetiapine XR versus no adverse events in the placebo group.Conclusions is that Quetiapine XR did not demonstrate efficacy relative to placebo in this 8 week study of pediatric bipolar depression. Quetiapine XR was generally safe and well tolerated [3].

Results from Evidence-based Medicine (EBM) Study

There may be bias in citing two clinical studies on the treatment of depression in children and adolescents with quetiapine, but this bias can be avoided through evidence-based medicine study. Evidence based medicine involving quetiapine in the treatment of depression in children and adolescents ma y may be first introduced in 2014. Suttajit and their colleagues carried out a systematic review and meta-analysis about Quetiapine for acute bipolar depression, in which they found that evidence for the use of quetiapine combined with mood stabilizers in children and adolescents with acute bipolar depression is too small to support the clinical practice by two study in children and adolescents of 11 RCT [4]. From then on, related research gradually increased.

In 2017 it was carried out by Maneeton and their colleagues that is a systematic review and meta-analysis about quetiapine monotherapy versus placebo in the treatment of children and adolescents with bipolar depression. It also considered as first report of meta-analysis about Quetiapine in treatment bipolar depression in youth by all cited articles only in adolescent bipolar depression treated by quetiapine. A total of 251 randomized patients in the three RCTs of quetiapine versus placebo in the treatment of bipolar depression for children and adolescents were eligible in this study. The pooled mean-changed score of the quetiapine-treated group was not greater than that of the placebo-treated group. Similarly, the pooled response and remission rates were not different between the two groups. The pooled overall discontinuation rate and the discontinuation rate due to adverse events were not different between the two groups. So they think that according to the findings in this result, quetiapine may not be efficacious in the treatment of bipolar depression in children and adolescents [5].

In 2020, other study was carried out by Srinivas and their colleagues that is a systematic review of randomized clinical trials about efficacy and safety of quetiapine for pediatric bipolar depression. They also found that quetiapine was no better than the placebo in treating pediatric bipolar depression. And new concept of High Placebo Response Rate (HPR)was suggested [6]. In 2021, Patel and their colleagues also found that there was no statistically significant in treatment and response rates between quetiapine and placebo in all RCTs. But they found Lurasidone and Olanzapine-Fluoxetine Combination (OFC) displayed a significant reduction in depressive symptoms and response was significantly higher for lurasidone (59.5% vs. 36.5%; $p < 0.001$) and OFC [7]. In fact, For youth with bipolar depression, up to 2 years of treatment with lurasidone was generally well tolerated, safe, and effective with relatively low rates of discontinuation due to AEs, minimal effects on weight, metabolic parameters or prolactin, and continued improvement in depressive symptoms [8,9].

Especially, The recent research has attracted psychiatrist's attention. To assess the relative efficacy and safety of second-generation antipsychotics for treating major depressive episodes in youths with bipolar disorder, DelBello and their colleagues retrieve four RCTs comparing placebo to lurasidone, quetiapine (1 each for immediate- and extended-release), and the OFC, which met all of the inclusion criteria. A systematic literature review using PRISMA guidelines and Network meta-Analysis (NMA) of Randomized Controlled Trials (RCTs) of second-generation antipsychotics for bipolar depression in youths 10 to 18 years of age was conducted. Evidence from 4 studies in this NMA indicated that lurasidone and OFC, but not quetiapine, were efficacious for the treatment of bipolar depression in youths [9]. This result has caused a strong reaction. The editorial also followed suit. The title is second-generation antipsychotics for bipolar depression in youths. They call on the best evidence synthesis is a strong call for further evidence. They also consider that DelBello et al. have filled this gap by conducting the first NMA of second-generation antipsychotics for major depressive episodes in youths with bipolar disorder. The NMA by DelBello et al. is arguably the best available evidence synthesis on the comparative efficacy and safety of second-generation antipsychotics for bipolar depression in youths [10]. So, it was limited that quetiapine was used in adolescent bipolar depression.

Expectation

This drug is still visible in clinical practice and is even quite common in treatment for children and adolescent bipolar depression. Expert opinion was efficacy and safety of pharmaceutical agents in adolescents with BD appear to mirror adults with BD. The similarities between adolescent and adult outcomes suggest that it is reasonable to utilize adult data to aid with clinical decision making in adolescents with BD [11]. But this quetiapine cannot be referenced from adult data to adolescents. In fact, Suttajit's meta-analysis have found that quetiapine is effective in adult, no effective in adolescent bipolar depression [4]. We hope to see that the treatment guidelines for bipolar depression should specify whether it is for adults or children and adolescents, and we also hope that there will be treatment guidelines for bipolar disorder in children and adolescents. In fact, treatment guidelines for bipolar disorder in children and

adolescents is existing [12]. It is pity that is a treatment guideline 5 years ago.

Pharmacotherapeutic for Child and Adolescent Bipolar Depression

It is a visible clinical fact that quetiapine has poor efficacy in treating bipolar depression in children and adolescents. The question we are facing is which drugs we can choose to effectively treat bipolar depression in children and adolescents.

Efficacy and safety of pharmaceutical agents in adolescents with BD appear to mirror adults with BD. Lithium/mood stabilizers are preferred first-line agents over antipsychotic medications, but the latter are second-line agents particularly in bipolar depression. When lithium is used, serum levels approaching 1.0 mEq/L are reasonable since younger people appear to require/tolerate higher levels [11]. Lamotrigine (LAM) as a anticonvulsant have a efficacy for bipolar depression in adult. A systematic review identified LAM as an effective and safe drug in Pediatric Mood Disorders (PMDs) especially, BDs. Overall, LAM was well tolerated with no major significant side effects and no cases of Stevens-Johnson syndrome. But there is inconsistent evidence to make conclusive recommendations on therapeutic LAM dosage for mood improvement in the pediatric population [13]. And divalproex and oxcarbazepine were not often used in bipolar depression in child and adolescent, except special clinical symptoms [14].

The atypical antipsychotic also was used for bipolar depression in child and adolescent. Lurasidone displayed a significant reduction in depressive symptoms and response [7-9]. A greater improvement in overall depression severity at week 6 with lurasidone (vs. placebo) treatment was observed in the presence of decreased need for sleep and irritability at study baseline in child and adolescent bipolar depression patients [15].

Suicide and non-suicidal self-injury (NSSI are common psychopathological phenomena in bipolar disorder and require timely treatment. Antidepressants often trigger suicide or worsen NSSI, so obviously antidepressants are not suitable for use [16]. Lithium is still one of few drugs that have been proven to reduce the risk of suicidality, and it may have utility in illnesses beyond affective disorders, especially for management soar suicide and NSSI [17]. Practically, as a primary agent or as an adjunct, lithium continues to claim a rightful place in the treatment armamentarium of child psychiatry. Larger findings are consistent with adult studies, showing that lithium is associated with decreased suicidality, less depression, and better psychosocial functioning, other mood stabilizer generally is similar to lithium. Given the paucity of evidence regarding lithium and other mood stabilizer in children and adolescents, these findings have important clinical implications for the pharmacological management of youths with BD.

Author Statements

Consent to Publication

All authors agree to publish the manuscript.

Competing Interests

There were not any financial and non-financial competing interests.

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Authors Contribution

Our authors have different contributions to this article and study. Dr. XM participated in collection of references and write draft. Dr. JHY participated in references review work. Prof. SFL and Prof. JWD participated in design and final review of article.

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