The use of antipsychotics in maintenance treatment of bipolar disorder

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ABSTRACT

Antipsychotics are often used in the treatment of the acute phase of bipolar disorder; however, once the acute phase has resolved and patients enter the maintenance phase, there is some debate as to whether or not to continue the antipsychotic. This article reviews studies examining the use of antipsychotics in the maintenance phase of bipolar disorder.

KEYWORDS

antipsychotic, bipolar disorder, maintenance phase

Treatment selection for the maintenance phase of bipolar disorder is often guided by illness severity, associated features such as rapid cycling or psychosis, and patient preference. Medication adherence during this phase is extremely important in order to prevent relapse and recurrence, reduce suicide risk, reduce cycling frequency, and improve overall function. Because of these many goals, selection of an appropriate treatment regimen is of utmost importance.

Antipsychotics are often used in the acute phase of bipolar disorder, most frequently in patients who have psychotic features. Once the acute phase has resolved and patients enter the maintenance phase, there is some debate as to whether or not an antipsychotic should be continued. Many providers believe that if the antipsychotic helped provide stability, it should be continued into the maintenance phase. Others argue that the risks of continuation therapy outweigh the benefits, especially considering the possibility of metabolic side effects and extrapyramidal symptoms (EPS).

REVIEW OF TREATMENT GUIDELINES

For guidance, seasoned providers often rely on previous clinical experience. Newer providers may find themselves reviewing guidelines for recommendations. Unfortunately, this does not provide a solid answer when it comes to the use of antipsychotics in the maintenance phase of bipolar disorder. The most recent American Psychiatric Association (APA) guidelines for bipolar disorder were published in 2002. At that time, the recommendation for antipsychotics during this period was as follows: ***While maintenance therapy with atypical antipsychotics may be considered, there is as yet no definitive evidence that their efficacy in maintenance is comparable to that of agents such as lithium or valproate***.[1] Fortunately, much more evidence has become available in the 11 years since this was published.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborated to update the CANMAT guidelines for the management of patients with bipolar disorder in January 2013 and could provide additional guidance for other countries/organizations in the process of updating their guidelines.[2] These guidelines list olanzapine, quetiapine, aripiprazole, risperidone long-acting injection, and adjunctive ziprasidone as first line options for the maintenance of bipolar disorder, in addition to lithium, lamotrigine, and valproate. These guidelines reference multiple randomized controlled trials as evidence for their recommendations, while acknowledging limitations in each of them.

ANTIPSYCHOTICS AS MONOTHERAPY

Three years following the development of the APA bipolar disorder guidelines, original research was published comparing the efficacy of olanzapine versus lithium for the prevention of mood episode relapse.[3] This was the first double-blind, randomized study to investigate the potential for an antipsychotic as monotherapy in the maintenance phase. There were 543 subjects from 87 sites worldwide included if they were diagnosed with bipolar disorder with a current manic or mixed episode, had a history of two or more manic or mixed episodes in the previous 6 years, and had a Young Mania Rating Scale (YMRS) total score $\geq$20. The trial had 4 phases: screening, open-label cotreatment for 6-12 weeks, double-blind taper over 4 weeks, and double-blind monotherapy for 48 weeks. In the 48 week monotherapy phase, subjects received 5-20mg of olanzapine daily and lithium titrated to a goal level of 0.6-1.2 mEq/L. The primary outcome of recurrence was defined as requiring

hospitalization for a mood episode or meeting the DSM-IV criteria for recurrence following remission. The results showed that 38.8% of lithium-treated subjects and 30.0% of olanzapine-treated subjects had a documented recurrence of either mania or depression. This established the non-inferiority of olanzapine based on the pre-specified margin of non-inferiority. Additionally, significantly fewer olanzapine-treated subjects were hospitalized for a mood episode during the double-blind period when compared to lithium-treated individuals ($p<0.03$). It should be noted that no difference was seen for subjects with high versus low serum lithium levels.

In 2007, a 26-week, double-blind, placebo controlled trial by Keck, et al. examined the efficacy and safety of aripiprazole monotherapy in subjects diagnosed with Bipolar I disorder.[4] Participants were stabilized on aripiprazole 15-30 mg daily then transitioned to a double-blind phase of either aripiprazole 15-30 mg daily or placebo for 26 weeks. They were followed for an additional 74 weeks on the same regimen if they did not have a relapse during the 26-week phase. Relapse was defined as discontinuation of the study due to lack of efficacy. This included hospital admission due to a mood episode, or addition to or increase in psychotropic medications other than the study drug. At 100 weeks, time to relapse was significantly longer with aripiprazole than placebo ($p=0.011$). The most common adverse effects associated with aripiprazole (≥5% and twice the placebo rate) were tremor, akathisia, dry mouth, hypertension, weight gain, vaginitis, abnormal thinking, pharyngitis, and flu syndrome. Mean weight gain for the aripiprazole group was 0.4 kg compared with a mean weight loss of 1.9 kg in the placebo group.

A 2010 study by Quiroz, et al. examined the safety and efficacy of long-acting injectable risperidone in subjects with current or recent (one mood episode within the previous 4 months) manic or mixed episodes. All participants were treated with open-label oral risperidone for 3 weeks then risperidone long-acting injectable (LAI) for 26 weeks. Participants who maintained stability were then assigned to either long-acting risperidone or placebo for up to 24 months. Recurrence was defined as meeting the DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode, requiring treatment intervention with a mood stabilizer, benzodiazepine, antidepressant, or antipsychotic other than the study drug, hospitalization for any bipolar mood episode, or a YMRS or MADRS score >12, or a required increase in risperidone LAI or supplementation with oral risperidone. Time to recurrence in the risperidone LAI group was significantly longer than the placebo group ($p<0.001$). Weight increase occurred more frequently in the risperidone LAI group. Those in the risperidone LAI group experienced a mean weight increase of 1.1 kg compared to a 0.5 kg weight loss in the placebo group.

ANTIPSYCHOTICS AS ADJUNCTIVE AGENTS

There have been five completed studies examining the use of antipsychotics as adjunctive therapy for the maintenance phase of bipolar disorder. Table 1 was adapted from Susan Leckband's presentation on antipsychotics in bipolar disorder at the 2013 CPNP Annual Meeting in Colorado Springs, CO. It provides brief results for the trials, while additional information is provided following the table.

An open-label, randomized study by Vieta, et al., examined the efficacy and safety of quetiapine compared with placebo in combination with lithium or divalproex for the prevention of recurrent mood events.[6] Subjects were first assigned open-label quetiapine 400-800mg daily plus lithium or divalproex (dose based on serum levels) for up to 36 weeks to achieve 12 weeks of clinical stability. Subjects were then randomized to double-blind treatment with quetiapine 400-800mg/day or placebo in addition to lithium or divalproex, again dosed based on

Table 1: Studies examining antipsychotics as adjunctive therapy for the maintenance phase of bipolar disorder

Authors/Year	SGA	Concomitant Therapy	N (SGA/ placebo)	% Relapse (SGA/placebo)	P value
Vieta, et al (2008)	Quetiapine	+ Lithium + Divalproex	336/337	18.5/49.0	<0.001
Suppes, et al (2009)	Quetiapine	+ Lithium + Divalproex	310/313	20.3/52.1	<0.001
Macfadden, et al (2009)	Risperidone LAI	+ Mood stabilizers + Antidepressants + Anxiolytics	65/59	23.1/45.8	0.01
Bowden, et al (2010)	Ziprasidone	+ Lithium + Valproate	127/113	19.7/32.4	0.01
Marcus, et al (2011)	Aripiprazole	+ Lithium + Valproate	168/169	17/29	0.014

serum levels for up to 104 weeks. The primary outcome of recurrence was defined using several criteria: YMRS or MADRS total scores ≥ 20 at two consecutive assessments or at the final assessment, discontinuation from the study due to an event (mania, depression, or mixed), hospitalization for mania, depression, or a mixed event, or initiation of an antipsychotic, an antidepressant, a mood-stabilizing agent other than lithium or divalproex, an anxiolytic other than lorazepam, or any other medication to treat mania, depression, or a mixed event. The percent of subjects having a recurrent mood episode was lower among those prescribed quetiapine in the double-blind phase (18.5% vs. 49.0%, p<0.001). The most common side effects occurring in ≥5% of the quetiapine group were somnolence, nasopharyngitis, and headache. The quetiapine group was also noted to have an average weight gain of 0.5 kg while the placebo group had an average weight reduction of 1.9 kg.

Similar to the above study performed by Vieta, et al., Suppes, et al. evaluated the efficacy of quetiapine plus lithium or divalproex in the prevention of recurrent mood symptoms.[7] The investigators in this study used identical methods as Vieta, et al., first assigning subjects to open-label quetiapine 400-800mg daily, then transitioning them to double-blind assignments of either quetiapine or placebo in addition to lithium or divalproex dosed based on serum levels. The primary outcome of recurrence was also identical to that used by Vieta, et al. Fewer subjects in the quetiapine group experienced a recurrent episode of mood symptoms when compared to placebo (20.3% vs. 52.1%, p<0.001). The most common side effects in the quetiapine group were sedation, weight gain, and hypothyroidism. Subjects in the quetiapine group had a mean weight gain of 0.5 kg while the placebo group had a mean weight loss of 2.0 kg.

A double-blind, placebo-controlled study by Macfadden, et al. was the first trial to examine relapse rates of subjects with bipolar disorder prescribed an adjunctive long-acting antipsychotic.[8] After a 16 week, open-label period of receiving risperidone LAI in addition to their treatment-as-usual (mood stabilizers, antidepressants, anxiolytics), subjects were randomized to a 52-week double-blind phase of risperidone LAI 25-50mg every 14 days or placebo, in addition to treatment-as-usual. Relapse was defined as meeting the DSM-IV criteria for a mood episode despite medication compliance. Participants also had to meet one of the three following criteria to be categorized as having a relapse: clinical worsening based on at least two rating scales (YMRS >15 or MADRS >15 and Clinical Global Impressions of Bipolar Disorder-Severity (CGI-BP-S) score ≥4 or Clinical Global Impressions of Bipolar Disorder-Change (CGI-BP-C) score ≥6 or Global Assessment of Functioning (GAF) score decreased by >10 points from baseline), hospitalization for worsening manic or depressive symptoms with any one of the above rating scale changes, or hospitalization for worsening manic or depressive symptoms with significant suicidal ideation. The relapse rate was 23.1% in the group receiving risperidone LAI compared to 45.8% in those receiving placebo (p=0.01). Additionally, time to relapse was longer in those receiving risperidone LAI when compared to placebo (p=0.01). The most common side effects in the risperidone group were tremor, insomnia, muscle rigidity, weight gain, and hypokinesia. Those enrolled in the risperidone group had a mean weight increase of 0.7 kg while those receiving placebo has a mean weight loss of 2.0 kg.

A double-blind, placebo-controlled trial by Bowden et al. examined the efficacy and safety of adjunctive ziprasidone given in combination with a mood stabilizer for the maintenance phase of bipolar disease.[9] Subjects who achieved stability for at least 8 weeks with ziprasidone in addition to either lithium or valproate were then assigned to either ziprasidone or placebo, in addition to the mood stabilizer, for 6 months. The primary outcome was the occurrence of a mood episode. Participants met the criteria for a mood episode if they were hospitalized for worsening psychiatric symptoms, had a YMRS or MADRS rating of ≥18 for 2 consecutive visits no more than 10 days apart, had a loss of effect or required an alteration to the treatment regimen, or if the study medication was discontinued by the investigator in the best interest of the patient. The results demonstrated that 19.7% of subjects in the ziprasidone arm required intervention for a mood episode, compared with 32.4% of subjects in the placebo arm (p=0.01). Time to intervention was also longer in those prescribed ziprasidone when compared to placebo (p=0.01). The only common side effect that occurred significantly more often in the ziprasidone group was tremor. The ziprasidone group experienced a mean weight loss of 0.8 kg while the placebo group experienced a mean weight gain of 0.5 kg.

A double-blind, randomized study by Marcus, et al., evaluated the efficacy and safety of adjunctive aripiprazole in subjects prescribed lithium or valproate who had not had an adequate response to the mood stabilizer after at least 2 weeks of therapy.[10] An inadequate response was defined as YMRS total score ≥16 or a reduction in YMRS ≤35% baseline. Subjects were assigned to either placebo or aripiprazole 10-30mg daily in addition to continued treatment with their mood stabilizer. Relapse was defined as any one of the following: hospitalization for a manic, mixed, or depressive episode, a serious adverse effect or worsening

symptoms accompanied by a YMRS and/or MADRS score >16, or discontinuation due to lack of efficacy as determined by the investigator and accompanied by a YMRS and/or MADRS score >16. At the end of the 52 weeks study period, relapse rate with placebo and mood stabilizer was 29% compared with 17% of those prescribed aripiprazole and mood stabilizer (p=0.014). The most common side effects of those in the aripiprazole group (≥5%) were headache, weight increase, tremor, and insomnia.

WEIGHING THE RISKS OF ANTIPSYCHOTIC USE

While the evidence described above focuses primarily on the benefits of antipsychotics in bipolar maintenance therapy, discussion of the risks is equally important. The potential for extrapyramidal symptoms (EPS) and metabolic abnormalities are factors that need to be discussed with patients when considering long-term use of an antipsychotic. Listed in table 2 are the incidence rates for EPS in the trials discussed above. It should be noted that these represent the occurrence of EPS during the randomization phase, while the occurrence of EPS during the pre-randomization phase was often higher.

Table 2: EPS incidence rates

Authors/Year	SGA	Treatment Group	Placebo group
Vieta, et al (2008)	Quetiapine	5.1%	4.6%
Suppes, et al (2009)	Quetiapine	11.0%	9.6%
Macfadden, et al (2009)	Risperidone LAI	30.8%	16.9%
Bowden, et al (2010)	Ziprasidone	Unavailable	Unavailable
Marcus, et al (2011)	Aripiprazole	Unavailable	Unavailable

In the studies above, average weight gain was 0.5-2 kg in treatment groups, with the exception of those taking ziprasidone who, on average, experienced a weight loss. Providers need to have honest discussion with their patients about this risk. In addition to the social stigma attached to bipolar disorder which can create difficulties for patients, this potentially obvious side effect could hinder a patient's willingness to continue taking a medication. Beyond weight gain is the concern for other metabolic factors, including an increased risk of developing diabetes and worsening lipid profiles.

CONCLUSION

As more and more information becomes available, practitioners will have more options for providing optimal care to each individual patient. Antipsychotics will continue to have an increased role in the maintenance treatment of bipolar disorder as either monotherapy or as an adjunct to a mood stabilizer. However, the decision of whether to use an antipsychotic, as with many others, needs to be a conversation between the provider and the patient. It is important to make patients aware of their options while at the same time using previous clinical experience to help guide treatment. The evidence described above provides a solid foundation for updating guidelines and shared decision-making.

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