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Is asenapine or aripiprazole more effective than a placebo for reducing episodes of mania in children with bipolar I disorder?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not asenapine or aripiprazole are more effective than a placebo for reducing episodes of mania in children with bipolar I disorder.

Study Design: Review of two randomized control trials (RCTs) published in 2013 and 2015, and a flexible-dose, open-label, extension study published in 2016.

Data Sources: Each article used was published in English and found using PubMed database. All articles were published in peer-reviewed journals.

Outcomes Measured: The clinical superiority of asenapine and aripiprazole were measured by a change in baseline in the Young Mania Rating Scale (YMRS) total score. A decrease in YMRS score indicates improved mania symptoms.

Results: Findling, et al. (2015) found that all studied doses of asenapine were more effective than a placebo at reducing the baseline score of the Young Mania Rating Scale (YMRS) [for 2.5 mg: -12.8 vs -9.6, $p=0.008$; for 5mg -14.9 vs -9.6, $p <0.001$; for 10mg: -15.8 vs -9.6, $p <0.001$]. Findling, et al. (2013) found that all doses of aripiprazole were more effective than a placebo using the same YMRS change from baseline [for 10mg: -14.1 vs -8.2, $p <0.001$; for 30 mg: -14.9 vs -8.2, $p <0.001$]. This article also examined the average time to withdrawal [for 10 mg 15.6 weeks vs 5.3, $p <0.001$; for 30 mg 9.5 vs 5.3, $p <0.05$]. The Findling, et al. (2016) open-label, extension study found that there was a greater mean change in baseline YMRS total scores in the placebo/asenapine population (-13.0 at 26 weeks and -15.2 at 50 weeks), a 79.2% total population of patients that were YMRS 50% responders, and 68.5% of all patients achieved YMRS remission.

Conclusions: Though each study reported an improvement of symptoms, the efficacy of asenapine and aripiprazole over a placebo for the treatment of mania episodes in children with bipolar I disorder cannot be determined due to the limitations in experimental design and validity.

Key Words: Bipolar, bipolar I disorder, treatment, asenapine, aripiprazole, children, mania episodes, placebo

INTRODUCTION

Bipolar disorder is the sixth leading cause of disability, affecting nearly 6 million people nationwide.[1] These patients are notorious for extreme changes in mood, affect, and behavior. There are two subclasses of bipolar disorder. Bipolar I disorder (BP1) is defined by the presence of manic episodes, including: recklessness, insomnia, grandiose thoughts, aggression, heightened irritability, and elevated self-esteem.[1] This manic state causes severe social and occupational impairment and may even require hospitalization. BP1 can also display periods of depression[1], though it is not required for diagnosis. Bipolar II disorder is alternatively characterized by depressive states and hypomania episodes. Hypomania consists of less severe manic symptoms which do not require hospitalization.[1] Children with bipolar disorder are particularly difficult to diagnose and often undergo multiple trials of different medications before achieving mood stabilization.[2] This review evaluates two randomized control trials and one flexible-dose, open-label, extension study to determine if asenapine or aripiprazole are more effective than a placebo in reducing mania episodes in children with BP1.

The exact cause of bipolar disorder is unknown, but there is certainly a genetic component. Data show that two-thirds of those diagnosed with bipolar have at least one family relative with unipolar or bipolar depression.[1] Furthermore, children with one parent diagnosed with bipolar disorder are at a 15-30% increased risk of developing it, and children with two parents diagnosed have a 50-75% increased risk.[1] Bipolar disorders are not the most common psychological disorder encountered in medical practice, but its symptoms are debilitating and result in severe financial and emotional disruption.

While recent data are unavailable, in 1991, the estimated total of direct medical costs associated with bipolar disorder was $7.6 billion.[3] More recent data from insurance claims

between 1998 and 2000 demonstrated that a single patient with bipolar spends between $7,200 and $12,100 per year on care, 15% of which goes towards prescriptions alone.[4] It is also important to note that the real cost of this illness must take into account the loss of productivity and detrimental impact to personal and professional relationships over time.

The emotional and behavioral swings indicating BP1 can present to behavioral health, family medicine, or emergency medicine providers for initial diagnosis and/or treatment. As such, it is important for all physician assistants to understand the medical management of this disorder. The current gold standard of treatment is combination management with a mood stabilizer (such as lithium), an antidepressant (such as Bupropion), and adjunctive psychotherapy. Antipsychotics are also added to treat acute mania episodes. Typical antipsychotics (such as chloropromazine) carry a large number of side effects, including: movement disorders, neuroleptic malignant syndrome, ophthalmologic problems, dermatologic problems, and increased seizure risk. Atypical antipsychotics (such as asenapine and aripiprazole) on the other hand, have fewer side effects and are therefore better tolerated in bipolar patients. The atypical class is currently considered first line treatment for acute mania in bipolar adults. It is important to study their efficacy in children so this population of patients can also experience fewer side effects with pharmacological management of their disease.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not asenapine or aripiprazole are more effective than a placebo for reducing episodes of mania in children with bipolar I disorder.

METHODS

This review examines two double-blinded, randomized control trials (RCTs) and one flexible-dose, open-label, extension study that examined a population of children aged 10-17 years old diagnosed with bipolar I disorder with either manic or mixed episodes. The interventions under study were the use of asenapine or aripiprazole as compared to a placebo. Though the studies used different medications, the intent was to determine the efficacy of either drug as compared to a placebo. This outcome was measured by a change from baseline using the Young Mania Rating Scale (YMRS) score and time to withdrawal.

Articles for this review were discovered by applying keywords such as: bipolar disorder, asenapine, aripiprazole, treatment, children, and mania. All articles utilized were published in English, in peer-reviewed journals, and found via searches on the PubMed database. Article selection was further refined based on relevance to the stated clinical question, and whether or not they included patient-oriented outcomes (Table 1). Inclusion criteria for this review contained at least two randomized control trials published after 2007, a study population of children, and a placebo comparison group. Patients over 18 years old, patients on multiple drug regimens for mania control, and drug-to-drug comparison studies were excluded. The summary statistics reported were mean changes from baseline, confidence intervals, p-values, and ANCOVAs.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Findling RL, Land-bloom RL, Szegedi A (2015)[5]	RCT	403	10-17	Primary diagnosis of BP1 with associated manic or mixed episodes, a total YMRS $\geq$ 20 at baseline, and a guardian living with the	Patients with a pervasive development disorder or other mood disorder, prohibited contaminant medication, or an uncontrolled, unstable clinically significant medical condition	53	Patients taking asenapine (2.5mg, 5mg, or 10 mg) BID vs matching placebo

				child who was able to ensure adherence			
Findling RL, Correll CU (2013)[6]	RCT	210	10-17	Primary diagnosis of BP1 with current manic or mixed episodes, confirmation of diagnosis by a second clinician, total YMRS $\geq$ 20 at baseline	Article states that "baseline characteristics have been stated previously," but referenced information could not be obtained	86	Patients taking 10mg or 30mg /day of aripiprazole vs matching placebo for 26 weeks
Findling RL, Land-bloom, RL (2016)[7]	Open-label, flexible-dose, extension study	321	10-18	Primary diagnosis of BP1 with a current manic or mixed episodes, total YMRS $\geq$ 20 at baseline, informed consent from a legal guardian	Patients with a pervasive development disorder, or other mood disorder, mental retardation, use of prohibited contaminant medications, pregnancy, HIV, high risk of self-harm or harm to others, involuntary inpatient commitment, or poor adherence to other medications	181	Patients taking open-label doses of asenapine

OUTCOMES MEASURED

The outcomes measured were the clinical superiorities of asenapine or aripiprazole as compared to a matched placebo. Drug efficacy was measured by a change in baseline in YMRS total score. The YMRS is an eleven-item, clinician-rated scale to assess the severity and symptoms of mania episodes.[5-7] Values can range from 0 (all symptoms are absent) to 60 (all symptoms are extreme). A decrease in YMRS score from baseline indicates improved mania symptoms.[5-7] The three articles all present data as continuous and could not be converted to dichotomous. The articles by Findling RL, et al. (2013)[6] and Findling RL, et al. (2016)[7] additionally give long-term efficacy results for asenapine in terms of time to failure to maintain effect. Findling RL, et al. (2016)[7] also assesses the total number of YMRS 50% responders and remitters.

RESULTS

The two randomized control trials used in this review aim to determine the effectiveness of either asenapine or aripiprazole as compared to a placebo in controlling mania episodes in children. The open-label, extension study determines the long-term effectiveness of asenapine in the same population. Efficacy was evaluated by determining the mean change from baseline scores of clinician-rated, interview-based surveys. The inclusion and exclusion criteria of all three articles (Table 1) are comparable, and all patients that began each trial are accounted for within that respective article's results.

Findling RL, et al. (2015)[5] conducted a double-blinded, randomized control trial consisting of 403 patients between the ages of 10-17 years old diagnosed with BP1 with current manic or mixed episodes. Before acceptance into the medication phase of the trial, each patient was required to undergo a 2- to 14-day screening/tapering period to ensure there were no contaminant medications present.[5] Study participants were then randomized and treated with asenapine at 2.5 mg, 5 mg, or 10 mg BID, or a placebo BID for 3 weeks.[5] The 2.5 mg dose was administered from day 1; the 5 mg dose group was administered as 2.5 mg BID for 3 days, then titrated up to 5 mg BID thereafter; and the 10 mg dose group was administered as 2.5 mg BID for 3 days, then 5 mg BID for 3 days, then 10 mg BID thereafter.[5]

The efficacy of asenapine was measured by determining the YMRS score changes. Participants were measured at baseline and day 21. The raw data for each participant's YMRS score report was not included in the published results of this study, but the overall mean change from baseline and p-value for each trial group was provided (Table 2). Since the YMRS scores are more negative for all 3 doses of asenapine than the placebo group, these data indicate that asenapine is superior to a placebo in reducing mania symptoms.[5] P-values less than 0.05 indicate

that the decrease in mania symptoms within each trial group were statistically significant and likely a result of the administration of asenapine.

Table 2: Mean Change in YMRS Total Score of the Findling RL, et al. (2015)[5] RCT

Treatment Group	Mean Change in YMRS	p-value
Placebo	-9.6	
2.5 mg of Asenapine	-12.8	p=0.008
5 mg of Asenapine	-14.9	p<0.001
10 mg of Asenapine	-15.8	p<0.001

A 30-week, randomized, double-blind, placebo-controlled trial by Findling RL, et al. (2013)[6] enrolled 210 patients diagnosed with BP1 between the ages of 10-17 years old that successfully completed a four-week aripiprazole acute treatment phase. These subjects were randomized in the acute-phase into three groups: 10 mg/day of aripiprazole, 30 mg/day of aripiprazole, and a matching placebo once daily for a 26-week extension study.[6] For safety, these doses were titrated up slowly in the acute phase of the trial, then continued at the target dose for the remaining 26 weeks.

Efficacy of aripiprazole was determined in two ways. The first method examined the overall time to withdrawal of the drug. The longer the time to withdrawal, the more effective the treatment group is at controlling symptoms of mania.[6] Out of the original 296 patients that completed the acute-phase, only 210 entered the extended-phase. Overall, only 32.4% of subjects competed the 30-week study.[6] The most common reason for withdrawal was lack of efficacy (22.7% for the 10 mg dose, 14.1% for the 30 mg dose, and 48.4% for the placebo).[6] Table 3 lists the average time to discontinuation of each drug group. These results show that the longest time to discontinuation was for the subjects taking the 10 mg/day dose of aripiprazole. As mentioned above, this increased time to withdrawal indicates a longer period of efficacy for the 10 mg aripiprazole group. Even though, the 95% confidence intervals (CI) and p-values (<0.05)

statistically support this claim, no other analyses were performed to assess if confounding variables are present within this data. As such, these results should be interpreted with caution.

Table 3: Median Time to Discontinuation of the Findling RL, et al. (2013)[6] RCT

Treatment Group	Median Time to W/D (weeks)	95% Confidence Interval (weeks)	p-value
Placebo	5.3	4.7-6.9	
Aripiprazole 10 mg/day	15.6	8.1-24.3	$p<0.001$
Aripiprazole 30 mg/day	9.5	6.1-13.9	$p<0.05$

Utilizing the mean change from baseline in YMRS total scores from week 1 through week 30, the efficacy of aripiprazole was further analyzed. Table 4 shows the mean change in baseline of YMRS total scores. The larger negative scores indicate that both doses of aripiprazole were superior to the placebo in reducing episodes of mania in children. Since the p-values are less than 0.05, the data are considered statistically significant, and therefore not due to random chance. Additionally, these values were analyzed using an analysis of covariance (ANCOVA) model that allowed researchers to control for continuous variables that have nothing to do with the treatment interventions, but might influence the outcome.

Table 4: Mean Change in YMRS Total Score of the Findling RL, et al. (2013)[6] RCT

Treatment Group	Mean Change in YMRS	p-value
Placebo	-8.2	
Aripiprazole 10 mg/day	-14.1	$p<0.001$
Aripiprazole 30 mg/day	-14.9	$p<0.001$

Findling RL, et al. (2016)[7] conducted a flexible-dose, open-label, 50-week extension study to evaluate the long-term efficacy of asenapine for the treatment of manic episodes in children aged 10-18 years old with BP1. In order to enroll into this study, participants were required to complete an acute-phase and adhere to the exclusion/inclusion criteria listed in Table 1. In the acute-phase, patients were randomized into placebo, asenapine 2.5 mg, 5 mg, or 10 mg BID groups for 3 weeks.[7] Of the 350 patients who completed the acute-phase, 321 were included

in the final analysis.[7] The first day of the extension-study overlapped with the last day of the acute-phase (day 21). In the extension-phase, all enrolled patients were given an open-label, fast-dissolving, sublingual asenapine tablet at 2.5 mg BID on day 1. On day 4, patients were increased to 5mg, then to 10 mg on day 7. For the remainder of the trial, patients were given flexible dosing based on tolerability and symptomology.[7]

Efficacy of long-term asenapine administration was assessed in three ways. First, the mean change from baseline in YMRS total scores was given, as seen in Table 5. These values show that the greatest improvement in YMRS scores was the acute-phase placebo group who began receiving asenapine at the beginning of the extension-phase (placebo/asenapine).

Table 5: Mean Change in YMRS Total Score of the Findling RL, et al. (2016)[7] Extension-trial

Treatment Group	Mean Change in YMRS at 26 Weeks	Mean Change in YMRS at 50 Weeks
Placebo/Asenapine	- 13.0	-15.2
Asenapine/Asenapine	- 4.9	- 6.5

The second efficacy assessment reviewed the time to failure to maintain effect from open-label baseline to any time point. This was defined as a <50% reduction from baseline in YMRS total score during the extension-phase out of the participants who already achieved a 50% reduction response during the acute-phase.[7] Of the 141 patients who had at least a 50% mean change from baseline in YMRS total score at the completion of the acute-phase, 46 patients (32.6%) failed to maintain a decrease in mania symptoms.[7] Since no CIs or p-values are reported for either of these assessments, the statistical significance of this data is questionable.

Finally, the percentage of responders and remitters from baseline to endpoint were used to determine efficacy. YMRS responders were defined as those who achieved a ≥50% improvement in YMRS total score; and YMRS remitters were required to obtain a YMRS total score ≤12.[7] Out of the 149 responders at baseline, 118 (79.2%) were still responders, and 102 of 149 (68.5%) were remitters at the end of 26-weeks.[7] There was no data reported for the 50-week

end-date. The article reports that these percentages suggest a large proportion of patients achieving clinically meaningful mania relief,[7] but no p-values or other statistical support data are given. Without support, these statements of drug efficacy are uncertain.

DISCUSSION

Although the study by Findling, et al. (2016) concluded that treatment with asenapine provided long-term mania symptom relief in children with BP1, the lack of statistical analysis leaves this claim unsupported. No other outliers were apparent in the remaining two articles.

Asenapine (brand name Saphris) and aripiprazole (brand name Abilify) are both atypical antipsychotic drugs that work on dopamine (D) and serotonin (5-HT) receptors. Aripiprazole is a quinolone antipsychotic that functions as a partial agonist at the D_2 and the $5\text{-}HT_{1A}$ receptors, and as an antagonist at the $5\text{-}HT_{2A}$ receptor.[8] Asenapine is a dibenzo-oxepino pyrrole antipsychotic with mixed serotonin-dopamine activity.[9] Aripiprazole is available as a pre-filled syringe, an IM injection that must be reconstituted with sterile water, an oral tablet, or a dissolving sublingual tablet that can be taken with or without food.[8] Asenapine is only available as a dissolvable sublingual tablet that must be taken at least ten minutes before consuming any liquids or foods.[9] There is no generic version of asenapine, and the cost is $21.94 per tablet.[9] Since the recommended dosing is one tablet taken twice a day, asenapine comes to a total of $1,316.40 per month. Brand-name aripiprazole is even more expensive and ranges in price from $2,364.76 (per single dose of a prefilled syringe) to $963.25 (for a 30-day supply of a 2 mg tablet).[8] Fortunately, a generic version is now available and averages $24.17 for a 30-day supply.[10] Medicare and most insurance companies cover both drugs.[8,9]

The FDA approved asenapine for use on August 13, 2009 and aripiprazole on June 1, 2012.[8,9] Both drugs are now readily available on the US market and are used for the treatment of

manic or mixed episodes of BP1, as well as schizophrenia in adults.[8,9] Aripiprazole is also used to treat major depressive disorder, Tourette's disorder, and irritability associated with autistic disorders.[8] Both drugs are can be used off-label to reduce psychosis/agitation associated with dementia.[8,9] Asenapine and aripiprazole are both associated with a black box warning due to adverse effects. These drugs increase mortality in elderly populations with dementia-related psychosis.[8,9] Aripiprazole has an additional black box warning for an increased risk of suicidal thoughts in children.[8] The side effects of both drugs are consistent with others in the atypical antipsychotic class, including: weight gain, metabolic effects, extrapyramidal symptoms, sedation, orthostatic hypotension, and QT prolongation.[11]

There were some limitations with this review due to an inadequate number of available RCTs. An open-label extension trial was selected to complete this review since the majority of the reported data were the results of the acute-phase, rather than the extension-phase. Upon further investigation, it was noted that this study did not compare different doses of asenapine to a control placebo, but rather examined the long-term affect of open-label asenapine dosing as compared to an acute phase. The efficacy data reported within this article is unsupported and therefore indeterminate. Additionally, the lack of RCTs made it difficult to select articles that examined a similar timeframe. One study assessed the efficacy of a treatment drug in the short-term, another study examines drug efficacy in the long-term, the yet another uses efficacy data from an acute-phase trial to complete long-term analyses. Having three RCTs comparing similar timeframes would allow for a more accurate assessment in regards to the proposed question.

Moreover, limitations within the studies themselves include issues with validity, blinding, and sample size. The validity issues in were mentioned above, but the Findling, et al. (2016) article also fails to blind both the participants and the administrators. This can lead to a bias

affect in the experimental outcomes. Finally, the low completion rates in the Findling, et al. (2013) and Findling, et al. (2016) studies (59% and 44.6%, respectively) limit the ability to draw definitive conclusions due to a small sample size.

CONCLUSION

After reviewing the data from all three articles, it is inconclusive whether there is statistically reinforced data to support the efficacy of either asenapine or aripiprazole over a placebo for reducing mania episodes in children with bipolar I disorder. Even though the Findling, et al. (2015) and Findling, et al. (2013) studies showed meaningful data that supports the efficacy of both asenapine and aripiprazole, the short-term nature and small sample size (respectively) of these trials leave the long-term benefits open for future research. Additionally, the Findling, et al. (2016) study lacks a placebo-control group and statistically supported data making it wholly unreliable. It should also be noted that all three articles in this review selected a patient population using the criteria explained in the Diagnostic and Statistical Manual of Mental Disorders, Version 4 (DSM-4).[5-7] A more detailed criterion list for manic episode diagnosis has since been updated in DSM-5.[5-7] It is unclear how this update would affect the inclusion/exclusion criteria in these studies; therefore, new research should be undertaken and include the new diagnostic criteria. Finally, the placebo-controlled studies are of great value, but they do not allow for a direct comparison of asenapine and aripiprazole efficacy. It would be beneficial to undertake research that compares asenapine and aripiprazole to each other. A drug-to-drug comparison analysis could discover which agent is the most successful in the pediatric population. Overall, more research is necessary to determine if asenapine or aripiprazole is more effective than a placebo in reducing mania in children with bipolar I disorder.

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