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Is Asenapine More Effective than Other Interventions in the Treatment of Adult Patients with Bipolar I Disorder?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Asenapine is more effective than other interventions in the treatment of adult patients with bipolar I disorder.

STUDY DESIGN: Review of three English language primary randomized controlled trial studies published from 2009-2010.

DATA SOURCES: Three randomized controlled trials studying the effectiveness of Asenapine in the treatment of mania in adult patients with bipolar I disorder in comparison to other interventions.

OUTCOME MEASURED: Outcomes measured were reduction in severity of manic symptoms and tolerability of the medication. The severity of manic symptoms was measured using the Young Mania Rating Scale (YMRS). The YMRS is a self report questionnaire completed by the patients. It includes rating scales for elevated mood, increased motor activity and energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behavior, appearance, and insight. Tolerability was based on adverse event assessment categorized in terms of maximum intensity and the investigator's opinion of the relationship to the trial medication used.

RESULTS: The articles reviewed showed Asenapine was not more effective than Olazapine and had mixed results when compared to placebo. The McIntyre 2009 3 week study showed Asenapine to be superior to placebo in YMRS response. The McIntyre 2010 3 week study showed Asenapine to be nonsuperior over placebo and inferior to Olanzapine in YMRS response. The McIntyre 2009 9 week extension study showed Asenapine to be noninferior to Olanzapine in YMRS response. Asenapine was well tolerated.

CONCLUSIONS: Based on the articles reviewed, it is unclear how effective Asenapine is in YMRS response rates. It may be a potential option for the treatment of mania in patients diagnosed with bipolar I disorder, but more research is needed.

KEY WORDS: Asenapine; Bipolar I Disorder; Olanzapine; Mania; Mixed state

INTRODUCTION

Bipolar I disorder, bipolar II disorder, and cyclothymic disorder all make up the broader spectrum known as bipolar disorder, a common and serious mental health condition.[1] Bipolar I disorder, specifically, consists of episodes of mania cycling with depression that most often begin quickly and escalate rapidly. An episode of mania is typically defined as an abnormally and continuously elevated, expansive, or irritable mood.[1] The impact can be devastating to the patient's physical and psychosocial health often interfering with occupational and social functioning and commonly leading to hospitalization. In fact, it is estimated that patients with bipolar disorder have suicide rates 2-3 times higher than that of the general population.[1] The etiology is unknown and there are no diagnostic tests or lab studies specific for a diagnosis of bipolar disorder. However, some risk factors have been identified. Key risk factors for bipolar disorder include female sex, family history of the disorder, and upper socioeconomic class.

It is estimated that bipolar disorder affects over three million people in the United States and accounts for one quarter of all mood disorders.[1] The lifetime prevalence is believed to be as high as 4%.[2] Therefore, bipolar disorders cross over into many scopes of PA practice and it is important for practitioners to be able to recognize the condition and provide proper treatment. Although there is no national database identifying how many healthcare visits each year occur due to bipolar disorder, it is estimated that $45 billion are spent annually on the disorder, making it the most costly behavioral health condition in the United States.[3,4]

There is no cure for bipolar I disorder. Treatment entails management of acute episodes as well as maintenance therapy. Manic episodes can be managed acutely with either lithium or atypical antipsychotics. Atypical antipsychotics work by blocking dopamine pathways in the brain. General side effects include blood clotting, tardive dyskinesia, significant weight gain,

and metabolic syndrome. Consequently, insufficient tolerability has contributed to high rates of nonadherence to treatment. Asenapine, a newer atypical antipsychotic, gained FDA approval in 2009 for the treatment of mania or mixed episodes associated with bipolar I disorder. It is formulated as a quick dissolving sublingual tablet that is rapidly absorbed with peak plasma concentrations occurring about one hour after administration. Current research is hopeful that Asenapine will prove to be a superior option in both efficacy and tolerability over other available treatments.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is Asenapine more effective than other interventions in the treatment of adult patients with bipolar I disorder?"

METHODS

A detailed search was completed by the author using the key words Asenapine, Olanzapine, bipolar I disorder, mania, and mixed state. The search engines used were OVID, Medline, and PubMed and the articles selected were published in English and in peer-reviewed journals from 2009-2010. Each article focused on outcomes that were of importance to the patient (Patient Oriented Evidence that Matters, or POEMS). Randomized controlled trails (RCTs) were searched for the following inclusion criteria: patient population 18 years old or greater with a diagnosis of bipolar I disorder and experiencing manic or mixed episodes. Three studies, all randomized clinical trials, were chosen comparing Asenapine to Olanzapine and/or placebo in the treatment of mania in adult patients with bipolar I disorder. Of these studies, two were double blind placebo-controlled, and the other was a double blind placebo-controlled extension study. Variable dosing of Asenapine and Olanzapine was incorporated into each study. Excluded studies were those that used Asenapine as treatment for conditions other than

bipolar I disorder. **Table 1** demonstrates the demographics of the studies included. Each study reported statistics based on severity of manic symptoms as rated by the patient. Statistics were reported using p-values, 95% confidence intervals (CI), relative benefit increase (RBI), absolute benefit increase (ABI), relative risk increase (RRI), absolute risk increase (ARI), number needed to treat (NNT), and number needed to harm (NNH).

OUTCOMES MEASURED

Outcomes measured in all of the studies included the improvement of mania severity as reported by the patient using the Young Mania Rating Scale (YMRS). The YMRS is self report questionnaire in which the patient rates their symptom severity in 11 different categories. These categories include elevated mood, increased motor activity and energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behavior, appearance, and insight. Symptom severity, especially in these categories, is important to the patient; thus qualifying this outcome as a POEM. The YMRS score ranges from 0-60. Clinical severity categories based on YMRS total score are mild (15-20), moderate (21-28), and severe (29-44). This paper evaluates the percentage of YMRS responders, which is defined as those experiencing greater than a 50% decrease from their baseline YMRS score upon completion of the trial medication.

Another outcome measured was tolerability to the medications used. This was evaluated by adverse events which were categorized based on level of intensity and the investigator's opinion on the relationship of the adverse event to the trial medication used. Vital signs were assessed at each visit. Additionally, blood samples, urinalysis, electrocardiograms, body weight, and metabolic indices were assessed throughout the trial. This paper evaluates those adverse events labeled as a serious adverse event, or SAE.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
McIntyre	RCT	488	18-65+; mean age of 39.4	Primary Dx of bipolar I disorder; YMRS $\geq$ 20; current manic/ mixed episode (< 3 mo ago); history of 1 or more moderate to severe episodes	Seizures; HIV+; Rapid-cycling; substance abuse or dependence; positive stimulant screen; pregnant or may become pregnant; use of clozapine within 12wks; previous trial enrollment; hypersensitivity to meds used; neuroleptic malignant syndrome	152	Asenapine SL (10 mg BID day one, 5 or 10 mg BID thereafter); Oral olanzapine (15 mg QD on day one, 5, 10,15, 20 mg QD thereafter); matched placebo
McIntyre	RCT	488	18-65+; mean age of 38.6	Primary diagnosis of bipolar I disorder; YMRS $\geq$ 20; current manic/ mixed episode (< 3 mo ago); history of 1 or more moderate to severe episodes	Seizures; HIV+; Rapid-cycling; substance abuse or dependence; positive stimulant screen; pregnant or may become pregnant; use of clozapine within 12wks; previous trial enrollment; hypersensitivity to meds used; neuroleptic malignant syndrome	146	Asenapine SL (10 mg BID day one, 5 or 10 mg BID thereafter); Oral olanzapine (15 mg QD on day one, 5,10,15, or 20 mg QD thereafter; matched placebo
McIntyre	RCT	504	18-73	$\geq$18 years old with bipolar I disorder; experiencing manic/mixed episodes; completed a previous 3 week trial; continued treatment could be of clinical benefit	Did not complete previous 3 week trial; rapid cycling mood course; substance abuse or dependence; imminent risk of harm to self or others; unlikely to comply	195	Asenapine SL (10 mg BID on day one, 5 or 10 mg BID thereafter); Oral olanzapine (15 mg QD day one, 5,10,15,20 mg QD thereafter)

RESULTS

This EBM review was done on three randomized controlled trials; two of which were three week comparative trials, and the other a nine week extension study. Each article used dichotomous data when presenting outcomes. The dosing of medications was the same in each trial study. The dosing was as follows: sublingual Asenapine (10 mg BID on day 1, followed by 5 or 10 mg BID thereafter) and oral Olanzapine (15 mg BID on day 1, followed by 5, 10, 15, or 20 mg QD thereafter). Visually matched placebo was incorporated into both 3 weeks studies, but it was not included in the 9 week extension study. The primary efficacy measured in all of the studies was the change in the YMRS score. This review focuses on YMRS responders which are defined as those having a $\geq$ 50% reduction from baseline YMRS score at study endpoint. All patients that participated in the study had a primary diagnosis of bipolar I disorder and were currently experiencing manic or mixed episodes. All patients were 18 years of age or older.

It is important to understand the statistical calculations that were used to evaluate the articles selected. The percentage of YMRS responders was considered for the efficacy rate for each intervention, with Asenapine being the Experimental Event Rate (EER) and Olanzapine or placebo being the Controlled Event Rate (CER). The EER and CER can be used to calculate the Relative Benefit Increase (RBI) and Absolute Benefit Increase (ABI). The ABI, which is the absolute arithmetic difference in rates of good outcomes between the experimental and control groups, can then be used to calculate the Numbers Needed to Treat (NNT). The NNT tells the practitioner the number of patients that need to be treated in order to obtain one additional good outcome as compared to the control medication.

In the McIntyre, 2009 three week study, 488 patients with a mean age of 39.4 years old enrolled in the study.[2] The YMRS score was assessed at baseline, days 2, 4, 7, 14, and study

endpoint (day 21). In order to qualify for the study, patients had to have a baseline YMRS score $\geq$ 20. Trial completion rates were 62.9%, 61.5%, and 79.6% for Asenapine-, placebo-, and Olanzapine-treated patients, respectively. YMRS response was analyzed using Pearson chi-square tests, with last observation carried forward (LOCF). All participants were randomly allocated into either an experimental group (Asenapine) or a control group (Olanzapine or placebo). The percentage of YMRS responders for Asenapine versus placebo were 42.3% and 25.2%, respectively. Asenapine showed a greater response over placebo, and the data is considered clinically significant with a p-value < 0.01. The NNT calculated for Asenapine versus placebo was 6 (95% CI: 3 to 17). The percentage of YMRS responders for Asenapine versus Olanzapine were 42.3% and 50.0%, respectively, and the NNT value was -13. However, the trial included Olanzapine as a way to assess assay sensitivity in the event that outcomes measured between Asenapine and placebo were not significantly different. Therefore, no p-value or 95% CI was available comparing Asenapine and Olanzapine. The results are summarized in **Table 2** and **Table 3**.

In the McIntyre, 2010 three week study, 488 patients with a mean age of 38.6 years old enrolled in the study.[3] This study shared many of the same characteristics as the McIntyre 2009 three week study, such as required baseline YMRS $\geq$ 20, YMRS responder analysis using Pearson chi-square tests and LOCF, and Olanzapine included to assess assay sensitivity. However, this study performed a post hoc analysis comparing YMRS response rates for Asenapine and Olanzapine on day 21. Trial completion rates were 67.0%, 58.2%, and 78.5% for Asenapine-, placebo-, and Olanzapine-treated patients, respectively. The percentage of YMRS responders for Asenapine versus placebo were 42.6% and 34.0%, respectively. Asenapine did not significantly differ from placebo (p-value > 0.05), and the NNT is 12 (95% CI: -∞ to -29 and

4 to ∞). The percentage of YMRS responders for Asenapine versus Olanzapine were 42.6% and 54.7%, respectively, and the NNT value was -9. Post hoc analysis showed YMRS response rates with Olanzapine to be significantly greater than those with Asenapine (p-value < 0.05). The results are summarized in **Table 2** and **Table 3**.

In the McIntyre, 2009 nine week extension study, Asenapine and Olanzapine were directly compared.[4] Completion of a prior three week trial was required to participate in the additional nine week extension study. Upon initiation of the trial, there was no rerandomization or identification of prior treatment groups. Those receiving placebo were blindly switched to Asenapine, but were only included in the safety analysis. A total of 504 patients enrolled in the trial, and completion rates were 62%, 53%, and 64% for Asenapine-, placebo/Asenapine-, and Olanzapine-treated patients, respectively. YMRS response rates at day 84 were 90% and 92% with Asenapine and Olanzapine, respectively. These rates are not significantly different (p-value >0.05), and the NNT is -50. The results are summarized in **Table 3.**

Table 2: Asenapine vs. Placebo on YMRS response

	Asenapine (EER)	Placebo (CER)	p-value	RBI	ABI	NNT
McIntyre, 2009 (3 weeks)	42.3%	25.2%	<0.01	0.68	0.171	6[a]
McIntyre, 2010 (3 weeks)	42.6%	34.0%	>0.05	0.25	0.086	12[b]

[a] 95% CI: 3 to 17
[b] 95% CI: -∞ to -29 and 4 to ∞

Table 3: Asenapine vs. Olanzapine on YMRS response

	Asenapine (EER)	Olanzapine (CER)	p-value	RBI	ABI	NNT
McIntyre, 2009 (3 weeks)	42.3%	50.0%	NA	-0.15	-0.077	-13
McIntyre, 2010 (3 weeks)	42.6%	54.7%	<0.05[a]	-0.26	-0.120	-9
McIntyre, 2009 (9 week extension)	92.0%	90.0%	>0.05	-0.02	-0.020	-50

[a] based on post hoc analysis conducted at day 21

This review also looked at safety and tolerability outcomes as measured by the percentage of treatment-emergent serious adverse events, or SAE. All three trials reviewed in this paper provided percentages of SAE, and these values were used to calculate relative and absolute risk increases (RRI and ARI), which in turn are used to calculate the Number Needed to Harm (NNH). The NNH can tell a practitioner how many patients can be treated with the experimental treatment over the control treatment before one patient will be harmed. **Table 4** and **Table 5** summarize the safety and tolerability data from the articles reviewed. There were no p-values or CI values available for this data.

Table 4: Serious Adverse Event Data for Asenapine vs. Placebo

	Asenapine (EER)	Placebo (CER)	RRI	ARI	NNH
McIntyre, 2009 (3 weeks)	4.10%	6.70%	-0.39	-0.026	-37
McIntyre, 2010 (3 weeks)	6.50%	7.10%	-0.08	-0.006	-167

Table 5: Serious Adverse Event Data for Asenapine vs. Olanzapine

	Asenapine (EER)	Olanzapine (CER)	RRI	ARI	NNH
McIntyre, 2009 (3 weeks)	4.10%	3.71%	0.66	0.004	250
McIntyre, 2010 (3 weeks)	6.50%	3.90%	0.66	0.026	39
McIntyre, 2009 (9 week extension)	12.0%	10.0%	0.20	0.020	50

DISCUSSION

Atypical antipsychotics have proven to be effective in the treatment of mania in bipolar patients, and their use in practice has increased considerably. Asenapine (Saphris®) is a newer atypical antipsychotic which gained FDA approval in 2009. It is approved in the United States for use in both schizophrenia and acute mania associated with bipolar disorder. The FDA issued a black box warning for elderly patients with dementia-related psychosis due to increase risk of stroke or death with Asenapine. Research is currently underway to determine how effective and tolerable Asenapine will be compared to other atypical antipsychotics and other treatment options.

The randomized controlled trials in this review demonstrated mixed results in terms of efficacy rates for Asenapine versus Olanzapine or placebo, and it is clear that additional research is needed to determine how effective Asenapine may be in the treatment of mania in bipolar patients.

The studies used in this review were not without limitations. In patients with bipolar disorder, nonadherence to treatment and concomitant medication use are significant concerns and can complicate trial results. The duration of the studies used in this review ranged from three

weeks to twelve weeks which is not an adequate amount of time to influence clinical decision making for a chronic mental health condition such as bipolar disorder. Additionally, the outcome used to measure efficacy (YMRS response) was assessed at one single point in time limiting the interpretation of data. In both three week trials, Olanzapine was used to assess assay sensitivity; therefore, comparisons between Olanzapine and Asenapine need to be interpreted with caution.[2,3]

CONCLUSION

The studies reviewed show that Asenapine is not more effective than Olanzapine, and the results were mixed regarding superiority of Asenapine over placebo. Asenapine may be an effective and tolerable option for treating mania in bipolar patients; although, the varying results in each article indicate more research is needed to establish more certain efficacy rates. The 2009 3-week study showed Asenapine to be superior to placebo. The 2010 3-week study showed that Asenapine was not clinically superior to placebo in YMRS response; however, the primary outcome measured in this article (least squares mean changes in YMRS score) did show superiority with Asenapine. The 2009, 9 week extension study had the longest duration and perhaps the most promising results for Asenapine which was found to be noninferior to Olanzapine and well tolerated. None of the studies included in this review proved Asenapine to be superior over Olanzapine in efficacy.

It is important to remember that bipolar I disorder is a chronic condition that typically requires lifelong therapy. Longer duration studies are needed to help understand the role Asenapine may play in treatment. Asenapine is a relatively new drug (FDA approved in 2009) and limited studies have been published to date regarding its use in bipolar disorder. Studies that utilize a more controlled setting that would limit concomitant medication use and nonadherence

to treatment would be beneficial. Additionally, incorporating patients experiencing rapid cycling bipolar disorder could provide insight since these patients typically have a more refractory course of illness. Another point of interest that is worth reviewing is route of administration. Asenapine was developed as a sublingual tablet which could be beneficial to those with manic episodes having trouble swallowing medication.

In conclusion, the articles in this review had mixed results regarding the efficacy rates of Asenapine as measured by YMRS response. More research is needed to clarify how to incorporate Asenapine into the clinical management of bipolar I patients experiencing manic episodes.

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