ORIGINAL RESEARCH
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Asenapine in the Treatment of Bipolar Depression

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ABSTRACT ~ Objectives: *Asenapine, a potent serotonin 7 (5-HT$_7$) receptor antagonist, was examined for efficacy as an antidepressant in depressed bipolar subjects. It was predicted that subjects with the genetic variant of the short form of the serotonin transporter (5HTTR) would be more likely to respond.* ***Experimental Design:*** *A subset of patients participating in a randomized, placebo-controlled study of the efficacy of asenapine in bipolar I depression also underwent genetic testing for the 5HTTR. Montgomery Åsberg Depression Rating Scale (MADRS) score was ≥ 26 prior to randomization to asenapine or placebo for 8 weeks. Gene testing was performed before breaking the blind.* ***Principal Observations:*** *Nine patients completing the study also underwent gene testing. At study end, the average MADRS improvement was −19.80 ± SD 8.59 for the 4 people randomized to asenapine and −3.80 ± 9.01 for the 5 people receiving placebo (*P = *0.021, t = 2.88). Anxiety, as measured by the Hamilton Anxiety Rating Scale (HAM-A), also improved in asenapine-treated patients (−15.40 ± 6.15 vs. −2.80 ± 7.95,* P = *0.023, t = 2.803). Six participants had the short form of the 5HTTR, and it is believed they influenced the significant outcome in this small sample.* ***Conclusions:*** *While this is a very small sample, asenapine appears to have a beneficial effect on both depression and anxiety in depressed bipolar I patients compared to treatment with placebo. Due to the large fraction of subjects with the short form, the hypothesis that the SF-5HTTR might increase asenapine response could not be adequately tested.* Psychopharmacology Bulletin. *2020;50(1):8–18.*

Depressive symptoms are responsible for the majority of symptomatic time in bipolar illness.[1,2] In type I bipolar patients, depression may occupy over 65% of symptomatic time, or nearly one third of their lives,[2,3] and underlies high rates of functional disability and suicide.[4,5] Treatment of bipolar depression can be

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problematic since antidepressants may be associated with destabilization of the illness.[6,7] There remains a critical need for agents that are both safe and effective in the treatment of bipolar depression.

Asenapine is a dibenzo-oxepino-pyrrole second-generation antipsychotic medication that can interact with a wide variety of serotonin (5HT) and dopamine receptors.[8] Importantly, it is an antagonist with reasonably high affinity to the dopamine D_2 receptor (K_i = 1.3 nM) and $5HT_{2A}$ (K_i = 0.06 nM) receptors,[8] through which it presumably mediates some of its antipsychotic and anti-manic properties.[9–11] Additionally, it also has high affinity to several 5HT receptors (5-HT_{2C}, Ki 0.03 nM; 5-HT_{2A}, Ki 0.06 nM; 5-HT_7, Ki 0.13 nM; 5-HT_{2B}, Ki 0.16 nM; 5-HT_6, Ki 0.25 nM) where it is also antagonistic. In preclinical studies, blockade of some of these receptors has demonstrated anti-depressive or anxiolytic efficacy (e.g., 12 [for $5HT_6$ and $5HT_7$]; 13 [$5HT_{2c}$]; 14 [$5HT_{2c}$]). In particular, several $5HT_7$ antagonist agents have demonstrated antidepressant properties (e.g., vorioxetine,[15,16] or LuAA21004[17]), specifically in bipolar disorder (e.g., lurasidone[18]). The utility of asenapine in ameliorating the depressive symptoms in mixed states is suggestive of potential efficacy in bipolar depression.[19,20] Consequently, asenapine appears to have a possible role in meeting an unmet clinical need.

The serotonin transporter (5HTTR) has been the focus of extensive investigation.[21] The serotonin transporter gene, solute carrier family 6 (neurotransmitter transporter), member 4 (*SLC6A4*), which encodes the protein that mediates the reuptake of synaptic serotonin back into the presynaptic neuron, has polymorphisms which alter its expression.[22,23] Variants in this gene, collectively known as the 'short form', reduce the number of 5HTTR pump units expressed in the synapse.[22,23] Despite some controversy, research generally supports a relationship between the short form of 5HTTR and depression.[22–28] Since subjects with the short form are expected to have elevated levels of synaptic 5HT, the short form provided a theoretical framework of how serotonin reuptake inhibiting antidepressants might lead to loss of antidepressant efficacy or destabilization of bipolar illness.[29,30] These same data also lead us to predict that individuals with the short form of the 5HTTR would be more likely to respond to a medication that blocks post-synaptic 5HT receptors.

Pharmacogenomics as an aspect of personalized medicine, is rapidly emerging as the new standard of care. In psychiatry, pharmacogenomics is still in its infancy.[31] Most data regarding pharmacogenomics in psychiatry relate to potential for side effects. There are emerging data that are beginning to identify predictors of response.

In this report, we present data regarding a subset of patients involved in a study designed to determine if asenapine added to unchanged

ongoing treatment might be effective in treating bipolar I depression. The parent study was a double-blind, randomized, placebo-controlled study of asenapine in bipolar I depression. The subset of patients presented in this report underwent pharmacogenetic testing for short-form variants of *SLC6A4*.

Methods

Study Design

The larger study was a randomized, placebo-controlled, 8-weeks asenapine monotherapy efficacy trial in depressed type I bipolar patients. Nine subjects underwent gene testing for the short form of the serotonin transporter. Subjects entered the study if they had type I bipolar illness (confirmed with Mini International Neuropsychiatric Interview (MINI).[32] They had to be ⩾ 18 or ⩽ 55 years of age and be able to understand and sign an informed consent. Depressive symptoms were quantified with the Montgomery Åsberg Depression Rating Scale (MADRS),[33] manic symptoms were measured with the Young Mania Rating Scale (YMRS),[34] anxiety was measured with the Hamilton Anxiety Scale (Ham-A),[35] the overall clinical impression with the bipolar version of the Clinical Global Impression (CGI-BD),[36] and suicidality was measured with the Columbia-Suicide Severity Rating Scale (C-SSRS).[37] A MADRS score ⩾ 26 was required for study entry. Patients were evaluated weekly for the first 2 weeks and biweekly thereafter for a total of 8 weeks.

After treatment, subjects were offered participation in the genetic aspect of the study. After signing a separate informed consent, they provided cheek swabs which were sent for gene analysis. Nine subjects underwent genetic testing. The samples had DNA extracted and were tested specifically for both the short form of the promoter of the 5HTTR and the L_G genotype of the 5HHTR-linked polymorphic region (rs25531). Both of these variants are associated with reduced protein expression of the serotonin transporter.[22,23]

Treatment

Only one patient in the asenapine group was off all other medications. Concomitant medications, which were unchanged for the duration of the entire study and at least 2 weeks prior to study entry, included for the asenapine group: three on lamotrigine, and one each on bupropion, venlafaxine, vortioxetine, methylphenidate, and gabapentin; and for the placebo group: one each on lamotrigine, lithium, fluoxetine, quetiapine,

ziprasidone, methylphenidate, alprazolam, lorazepam, and methadone. They were given either unflavored sublingual asenapine or placebo that was started at 5 mg twice daily. The dose could be increased to 10 mg twice daily or decreased to 5 mg once daily based on tolerance or clinical response. Rescue lorazepam was available for the first 4 weeks of the study, but none of the subjects presented here used any rescue doses.

Statistical Analysis

The primary outcome measure was the difference in improvement from baseline to study end in subjects that had a low expressing genotype of the 5HTTR versus the long form. Inadequate numbers of patients with the long form prevented that analysis. Instead, we examined the effects of having a short form of 5HTTR on change from baseline to days 7, 14, 28, 42 and 56 (study end) in active and placebo treated patients for both depression and anxiety with an unpaired, 2-tailed, Student's T-test. Missing data were remedied with last observation carried forward. Statistical significance was set at probability (P) < 0.05. All statistical analysis was performed by Prism version 7.00.

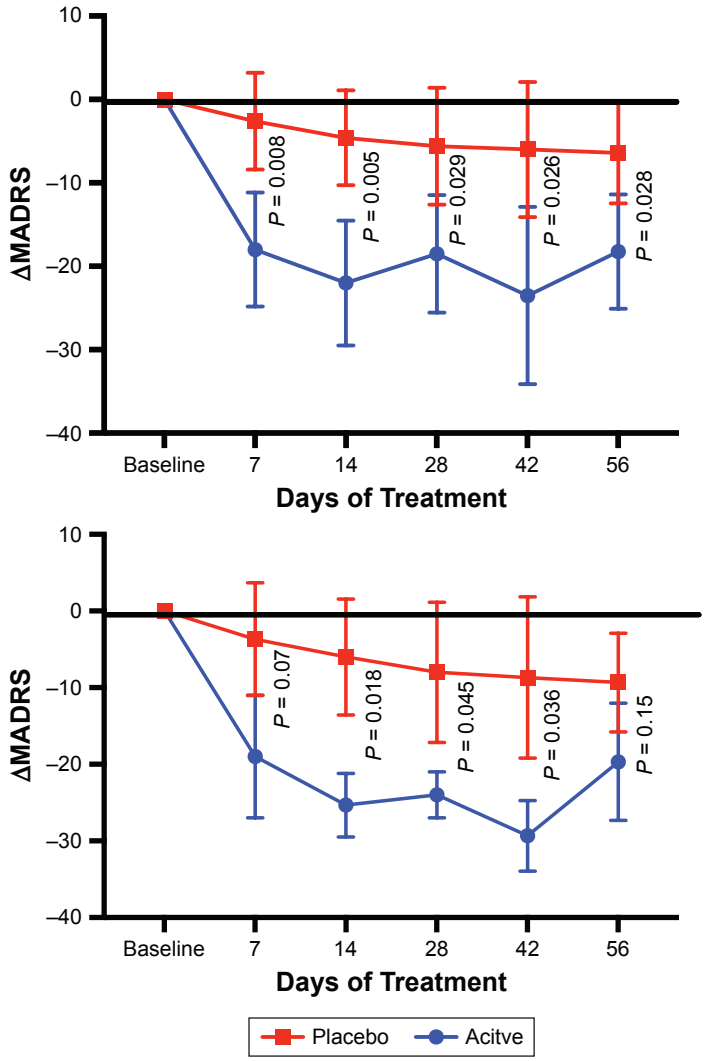
Results

Effect on Depression

Improvement in MADRS was statistically significantly greater in the asenapine group than the placebo group across genotypes, measured as changes from baseline to endpoint (mean $-19.80 \pm$ SD 8.59 vs. -3.80 ± 9.01, respectively; t = 2.875, $P = 0.021$) (Figure 1). Similarly, all other time points were also significant (day 7 [-22.00 ± 8.63 vs. -2.60 ± 5.81; t = 4.168, $P = 0.0031$]; day 14 [-28.40 ± 6.03 vs. -4.60 ± 5.68; t = 6.425, $P = 0.0002$]; day 28 [-26.40 ± 6.99 vs. -5.80 ± 7.16; t = 4.606, $P = 0.0017$]; day 42 [-24.40 ± 9.24 vs. -6.20 ± 8.17; t = 3.248, $P = 0.0117$]) (Figure 1). Comparing only 6 subjects with the short form of the 5HTTR (3 received placebo and 3 received asenapine [Table 1]), we found that differences in depression were no longer significant (-19.67 ± 7.64 vs. -9.33 ± 6.43, t = 1.79, $P = 0.15$, Power = 0.44). The effect size for subjects with the short form was 0.6. While many of the ongoing evaluations throughout the study are significant (Figure 1), it is important to note that the study was not intended to examine those points, and the significance would vanish if we corrected for multiple t-tests.

FIGURE 1

The Mean Change from Baseline in MADRS Total Scores Throughout the Study



Top is the entire sample, bottom is the 6 individuals who have the short form of the serotonin transporter. Graphed numbers are means +/− standard deviation.

The change in the Clinical Global Impression for Depression (CGI-D) was significantly greater for asenapine-treated subjects (−2.8 ± 0.5) versus placebo (−0.2 ± 0.37; t = 3.75, P = 0.006). When only subjects with the short form were examined, the CGI-D at end of study was not significant (−2.0 ± 1.0 vs. −0.67 ± 0.58; t = 2.0, P = 0.12, Power = 0.8) (Figure 1). The overall effect size of the asenapine treatment as measured by the MADRS was 1.82, which means that the difference between the

TABLE 1

The Genotype of the 5HTTR Gene (*SLC6A4*) in Whom Genomic Testing was Completed

	ASENAPINE TREATED		PLACEBO TREATED	
PATIENT ID	SHORT FORM	LONG FORM	SHORT FORM	LONG FORM
2002				L_A/L_A
2004	S/L_A			
2007			L_A/L_G	
2008		L_A/L_A		
2009			S/L_A	
2010				L_A/L_A
2011	S/L_A			
2013	L_A/L_G			
2014			S/S	

(Note the missing numbers represent either screen failures [n = 3] or did not undergo genetic testing, [n = 1].) S and L_G are the genotypes associated with lower expression of the serotonin transporter protein.

means is nearly 2 standard deviations. For the subjects with the short form, the effect size was 0.63.

Effect on Anxiety

Anxiety also improved significantly in the asenapine-treated subjects compared to placebo-treatment on day 14 (-19.40 ± 9.84 vs. -4.40 ± 5.23; t = 3.011, $P = 0.0168$), day 28 (-19.00 ± 3.32 vs. -4.60 ± 7.44; t = 3.954, $P = 0.0042$), day 42 (-16.80 ± 5.76 vs. -4.00 ± 5.70; t = 3.531, $P = 0.0077$) and endpoint day 56 (-15.40 ± 6.15 vs. -2.80 ± 7.95; t = 2.803, $P = 0.0231$) (Figure 2). The overall effect size of the asenapine treatment was 1.9.

For the 6 subjects who had the short form and sufficient data, the change in anxiety was -19.0 ± 5.57 for asenapine-treated individuals, compared to -6.0 ± 6.25 for placebo-treated subjects (Figure 2). P was equal to 0.055 (t = 2.69, Power = 0.77). The effect size was less than half of the entire sample at 0.74.

As with the analysis of the depressive symptoms, many of the ongoing evaluations throughout the study are significant (Figure 2), so it is important to note that the study was not intended to examine those points, and the significance would vanish if we corrected for multiple t-tests.

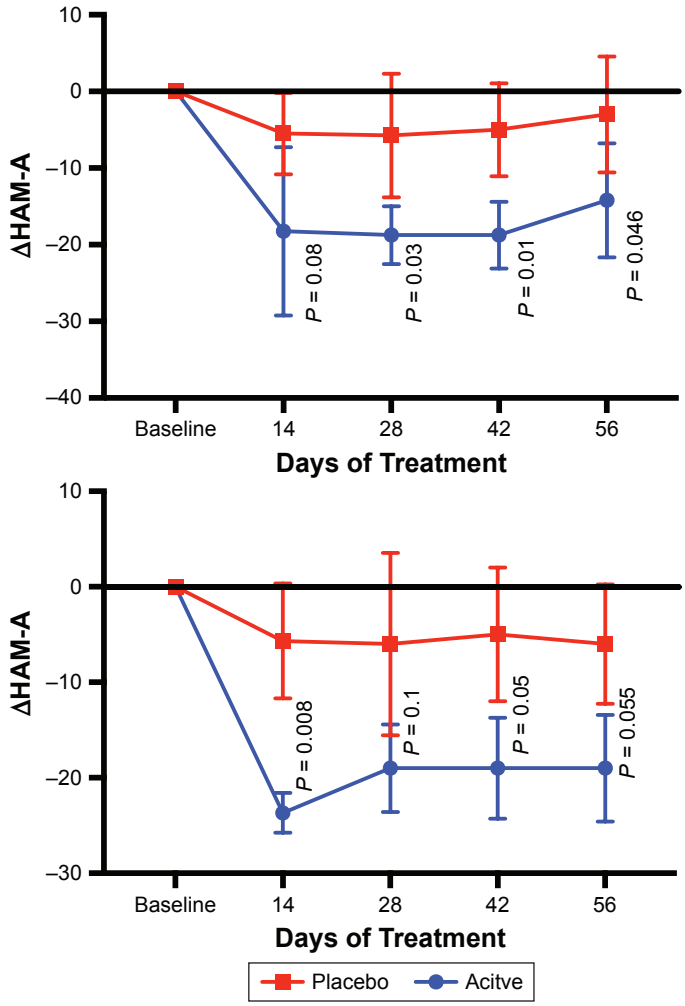
Safety

Effect on Mania

Manic symptoms did not significantly change from the low baseline (asenapine group and placebo group were 8.60 ± 2.41 and 5.00 ± 4.53,

FIGURE 2

The Mean Change from Baseline in HAM-A Total Scores Throughout the Study



Top is the entire sample, bottom is the 6 individuals who have the short form of the serotonin transporter. Graphed numbers are means +/− standard deviation.

respectively) on day 7 (0.200 ± 6.870 vs. −1.000 ± 2.828; $P = 0.7273$), day 14 (−4.400 ± 3.507 vs. −3.400 ± 5.128; $P = 0.7282$), day 28 (−2.800 ± 7.918 vs. −2.400 ± 4.159; $P = 0.92$), day 42 (−5.600 ± 4.037 vs. −2.200 ± 3.962; $P = 0.2158$) or endpoint day 56 (−4.600 ± 3.715 vs. −1.800 ± 5.167; $P = 0.35$).

Effect on Suicide

Suicidal ideation as measured by the C-SSRS was not significant at any point in the study. There were no discontinuations due to suicidal

ideation, no suicide attempts, and no self-injury by anyone at any point in the study. C-SSRS suicide risk scores were low at baseline (Placebo 1.2, asenapine 0.2; ns), and changed minimally at study end (0 ± 0.3 vs. -0.6 ± 0.6; ns).

Side Effects

All patients experienced at least one adverse event (AE). Patients receiving asenapine experienced dysgusia (60%), gastrointestinal (GI) upset (60%), weight gain (40%), pain of some sort (40%), and increased cholesterol (20%). Patients receiving placebo experienced dysgusia (40%), GI upset (40%), fatigue (40%), akathisia (20%), and increased triglycerides (20%). There did not appear to be a difference in the incidence of AEs in patients with or without the short form (mean ± SD).

Genomic Testing

Three subjects receiving active medication, and three subjects receiving placebo were found to have a short form of 5HTTR. Table 1 lists the genotype of the patients in whom genomic testing was completed.

Discussion

Asenapine has been approved in the United States and the European Union for the treatment of acute mania with or without mixed features in bipolar I disordered patients and specifically, it reduces depressive symptoms in these manic states.[1,38,39] In this study, we attempted to preliminarily determine whether the genetic variant of the short form of the 5HTTR might predict response. The larger study was performed at two sites, but gene testing was done in only one site. The results of the entire sample will be presented elsewhere, in this report we focus on the subset of patients in whom genetic testing was completed. Unfortunately, the study was terminated early by the sponsor for non-safety related reasons, significantly limiting sample size.

Despite the very small sample, the results across genotype were highly significant for both depressive (Figure 1) and anxiety symptoms (Figure 2). However, when only the subjects with the short form of the 5HTTR gene (*SLC6A4*) are included in the analysis, the results do not reach statistical significance at end point for either depression (Figure 1) or anxiety (Figure 2). The effect size for the 6 subjects with the short form was around half of the effect size for the entire sample. For the subjects with just the short form, the power for depression

was moderate (0.44), but high for anxiety (0.77). This subanalysis does not support the hypothesis that individuals with depression and the short form of 5HTTR may respond better to serotoninergic blockade. However, there is a notable difference in the power of the sample between anxiety and depression (0.77 vs. 0.44, respectively), and power increases with reduced variance. This may be indirect evidence that subjects with the short form of 5HTTR and anxiety may preferentially benefit from post-synaptic 5HT blockade. Larger studies will be needed to confirm this interpretation, and it may be more reasonable to focus on anxiety.

The safety profile of asenapine in the current study does not appear to depart from previous placebo-controlled reports.[38,39] Additionally, we did not note any difference in the prevalence of AEs in asenapine-treated patients with or without the short form. However, this final point is tentative given the small number of subjects with the long form of the 5HTTR gene.

There are significant limitations to this study, most prominently the small sample size. Additionally, the asymmetrical distribution of the short form of 5HTTR (74% with the short form) in our sample further limited testing of the effect of the short form in predicting outcome. Furthermore, this exploratory study suggests that response of anxiety to asenapine may be better predicted by the short form of 5HTTR, but subjects were recruited for presence of depression, not anxiety. Despite these limitations, these data at least suggest that the short form of the 5HTTR may not be driving positive effects of asenapine on depression and anxiety.

Conclusions

These results provide provisional evidence that asenapine may be effective in treating bipolar depression and anxiety, but suggest that these findings may not be related to the short form of the 5HTTR. There is indirect evidence that the short form may be a better predictor of response to anxiety. Future studies examining the effects of genetic variation in bipolar depression are indicated. ✤

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