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The geriatric mania asenapine study (GeMS)

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ABSTRACT

Rationale: Population aging results in growing numbers of psychiatric disorders among older patients. Yet, there is a paucity of studies on elderly mania.
Objective: To evaluate the effect of asenapine on older manic inpatients.
Methods: Thirty-four elderly patients suffering from a manic episode, mean age 67.2 years were enrolled in an open-label 3-weeks study of asenapine treatment. Inclusion criteria: (1) DSM-IV criteria for manic episode (2) age above 60 years, (3) episode severity necessitating inpatient treatment, (4) Young Mania Rating Scale (YMRS) score at baseline >20, and (5) no prior asenapine treatment. Participants were prescribed asenapine 5 mg BID for 3 days and then dose increased to 10 mg BID till day 21 (study completion).
Results: Twenty-five patients completed the study. YMRS score decreased from a baseline mean of 27.0 ± 8.8 to 13.3 ± 12.0 at the end of the study ($p < 0.001$). Fourteen patients (56% of completers) achieved remission (YMRS score < 12). MADRS score decreased from a baseline mean of 7.6 ± 5.6 to $4.4 + 5.1$ at the end of the study ($p < 0.05$); low baseline score should be noted. Sleep duration increased from a baseline median of 5.7 hours to 7.0 h at the end of the study ($p < 0.05$). Seven patients discontinued treatment due to adverse events. Two patients passed-away after study completion.
Conclusion: We tentatively conclude that the efficacy of asenapine in reducing acute manic symptoms and achieving remission in the elderly is supported in this study. Caution is needed in patients with co-morbid physical conditions.

1. Introduction

Recently one of Israel's largest health maintenance organizations analyzed the epidemiology of schizophrenia and bipolar affective disorder (BAD) (Kodesh et al., 2012). A total of 8848 adult patients were diagnosed with BAD (crude prevalence rate of 5 per 1000). The prevalence of bipolar disorder was 3.5 per 1000 in men and 4.4 per 1000 in women. In both sexes, rates of BAD diagnosis increased similarly over the years until the ages of 55–64 years then plateauing. Rates were higher among females in all age groups. The highest rates of BAD were observed among elderly women aged 75–84 years. Although it is commonly assumed that manic episodes in the elderly are due to exacerbation of BAD, there are several disorders that may present with mania in late life (Stone, 1989). This topic is much less investigated and has a heterogeneous origin, such as late-onset bipolar disorder, pre-existing depressive disorder converting to bipolar disorder, schizoaffective disorder or secondary mania caused by somatic illness or medication (Al Jurdi, Pulakhandam, Kunik, & Marangell, 2005).

Second generation antipsychotics have become the mainstay of treatment in BAD and in the last decade rates of use second generation antipsychotics in BAD have increased. This is reflected in the overall antipsychotic use in the USA increasing from 6.2 million treatment visits in 1995 to 14.3 million visits by 2008. Use of second generation antipsychotics especially expanded for BAD reaching a high of 34% exposure (Alexander, Gallagher, Mascola, Moloney, & Stafford, 2011). Nevertheless, scant research was published focusing on the use of second generation antipsychotics for elderly BAD patients (Maher et al., 2011). Asenapine is a second generation antipsychotic approved for bipolar disorder and schizophrenia. It has been widely investigated in adult BAD patients (Poo & Agius, 2014) but only two small trials were published focusing on elderly manic patients (Baruch, Tadger, Plopski, & Barak, 2013; Sajatovic et al., 2015).

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The aim of the present study was to assess the short-term response to asenapine treatment in elderly patients admitted to a tertiary care psychiatric center due to acute mania.

2. Experimental procedures

Consecutive elderly inpatients suffering from a manic episode were enrolled from 2 tertiary care psychiatric centers in Israel. This was an open-label 3-weeks study of asenapine for acute mania in the elderly. In each participating center patients fulfilling inclusion criteria were offered asenapine treatment. Consenting participants were prescribed asenapine 5 mg BID for 3 days and then dose was increased to 10 mg BID till day 21 (study completion).

2.1. Inclusion and exclusion criteria

Elderly participants were included in the study according to the following criteria: (1) fulfillment of the DSM-IV criteria for a manic episode (2) age above 60 years, (3) episode severity necessitating inpatient treatment, (4) Young Mania Rating Scale (YMRS) score at baseline >20, and (5) no previous treatment with asenapine. Exclusion criteria: (1) alcohol or drug abuse (or dependence), (2) unstable physical illness of any kind, (3) dementia of any kind and (4) history of stroke, or at a high risk for stroke.

No other psychotropic medications were allowed during the 3-week study. No use of beta-blockers, benzodiazepines, non BDZ hypnotics or other antipsychotics was allowed.

2.2. Objective

Primary: assessment of the effect of asenapine treatment in elderly manic patients as reflected by change in the total scores of the Young-Mania Rating Scale YMRS and the Clinical Global Impression-Severity (CGI-S) scales.

Secondary:

1) Assessment of asenapine's effects on depression as reflected by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score and sleep parameters as reflected by the Maryland Sleep Questionnaire (MSQ) score.

Participants were assessed at baseline, at day 2 and day 21. The percentages of responders ($\geq$50% decrease in YMRS total score from baseline at week 3) and remitters (YMRS total score $\leq$12) was also calculated after 3 weeks of treatment or at discontinuation. These response and remission criteria are consistent with those used in other published studies (Patel, Patrick, Youngstrom, Strakowski, & Delbello, 2007) and are considered to be clinically meaningful by clinicians.

Sleep quality and disturbances were assessed using the MSQ (Rao et al., 2005). The Maryland Assisted Living Study research group developed the MSQ at the Johns Hopkins University. It includes 11 items scored on a three-point Likert scale, with '0' being little or no disturbance present, '1' being mild to moderate, and '2' being chronic and severe disturbance present. The questionnaire assesses symptoms of insomnia (problems with sleep latency, sleep maintenance, early morning awakening, and duration of night-time sleep disturbance), excessive daytime sleepiness (symptoms of sleep apnea such as snoring and gasping at night, increased sleepiness, and napping during the day), chronicity of sleep problems, and unusual and excessive dreams. Participants were assessed at baseline, at day 2 and day 21.

Assessment of depressive symptoms was measured by the MADRS. Participants were assessed at baseline, at day 2 and day 21. The percentage of responders ($\geq$50% decrease from baseline) and remitters ($\leq$10) was assessed on day 21.

The study was approved by each center's ethical committee (IRB).

2.3. Statistical analysis

Variables are presented as mean and standard deviation (SD). The last observation-carried-forward (LOCF) method was used for missing values. The two-tailed *t*-test and nonparametric test tested for differences between the evaluations for qualitative parameters. The paired *t*-test and nonparametric Sign Rank Test were applied for testing differences between baseline assessment and end-of-study assessments for quantitative parameters. Examination of differences between the categorical parameters was based on the Pearson Chi-square and Fisher's Exact tests. All tests applied are two-tailed, and *p* value of 0.05 or less was considered statistically significant. The data was analyzed using the Statistical Analysis System software; SAS Institute, 1990.

3. Results

Thirty-four consecutively admitted elderly inpatients suffering from a manic episode were included in the study. Patients signed an informed consent form after detailed explanation of the study protocol.

3.1. Demographic data

Twenty-two of the 34 patients were women (64.7%), mean age for the group was 67.2 years, range: 60–75 years old. Seventeen (50%) of patients were married. The majority of patients (27/34) had elementary or high school education. All were suffering from a DSM-IV-defined diagnosis of a manic episode. Mean age at first diagnosis of BAD or schizoaffective disorder for the group was 37.8 years. In 11 of the participants there was a history of suicide attempt. Physical comorbidity in the sample was as follows: 15 patients were overweight or obese, 8 patients suffered from diabetes, 7 from hypertension, 3 from esophageal reflux and 3 from osteoarthritis.

3.2. Response (Table 1)

Twenty-five patients completed 21 days of treatment with asenapine. YMRS total score decreased from a mean of 27.0 ± 8.8 at baseline to 13.3 ± 12.0 at study's end (day 21). This decrease was statistically significant ($p < 0.001$). There were 14 (56%) patients who achieved remission (YMRS < 12) at the end of the study. Corresponding decrease in the CGI-BP was observed from a mean of 5.5 ± 1.7 at baseline to a mean of 3.1 ± 1.3 at completion ($p < 0.01$).

MADRS total score decreased from a mean of 7.6 ± 5.6 at baseline to 4.4 ± 5.1 at the end of the study. This decrease was statistically significant ($p < 0.05$), however, the low baseline score

Table 1
Change in outcome score.

	Baseline score	2 days	21 days
CGI mania	5.5 ± 1.7	4.8 ± 1.6	3.1 ± 1.3
CGI depression	1.5 ± 0.9	1.3 ± 0.9	1.4 ± 0.8
YMRS	27.0 ± 8.8	21.5 ± 10.5	13.3 ± 12.0
MADRS	7.6 ± 5.6	6.2 ± 5.5	4.4 ± 5.1
MSQ (item 5)	5.8	6.2	7.0

CGI = Clinical Global Impression; YMRS = Young Mania Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MSQ = Maryland Sleep questionnaire.
All scores are mean $\pm$ SD. MSQ scores are median.