Asenapine Once Daily Versus Twice Daily: Impact on Patient Acceptance in a Randomized, Open-Label, 14-Day Clinical Trial

To the Editor: Asenapine is a newly approved, second-generation antipsychotic with demonstrated efficacy for the treatment of schizophrenia.[1,2] However, the acceptance of asenapine is compromised in some patients by its associated daytime sleepiness. The US Food and Drug Administration recommended dose for asenapine as the acute treatment of schizophrenia is 5 mg twice daily,[3] but its terminal half-life of approximately 24 hours[3] suggests that it can be administered as a single bedtime dose. In the present study, we conducted a randomized, open-label trial to determine if asenapine 10 mg at bedtime was more acceptable to patients than asenapine 5 mg twice daily.

Method. This trial was conducted at the Central Regional Hospital in Butner, North Carolina. This trial was approved by the Institutional Review Board of Duke University Medical Center, and all patients signed informed consent to participate in the trial. Newly admitted men and women at least 18 years of age with clinical diagnoses (based on *DSM-IV* criteria) for schizophrenia or schizoaffective disorder in an acute exacerbation were included in the trial. Potential participants were excluded if they had a history of poor therapeutic response or sensitivity to asenapine, had received an injection of a depot antipsychotic medication within 1 treatment cycle prior to randomization, or had clinically significant medical illness. Women of child-bearing potential had negative serum pregnancy tests immediately prior to starting the trial.

Participants were randomly assigned to receive asenapine 5 mg twice daily or 10 mg at bedtime sublingual for up to 14 days. At day 14 or end of study, participants rated their overall acceptance of asenapine on a Likert scale with 1 = very acceptable, and 7 = completely unacceptable. The Brief Psychiatric Rating Scale (BPRS; 16–item version[4]) was completed at baseline and on days 3, 7, and 14 or end of study. Four potential side effects of asenapine (insomnia, daytime sleepiness, oral dysesthesia, and orthostatic faintness) were assessed on days 3, 7, and 14 or end of study on a scale from 0 to 4, with 0 as no such side effect noticed and 4 as the most severe case that may lead to treatment discontinuation.

Results. Thirty patients (17 women and 13 men) ranging in age from 20 to 61 years were randomly assigned to asenapine 5 mg twice daily (n = 18) or asenapine 10 mg at bedtime (n = 12). At the end of study, patients in the bedtime group reported significantly better acceptance of asenapine than the twice-daily group (mean ± SD scores: 1.7 ± 0.5 vs 3.9 ± 0.5, $P < .05$).

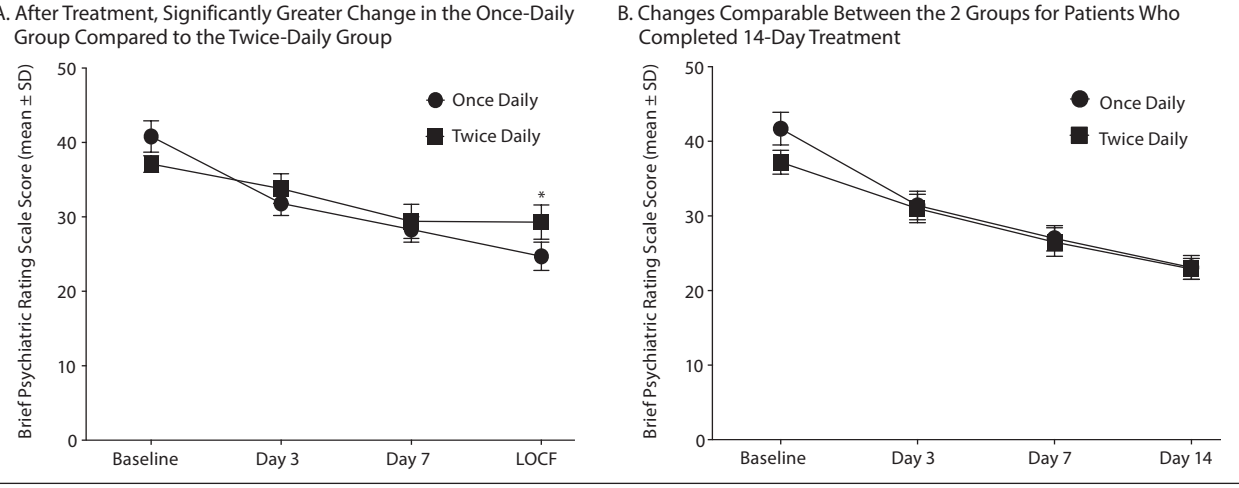
The treatment completion rate was 83% in the bedtime group (n = 10) versus 56% in twice-daily group (n = 10). In the bedtime group, all treatment discontinuations were due to inadequate therapeutic effect (17% of the total participants [n = 2]). In the twice-daily group, 22% of the participants (n = 4) discontinued their treatment due to inadequate therapeutic effect, and another 22% (n = 4) discontinued their treatment due to intolerable side effects. Except for 1 case of akathisia, all side-effect–related treatment discontinuations were due to severe daytime drowsiness.

Both 10 mg at bedtime and 5-mg twice-daily dosing regimens were effective in improving patient psychopathology. In Figure 1A, which displays the intention-to-treat population, a greater BPRS reduction was found in the bedtime group ($P < .05$) than in the twice-daily group. In Figure 1B, which displays completers only, BPRS changes were comparable between the 2 groups. These results suggest that the higher treatment completion rate in the bedtime group accounted for their greater BPRS reduction.

Patients in the twice-daily group consistently reported more severe daytime sleepiness at every visit. At day 14, patients in the twice-daily group rated daytime drowsiness at 1.3 ± 0.2, which is significantly higher than the rating of 0.1 ± 0.1 in bedtime group ($P < .05$). The treatment groups showed no differential pattern of tolerability on insomnia, oral dysesthesia, or orthostatic faintness.

In summary, our study demonstrated that asenapine 10 mg at bedtime was more acceptable to patients than asenapine 5 mg twice daily. A higher percentage of patients completed their treatment with asenapine 10 mg at bedtime; treatment discontinuation because of intolerable side effects, especially daytime drowsiness, in twice-daily group accounted for this difference. This result suggests that prescribing asenapine at a once-daily bedtime dose of 10 mg will result in more successful treatment outcomes. The limitations of this study are its small sample size and open-label design.

Figure 1. Change in Brief Psychiatric Rating Scale (BPRS) Scores



*$P < .05$.
Abbreviation: LOCF = last observation carried forward.

Trial Registration: ClinicalTrials.gov identifier: NCT01549041

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