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Asenapine for the Control of Physical Aggression: A Prospective Naturalist Pilot Study

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ABSTRACT *~ It has been previously purported that higher relative affinity to the dopamine D4 receptor compared to D2 (i.e., D4/D2 affinity ratio > 1) may underlie unique antiaggression potency. Asenapine is a newer antipsychotic that also has D4/D2 affinity ratio > 1. It has demonstrated efficacy in reducing acute agitation in a placebo-controlled study. We performed a prospective naturalistic, pilot, proof of concept study on an inpatient psychiatric unit. Among patients with aggression at time of admission (⩾ 12 on Refined Aggression Questionnaire [RAQ], or ⩾ 2 on Modified Overt Aggression Scale [MOAS]), asenapine treatment was associated with a significant reduction in total aggression as measured by the MOAS (–14.7 ± 11.59 vs. –5.4 ± 10.12, P = 0.045), and particularly physical aggression (–8.0 ± 5.06 vs. –0.78 ± 2.40, P < 0.0001) compared to treatment that did not include asenapine. These data suggest that asenapine may be useful in the targeted treatment of aggression, and provide some support for the D4/D2 affinity ratio hypothesis.* Psychopharmacology Bulletin. *2017;47(1):27–32.*

Introduction

Aggression is a major problem is psychiatric illness. It is one of the most common reasons for inpatient psychiatric admission.[1] Despite this, it is rarely the topic of research or the target of pharmacologic treatment trials. Current standard of care for the treatment of aggression includes use of mood stabilizers, antipsychotics, and antidepressants.[2,3] Nonetheless, clinical outcome with these interventions is frequently suboptimal.

The most effective agent in reducing aggressive and violent behaviors is clozapine.[4] In both open and randomized trials, clozapine has shown superiority over haloperidol, risperidone, and olanzapine.[5,6] This anti-aggression property occurs at therapeutic dosage and is independent of the antipsychotic effect or sedation.[5–7]

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Clozapine is almost unique among all the antipsychotics in having a D4/D2 affinity ratio that is greater than one, and this has been purported to be the antiaggression mechanism of clozapine.[7] Asenapine is a newer antipsychotic that also has a D4/D2 affinity ratio that is greater than one.[8]

To examine the hypothesis that an agent with D4/D2 > 1 may have antiaggression properties, we performed a prospective, naturalistic, pilot study of patients being admitted to an inpatient psychiatric unit. We examined the levels of aggression at admission and discharge as a function of treatment, and compared patients receiving asenapine with other antipsychotic medications.

Methods

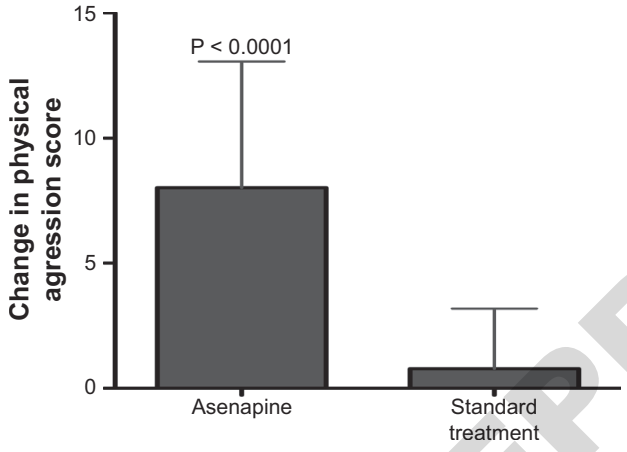
This was a prospective, naturalistic, observational study of patients admitted to the inpatient psychiatric unit and treated as is clinically appropriate. All patients admitted to the unit for a two months period were approached and invited to participate in the study. The Refined Aggression Questionnaire (RAQ[9]) and Modified Overt Aggression Scale (MOAS[10]) were completed on admission and again at discharge. Since our psychiatric emergency room routinely assesses aggression risk with the Brøset scale,[11] we included that as a measure as well. Patients' ratings were stratified and separated into aggressive ($\geqslant$ 12 on RAQ, or $\geqslant$ 2 on MOAS) and non-aggressive. Aggressive patients were then divided into those receiving asenapine or not receiving asenapine. The treating psychiatrist was not involved in the ratings and made her decisions exclusively for clinical reasons. Nonetheless, she was aware of the study and the hypothesis being tested. The primary outcome measure was the change in aggressive scores in patients on asenapine or not on asenapine. Secondary analyses examined subscores for physical aggression, verbal aggression, and aggression towards property. All the data were evaluated with t-tests. Since the primary outcome measure involved asenapine, no correction for multiple t-tests was required for that analysis, other t-tests were used more for understanding the data rather than measuring outcome (e.g. to examine the groups at baseline or to determine if patients improved), thus correction for multiple t-tests was not performed.

Results

A total of 48 subjects (26 men and 22 women) met criteria for inclusion in the study. Mean age was 43.0 ± standard deviation [SD] 16.47 years (range 18–89). Fourteen had schizophrenia, 14 had bipolar disorder,

FIGURE 1

In Comparison to Standard Treatment, Asenapine Significantly Decreased Physical Aggression Over a Hospitalization Admission as Measured by the MOAS



4 had major depression, 3 had substance-induced mood disorder, and 11 had a different diagnosis. The total duration of illness (DOI) was 24.15 ± 9.90 years (range 0.06–39). The length of hospitalization stay (LOS) was 4.6 ± 1.48 days (range 2–8).

Five patients received asenapine (3 with schizophrenia, and 2 with bipolar disorder) ($\chi^2 = 3.98$, P = 0.6). All 5 patients receiving asenapine had a history of previous aggression or violence ($\chi^2 = 1.51$, P = 0.22). The LOS was not different among these 5 compared to the control subjects (asenapine 5.0 ± 2.16 vs. 4.5 ± 1.44 days, t = 0.57, df = 37, P = 0.6). Similarly, total DOI, DOI of current episode, and age were not different in the 2 groups (asenapine 10.3 ± 10.3 vs. 11.9 ± 10.03 years, t = –0.34, df = 44, P = 0.7; 32.2 ± 26.6 vs. 23.6 ± 58.2 days, t = 0.33, df = 43, P = 0.75; 34.3 ± 18.2 vs. 43.7 ± 16.26, t = –1.23, df = 45, P = 0.23; respectively). The primary outcome measure is presented in Figure 1, the other data are presented in Table 1.

Discussion

Patients receiving asenapine experienced a greater reduction in the level of aggressive or disruptive behavior than patients receiving treatment as usual (TAU) (Table 1). This reached statistical significance for physical aggression (Figure 1).

Aggression and hostility are complex behaviors and etiologically associated with multiple factors including previous aggression, a history of exposure to violence, and substance abuse.[12,13] As such, it is

TABLE 1

Outcome in Asenapine Treated Patients, Versus Those Receiving Treatment as Usual (TAU)

VARIABLE	ASENAPINE @ BASELINE ± SD (n = 5)	ASENAPINE @ DISCHARGE ± SD (n = 5)	TAU @ BASELINE ± SD (n = 42)	TAU @ DISCHARGE ± SD (n = 42)	BASELINE t (df)	BASE-LINE P	DIS-CHARGE t (df)	DIS-CHARGE P
Brøset	1.4 ± 1.95	0.6 ± 1.34	0.48 ± 1.0	0.1 ± 0.62	1.8 (45)	0.8	1.5 (45)	0.14
MOAS total	19.0 ± 9.80	1.4 ± 2.61	5.69 ± 11.10	0.43 ± 1.80	2.56 (45)	***0.01***	1.09 (45)	0.28
MOAS PA	9.6 ± 3.58	0	0.86 ± 2.73	0.10 ± 0.62	6.57 (45)	***0.0001***	–0.34 (45)	0.73
MOAS VA	3.6 ± 2.5	0.6 ± 0.89	1.1 ± 1.93	0.24 ± 0.79	2.69 (45)	***0.01***	0.96 (45)	0.34
MOAS Anger	1.2 ± 2.68	0	2.6 ± 5.16	0	–0.58 (45)	0.56		ns
MOAS AAP	4.8 ± 7.82	0.8 ± 1.79	0.91 ± 2.58	0.095 ± 0.62	2.43 (45)	***0.019***	1.88 (45)	0.067
RAQ total	29.2 ± 11.56	23.8 ± 14.10	25.8 ± 11.94	21.4 ± 11.93	0.6 (45)	0.55	0.37 (41)	0.71
RAQ PA	7.4 ± 5.32	5.25 ± 5.12	5.8 ± 4.48	4.4 ± 3.73	0.73 (45)	0.47	0.42 (41)	0.68
RAQ VA	7.2 ± 3.16	6.3 ± 3.20	6.3 ± 3.50	6.6 ± 3.35	0.54 (45)	0.6	0.36 (41)	0.72
RAQ Anger	7.0 ± 3.16	5.0 ± 5.29	6.3 ± 3.82	5.4 ± 3.86	0.39 (45)	0.7	–0.18 (41)	0.85
RAQ Hostility	7.6 ± 3.78	7.25 ± 4.11	7.6 ± 4.32	6.3 ± 3.98	–0.02 (45)	0.98	0.46 (41)	0.65
Delta MOAS total		14.7 ± 11.59		5.4 ± 10.12			2.06 (45)	***0.045***
Delta MOAS PA		8.0 ± 5.06		0.78 ± 2.40			5.85 (45)	***0.0001***
Delta MOAS VA		2.5 ± 2.51		0.9 ± 1.82			1.97 (45)	***0.055***
Delta MOAS Anger		1.0 ± 2.45		2.6 ± 5.21			–0.75 (45)	0.46
Delta MOAS AAP		3.3 ± 7.23		0.8 ± 2.49			1.7 (45)	0.095

Abbreviations: MOAS, Modified Overt Aggression Scale; RAQ, Refined Aggression Questionnaire; PV, Physical Aggression; Verbal Aggression; AAP, Aggression Against Property; SD, Standard Deviation; n, number or sample size; df, degrees of freedom; P, probability.

unlikely that a single intervention will eliminate this behavior. However, clozapine appears to be more effective than other antipsychotic in reducing aggressive and disruptive behavior, and this effect is independent of both its antipsychotic or sedative effects.[5–7] Previously, it has been suggested that the higher D4 receptor affinity versus D2 receptor affinity of clozapine may be related to the reduced aggressive behavior.[7] Asenapine is a useful agent to examine this hypothesis, since it has a D4/D2 ratio that is > 1.[8]

Asenapine has been shown to be effective in reducing acute agitation.[14] That study did not report aggression scores in the recruited subjects, and was not powered to examine subscores of the Excited Component of the Positive and Negative Syndrome Scale.[14]

There are shortcomings of this pilot study: this was an uncontrolled study and the treating clinician was aware of the study and the hypothesis being examined; other psychopathologic symptoms were not measured; the reduction in aggression was seen in only one scale (the MOAS) and not the other (RAQ), reducing the generalizability of the data; and the sample size was limited, which resulted low power for many of the analyses.

Nonetheless, the data clearly shows that asenapine appears to be more effective than TAU in reducing overall aggression and physical aggression in acutely ill psychiatric patients. This exploratory study suggests that additional research is indicated for examination of asenapine in the treatment of aggression, and offers initial support for the D4/D2 ratio hypothesis for the treatment of aggression. ✤

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