Asenapine, Aggression, and Affinity

To the Editor: Aggression and hostility may exhibit themselves as symptoms of a psychotic illness or independent of psychosis. They are important treatment targets. As such, the recent post hoc analysis by Citrome and colleagues[1] is an important contribution to the literature. In their introduction, the authors note that clozapine is the most effective antiaggression medication available. Importantly, the antiaggression effect of clozapine is *independent* of its antipsychotic effect.

My colleagues and I have previously posited that the antiaggression effect of clozapine is mediated by the relatively greater blockade of dopamine D_4 compared to D_2.[2] We expressed this as a D_4/D_2 affinity ratio of >1, but we specifically meant that receptor occupancy had to be greater at D_4 versus D_2 for the antiaggression effect to appear. In that paper, we proposed that asenapine (which also has D_4/D_2 affinity >1) would also be effective as an antiaggression drug.[2]

We tested that hypothesis with a prospective naturalistic study,[3] in which we recruited patients with a Modified Overt Aggression Scale score ≥ 2 or a Refined Aggression Questionnaire score ≥ 12. These were all patients with demonstrated aggression at the time of admission. Patients treated with sublingual asenapine had greater reductions in aggression as measured by both scales, and the effect was independent of diagnosis. That study compared asenapine with active treatment, not placebo.[3]

The antiagitation and antiaggression effects of asenapine have also been demonstrated across an array of psychiatric diagnoses in a comprehensive psychiatric emergency program (CPEP, with the Positive and Negative Symptom Scale-Excited Component [PANSS-EC])[4] and in acutely manic subjects (with the hostility, irritability, and disruptive behavior items of the Young Mania Rating Scale, and the PANSS-EC).[5] The CPEP study included responders with schizophrenia, schizoaffective, bipolar, major depressive, anxiety, and posttraumatic stress disorders.[4] The recent study by Citrome et al[1] was a post hoc analysis that looked mainly at a single PANSS item (hostility) as well as the PANSS-EC. Again, Citrome and colleagues demonstrated that the effect was independent of control of psychosis, but because the study only recruited people with schizophrenia, they could not examine to see if the effect is independent of diagnosis. The authors note that the full antihostility effect was seen at 3.8 mg/24 hours,[1] when D_4 receptor occupancy is expected to exceed 90%.

The other agent with a $D_4/D_2 > 1$ is loxapine. Interestingly, this agent is approved for control of agitation in schizophrenia and bipolar illness, and we demonstrated in a naturalistic study that the effect of inhaled loxapine on aggression is independent of diagnosis.[6]

It is important to consider aggression/hostility as an independent behavior in pharmacologic studies because it probably has its own biochemistry/neuroanatomy. This trend is already ongoing in suicide/suicide ideation, which is now the primary target of pharmacologic studies. Given the high rates of morbidity and the high costs associated with aggression, similar attention regarding the most appropriate pharmacologic intervention is needed.

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