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# Mode of Action of Asenapine vs. Other Antipsychotic Drugs

## An experimental analysis

**AKADEMISK AVHANDLING**

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## ABSTRACT

Antipsychotic drugs (APDs) are used in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. Generally, the so-called atypical APDs, such as clozapine, may in contrast to typical APDs improve not only positive, but also negative symptoms and some aspects of cognitive impairment associated with schizophrenia. However, as also the atypical APDs may be associated with severe side effects such as weight gain, dyslipidemia, increased prolactin levels and even agranulocytosis, the need for novel and improved pharmacotherapy in this area is considerable. This need is underlined by the fact that in recent years, the beneficial effects of low doses of atypical APDs in the treatment of depressive symptoms in uni- as well as bipolar depression have been increasingly recognized.

The antipsychotic drug risperidone is one of the most commonly prescribed APDs in the world. In similarity with clozapine, risperidone has, however to a smaller extent, affinity for  $\alpha_2$ -adrenoceptors, an effect that otherwise distinguishes clozapine from most other APDs. We therefore examined if additional  $\alpha_2$ -adrenoceptor blockade could enhance the efficacy of risperidone. The antipsychotic-like effect, extrapyramidal side effect (EPS) liability and effects on critical neurotransmitter systems in the brain were studied. Our data propose that the  $\alpha_2:D_2$  ratio by risperidone is indeed not optimal and that its antipsychotic-like efficiency can be enhanced by adjunctive treatment with an  $\alpha_2$ -adrenoceptor antagonist, e.g. idazoxan, allowing for reduced dosage and a subsequent reduced EPS liability, yet with maintained efficacy.

Asenapine is a recently approved APD with a unique receptor binding profile, developed for the treatment of schizophrenia and bipolar disorder. Clinical studies have shown that asenapine possesses, in addition to its effect on psychosis and mania, a well tolerated side effect profile. Using a range of well established preclinical methods we therefore analyzed experimentally the mode of action of asenapine, demonstrating an antipsychotic-like activity, low EPS liability and an atypical profile as regards its effects on critical neurotransmitter systems in the brain. Notably, asenapine increased prefrontal dopamine release and subsequently, via a  $D_1$  receptor-mediated mechanism, glutamatergic NMDA-induced transmission in the medial prefrontal cortex (mPFC), mechanisms implicated in cognitive functioning. Moreover, the release of noradrenaline and serotonin was also increased in the mPFC, generally indicating antidepressant activity. The profile of asenapine was shown to be similar in several important aspects to other potent atypical APDs, e.g. clozapine, which is the most efficacious APD presently known, but differs from typical APDs, e.g. haloperidol. It was furthermore shown that different mechanisms are involved in the effects of asenapine on subcortical and cortical dopamine regulation. These data indicate that the dopamine release in the mPFC may largely depend on an intracortical action. Specifically, asenapine in the mPFC was shown to exhibit a pharmacologically significant 5-HT<sub>2A</sub> receptor and  $\alpha_2$ -adrenoceptor antagonistic activity *in vivo*, which may contribute to the enhanced prefrontal monoamine release.

In other experiments, the combination of low doses of asenapine and the SSRI escitalopram was studied, demonstrating an augmentation of monoaminergic effects of escitalopram as well as facilitation of glutamatergic NMDA- and AMPA receptor-mediated transmission in the mPFC. The results may indicate a mode of action similar to that recently proposed to mediate the rapid and potent antidepressant effects of ketamine and scopolamine. Collectively, our results support, in principle, the clinical utility of adjunctive asenapine in treatment-resistant MDD, and indicate a fast onset of action.