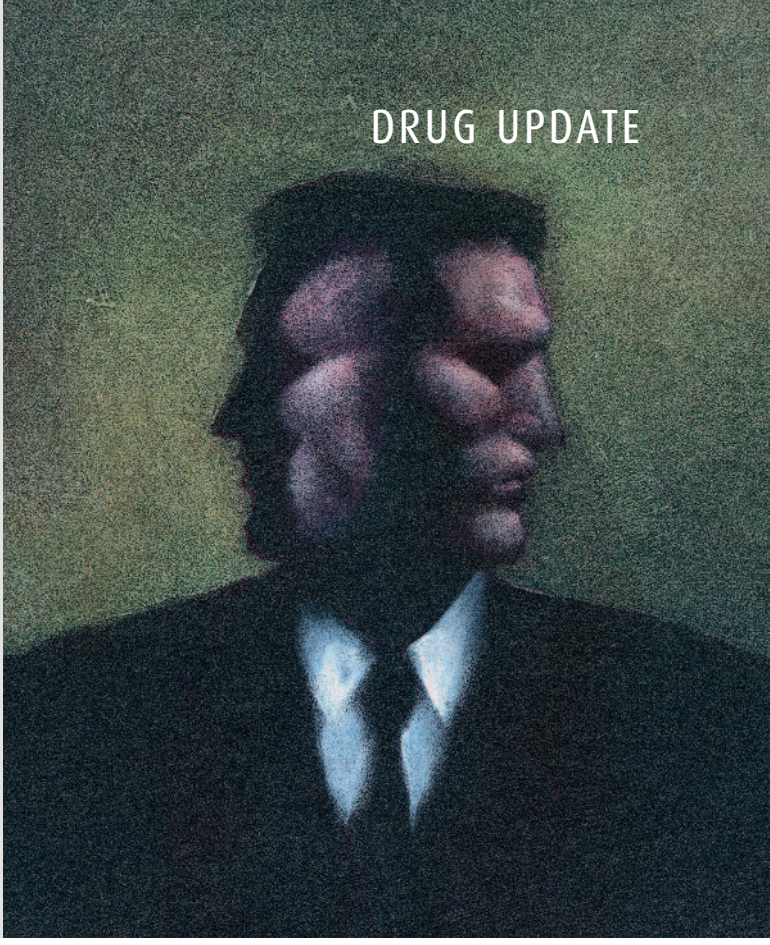

The place of asenapine in the treatment of schizophrenia and bipolar disorder

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With several second-generation antipsychotics already available, where does asenapine fit in the treatment of patients with psychotic disorders?

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In the past 20 years, seven second-generation ('atypical') antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, amisulpride, ziprasidone, asenapine), in addition to clozapine, have been introduced in Australia for the treatment of patients with schizophrenia. Their improved tolerability, especially in relation to extrapyramidal side effects, led to them quickly replacing the older 'typical' antipsychotics. As atypicality is mainly ascribed to stronger serotonin $5HT_{2A}$ receptor affinity compared with affinity for the dopamine D_2 receptor (with the exceptions of aripiprazole and amisulpride), why do clinicians need the latest antipsychotic asenapine with the same mode of action? This article attempts to place asenapine in the context of first- and second-line treatment for patients with psychotic disorders, relying on clinical experience as much as level 1 evidence.

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WHAT IS ASENAPINE?

Asenapine is a second-generation antipsychotic with approved indications for the treatment of adults with schizophrenia and the treatment and prevention of relapse of manic or mixed episodes in those with bipolar I disorder. Pharmacologically it is a tetracyclic of the dibenzo-oxepino pyrrole class. Relative to its D_2 receptor activity, asenapine possesses higher affinity for a range of serotonergic ($5HT_{2A}$, $5HT_{2C}$, $5HT_6$, $5HT_7$), noradrenergic (α_{2A}, α_{2B}, α_{2C}) and dopaminergic (D_3, D_4) receptors. It also has appreciable affinity for $5HT_{1A}$, α_1, D_1, H_1 and H_2 receptors,[1] but has insignificant affinity for muscarinic receptors. Preclinical studies have shown that asenapine causes dose-dependent increases in prefrontal dopamine, noradrenaline and acetylcholine levels, proposed as mechanisms for favourable effects on cognition and negative symptoms in schizophrenia.[2] Its relatively slow dissociation from the D_2 receptor may account for its tendency to cause more extrapyramidal side effects at higher doses compared with olanzapine.

CLINICAL ISSUES WITH ASENAPINE

Asenapine wafers must be taken sublingually. For patients with schizophrenia, the starting dose is 5 mg twice daily; for those on monotherapy for bipolar 1 disorder, the starting dose is 10 mg twice daily and decreases to 5 mg twice daily if added to lithium or sodium valproate. Low bioavailability when swallowed (<2%) means that it is almost impossible to take a lethal oral overdose of asenapine. Patients must be forewarned that sublingual asenapine is often associated with transient mucosal numbness (hypoesthesia) or bitterness (dysgeusia).[3] They should not eat or drink for 10 minutes after administration

because this will slightly reduce the 35% sublingual bioavailability. The wafer should not be chewed or handled with wet fingers.

Sublingual asenapine is rapidly absorbed, reaching peak plasma concentrations in 0.5 to 1.5 hours, and it has a mean terminal half-life of about 24 hours. The kinetics of asenapine are not linear, so 10 mg twice daily produces blood concentrations about 1.7 times that of a 5 mg twice daily dose.[3] This suggests that in schizophrenia the first dose increase should be to 15 mg/day (5 mg in the morning, 10 mg at night) rather than going directly to 10 mg twice daily, especially in outpatients or those experiencing their first episode.

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 (CYP450) isoenzymes (predominantly CYP1A2). Dose adjustment down may be needed when fluvoxamine, a CYP1A2 inhibitor, is coadministered. Alternatively, asenapine, a weak CYP2D6 inhibitor, may interact with the metabolism of paroxetine and fluoxetine (both inhibitors and substrates of CYP2D6) to cause increases in blood levels of these antidepressants. No dosage adjustments are required for patients with mild-to-moderate hepatic impairment, but asenapine use should be avoided in those with severe liver impairment. No dosage adjustment is required in patients with renal impairment. The most common side effects experienced with asenapine are sedation (related to H_1 receptor antagonism) and dose-dependent extrapyramidal side effects, especially akathisia. Orthostatic hypotension and dizziness (related to α_1 receptor antagonism) do not commonly occur. Although some weight gain occurs in about 10% of patients on long-term asenapine treatment[5,7,9] (related to the effects of the H_1 and $2HT_{2C}$ receptors) and minor changes in fasting glucose and cholesterol levels have been reported, asenapine appears to have little or no effect on triglyceride levels or rates of metabolic syndrome or elevated HbA_{1C}. Asenapine has no clinically significant effect on QTc interval.[4] Significant elevation of prolactin levels is uncommon, with rates being comparable to those associated with use of olanzapine[5] and substantially lower (9% *v.* 79%) than those associated with use of risperidone.[6] Abrupt switching from antipsychotics with strong anticholinergic actions (e.g. olanzapine) to asenapine could lead to cholinergic rebound syndrome because of asenapine's very low muscarinic receptor affinity. Hypersensitivity reactions have been reported. Asenapine is a category C drug; it should not be used in pregnancy and should be avoided during breastfeeding.

HOW DOES ASENAPINE COMPARE WITH OTHER SECOND-GENERATION ANTIPSYCHOTICS?

Asenapine has fairly comparable efficacy and safety to other second-generation antipsychotics in the treatment of patients with schizophrenia and bipolar I disorder.[1-3] Its overall efficacy has been reported to be less than that of olanzapine for patients with schizophrenia in one study,[5] although there is emerging evidence that asenapine may have an advantage in patients with schizophrenia and predominantly negative symptoms.[7] Asenapine has not been tested in patients with treatment-resistant schizophrenia. Although asenapine has been shown to be as effective as olanzapine in patients with acute bipolar 1 manic and mixed episodes in short and medium-term studies[8,9], it has not been evaluated in studies of bipolar depression or bipolar relapse prevention.[9] Asenapine is associated with more frequent extrapyramidal side effects than olanzapine,[5] but less weight gain than either risperidone[6] or olanzapine.[5] Less weight gain is particularly relevant to the treatment of patients with bipolar disorder who appear particularly prone to the metabolic side effects of second-generation antipsychotics.[10]

The relative rates of less common adverse effects of asenapine compared with other second-generation antipsychotics are available elsewhere.[2]

WHERE DOES ASENAPINE FIT?

The available evidence from randomised controlled trials alone does not show what patient subgroups might potentially respond to a particular second-generation antipsychotic, and the author relies on clinical experience to formulate the following proposals. Although oral risperidone is often recommended as first-line treatment, the author takes the view that there are now more tolerable alternative oral antipsychotics in most cases. He concludes that asenapine may be considered a first-line second-generation antipsychotic in at least a subgroup of patients with schizophrenia or bipolar 1 disorder. In those patients with predominantly negative symptoms of schizophrenia or patients with bipolar type I and no depressive episodes, asenapine may be preferred, especially in those with cardiac or metabolic risk factors. Where extrapyramidal side effects are a major concern, quetiapine seems the best treatment option, as long as a weight control intervention is in place. The author views olanzapine as a second-line treatment option, in accordance with the recommendations of other authorities,[11] but it should be remembered that adherence in nonresponsive patients must always be monitored and depot second-generation antipsychotic formulations considered whenever adherence is in doubt.

CONCLUSION

There are eight second-generation antipsychotics available on the PBS (the second-generation antipsychotic sertindole is not listed on the PBS) and it is difficult for GPs to decide which one should be offered as first-line treatment. For asenapine, the chief distinguishing features are its efficacy in both patients with bipolar 1 disorder and schizophrenia, and its potential as a first-line option in patients with predominantly negative symptoms.

Efficacy should almost always be the primary concern, as long as this is backed up by stringent management of safety concerns and adverse events. Irrespective of which second-generation antipsychotic is prescribed, it is essential to offer cardiometabolic assessment, monitoring and intervention. If oral antipsychotics are used, the most important way to improve effectiveness is to ensure adherence, and a clearly defined adherence intervention (e.g. pill counts or checking repeat prescriptions are filled) should be considered for all patients. The broad range of second-generation antipsychotics now available in Australia permits a personalised medicine approach, at least in terms of side effects, while we await the next generation of pharmaceutical agents for the psychotic disorders. MT

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