

Graylands Hospital Drug Bulletin

Asenapine

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Asenapine (Saphris®) is a new second generation antipsychotic (SGA) indicated in Australia for:

- Treatment of schizophrenia in adults
- Treatment of acute manic or mixed episodes associated with bipolar 1 disorder in adults as monotherapy or in combination with lithium or sodium valproate, and
- Prevention of relapse of manic or mixed episodes in bipolar 1 disorder in adults as monotherapy or in combination with lithium or sodium valproate¹

Asenapine was listed on the Pharmaceutical Benefits Scheme (PBS) on 1st December 2011. These indications differ slightly from those listed above, and are outlined below in Table 1.

Table 1: PBS indications for asenapine²

PBS Indication	Streamlined Authority Number
Schizophrenia	1589
Treatment, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder	3935
Maintenance treatment, as monotherapy, of bipolar I disorder	3936

Asenapine has very low bioavailability when swallowed (<2%) due to high hepato-gastrointestinal first-pass metabolism,³ therefore, a sublingual dosage form was developed. When administered sublingually, asenapine is rapidly absorbed through the buccal mucosa with an absolute bioavailability of 35% after a 5mg dose.³

Absorption and bioavailability are reduced with water, therefore eating and drinking should be avoided for 10 minutes after asenapine administration.^{1, 3}

Pharmacology

As with most other SGAs, asenapine exhibits a higher binding affinity for the serotonin 5HT_{2A} receptor compared with dopamine D₂ receptors (38x higher affinity to 5HT_{2A}).^{4, 5} Asenapine shows high affinity for and behaves as a potent antagonist at a wide array of serotonin receptors, adrenoceptors, dopamine receptors and histamine receptors.⁴

Asenapine exhibits little muscarinic receptor antagonist effects, unlike clozapine and olanzapine. Given that D₂ receptor occupancy has been deemed necessary for antipsychotic efficacy, it is important to note that a 5mg twice daily dose results in roughly 75% D₂ occupancy, while occupancy is 85% with a 10mg twice daily dose.⁵

This drug's molecular structure is similar to the antidepressant mirtazapine and may promote cortical serotonin and noradrenaline activity but there is no evidence for using it in the treatment of depression or anxiety. Its pharmacodynamic profile suggests some treatment possibilities in these clinical areas however. Asenapine's 5HT_{1A}, 5HT_{2A}, and 5HT_{2C} receptor pro-cognitive and antidepressant potentials are similar to other SGAs.⁵⁻⁷

Efficacy

Schizophrenia

Four short-term, placebo-controlled and active-controlled studies were conducted using the asenapine dose range 5-10mg twice daily. Two of these studies supported asenapine's efficacy in schizophrenia. The other two studies consisted of one negative study (asenapine was not significantly more effective than placebo, but olanzapine was) and one failed trial (neither asenapine nor olanzapine were significantly more effective than placebo).⁸

Longer-term studies have also demonstrated efficacy of asenapine. A one-year double-blind study was conducted in 1225 patients receiving asenapine or olanzapine.⁸ Discontinuation rates were higher for asenapine (61.4% vs. 42.8%), with 25.1% of patients discontinuing because of lack of efficacy with

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asenapine, compared to 14.5% with olanzapine. Using last observation carried forward (LOCF) analysis, both medications had similar efficacy at week 6, but olanzapine was significantly more effective at endpoint. Among those who completed the trial, olanzapine and asenapine were similarly effective.⁸

A maintenance phase placebo-controlled trial involved an open-label 26-week period where all patients received asenapine, followed by a 26-week double-blind period where patients were assigned either asenapine or placebo.⁹ Asenapine was more effective in preventing relapse of schizophrenia, with 12.4% of asenapine patients relapsing compared to 46.9% of those taking placebo.⁹ Only patients who responded to asenapine entered the double-blind treatment phase.⁹

Bipolar Disorder, Monotherapy

A total of 680 patients completed two identically designed, 3-week placebo-controlled and olanzapine-controlled trials looking at the effect asenapine had in subjects with acute manic or mixed episodes. Patients were originally given asenapine 10mg bd, olanzapine 15mg/day or placebo. After the first day doses were flexible within the range asenapine 5-10mg bd and olanzapine 5-20mg daily. Asenapine and olanzapine were significantly more effective than placebo, as measured by a reduction in the Young Mania Rating Scale (YMRS) in both of these trials.^{10, 11}

Patients who completed either of these 3-week trials were eligible to enter a 9-week, double-blind extension study. There were 504 patients enrolled in this study, with 308 completing it. Those taking the active medication continued the same regimen, while those taking placebo were switched to asenapine. The primary outcome was the mean change from baseline in YMRS total score, which was -24.4 for asenapine and -23.9 for olanzapine, indicating no significant difference between the two treatments.¹²

Two hundred and eighteen patients enrolled in a 40-week extension study that was available to patients who had completed the 3-week and 9-week trials. Patients were maintained on the same medication they had received in the previous trial. This study focussed on safety and tolerability of the medications and efficacy was only a secondary assessment.¹³

Bipolar Disorder, adjunctive to lithium or sodium valproate

Asenapine efficacy adjunct to continued mood stabiliser therapy was studied in a 12-week trial in patient not fully responsive to their current treatment.¹⁴ Patients continued their mood stabiliser therapy (lithium or sodium valproate) and were randomised to receive flexible-dose asenapine 5-10mg bd or placebo. At the end of the 12 weeks, 116 patients completed the study and asenapine was significantly more effective than placebo.¹⁴

Thirty-four patients completed a 40-week extension phase of this study. There was no difference between

placebo and asenapine at the end of this period in terms of efficacy measures³ though the extension phase was not powered for statistical comparison.¹⁴

Pharmacokinetics

Asenapine is rapidly absorbed following sublingual administration,¹ with peak plasma concentrations within 0.5-1.5 hours.⁵

It is extensively metabolised, primarily via glucuronidation, by uridine diphosphate-glucuronyl-transferase (UGT) 1A4, and oxidation via cytochrome (CYP) P450 1A2.¹ CYP3A4 and 2D6 are involved in the metabolism of asenapine but to a lesser degree.¹⁵ Asenapine's metabolites are inactive.³

The terminal elimination half-life of asenapine is approximately 24 hours, and steady state is achieved within 3 days of twice daily dosing.¹

Dosing

The recommended dose of asenapine is 5-10mg twice daily.

In schizophrenia, the initial dose should be 5mg bd, then increased to 10mg bd if required.¹

For the treatment of bipolar disorder, the recommended starting dose when used as monotherapy is 10mg bd, with a final dose recommendation of 5-10mg bd based on efficacy and tolerability.¹ When used in combination with lithium or sodium valproate, commence at 5mg bd and increase the dose to 10mg bd depending on clinical response.¹

There is very little experience and no literature supporting the use of asenapine outside the recommended dose range of 10-20mg daily.⁶

The original studies of asenapine used a twice daily dosage. As a result the asenapine Australian product information recommends twice daily dosing of the drug even though the 24-hour half-life would support once daily dosing. Communications with Lundbeck have revealed that the decision for twice daily dosing was based on the idea that we need to achieve adequate D2 blockade of receptors over a long enough time period, which is only achieved with twice daily dosing.¹⁶

Pharmacokinetic modelling showed that asenapine has an initial more rapid, followed by a slower elimination phase. Twice daily dosing ensures adequate blockade of the D2 receptors, thereby maintaining therapeutic efficacy.

This logic raises an interesting question about what makes an atypical antipsychotic atypical. One theory proposes that it is the ratio of serotonin blockade to dopamine blockade and that typical antipsychotics are relatively selective D2/D3 receptor antagonists.¹⁷ By contrast, another theory suggests fast dissociation from the D2 receptor makes an antipsychotic more accommodating of physiological dopamine transmission,

permitting an antipsychotic effect without motor side effects, prolactin elevation, or secondary negative symptoms.¹⁸ If the “fast off” theory is correct, then twice daily dosing may reduce the atypical profile of the drug.

Administration

Asenapine is only available in a sublingual dosage formulation due to low oral bioavailability.¹ It is available in two strengths, 5mg and 10mg.¹

Asenapine is absorbed directly through the buccal mucosa. This is unlike the other orally disintegrating antipsychotic formulations of olanzapine and risperidone, which are dissolved in the mouth but absorbed through the gut.¹

The sublingual tablet should not be crushed, chewed or swallowed, but placed under the tongue and left to dissolve.^{1,3} It dissolves rapidly in the mouth, but it may take up to 10 minutes for the entire dose to be absorbed. Patients are therefore instructed not to eat or drink for 10 minutes after administration, and asenapine must be taken last if used in combination with other medications.¹ Studies have shown drinking 2 minutes after administration reduced asenapine exposure by 19%, while drinking after 5 minutes reduced exposure by 10%.¹

Interactions

The use of asenapine in combination with other drugs has not been extensively evaluated. Given the primary central nervous system (CNS) effects of asenapine, caution should be used when it is taken in combination with other centrally acting drugs or alcohol.¹

Asenapine may enhance the effects of antihypertensive agents due to its propensity to cause orthostatic hypotension.¹

Asenapine is cleared primarily by UGT1A4 and CYP1A2. Fluvoxamine, a potent CYP1A2 inhibitor significantly reduced metabolism of asenapine.

Asenapine appears to be at most a weak inhibitor of CYP2D6. Asenapine should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.¹

Adverse effects

The most frequently reported adverse effects from asenapine use have been somnolence, dizziness, akathisia, weight gain, oral hypoesthesia (numbing) and a bitter/bad taste.^{1,15} Akathisia appears to be the only dose-related adverse effect.¹⁵

Clinically significant weight gain occurs less frequently with asenapine treatment compared to several other SGAs.¹⁵ Direct comparisons with other antipsychotics are limited, but asenapine shows a more favourable weight gain profile compared to olanzapine.¹⁵ Effects on lipids, fasting glucose and cholesterol are small.⁸

Asenapine can prolong the QTc interval, having a similar effect to that seen with quetiapine.¹⁵ The effect on prolactin levels appears not to be clinically relevant, with changes comparable to that of olanzapine.¹⁵

In September 2011, the US Food and Drug Administration released a safety announcement relating to serious allergic reactions reported with the use of asenapine.¹⁹ Fifty-two cases of type 1 hypersensitivity reactions have been reported. Symptoms include anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue and dyspnoea. Eight cases occurred after the first dose despite type 1 hypersensitivity reactions typically occurring after previous exposure to the drug. Many of the cases have limited information, but the evidence supports a temporal association between the onset of the reactions and asenapine use.¹⁹

The bitter taste caused by asenapine has been largely alleviated by the introduction of a black cherry flavour in other countries.⁸ This flavour is currently unavailable in Australia and there is no information regarding when, or if, it will become available.

Conclusion

The role of asenapine in the treatment of schizophrenia and bipolar disorder is likely to be in patients where metabolic syndrome or prolactin elevation from other agents is an issue.

Obstacles to the first-line use of asenapine include the recommendation for twice daily dosing, the need to avoid eating and drinking for 10 minutes after administration and the unpleasant taste and oral numbness it can cause.

Asenapine Summary:

- Indicated for schizophrenia and bipolar disorder
- Available in 5mg and 10mg wafers which must be absorbed through the buccal mucosa
- Twice daily dosing
- Patient should not eat or drink for 10 minutes after administration
- Common side effects: bitter taste, akathisia, oral hypoesthesia, somnolence, dizziness, weight gain
- Few clinically relevant drug interactions (fluvoxamine may inhibit metabolism of asenapine)

Citalopram causes QT prolongation: change to recommended maximum dose

The Therapeutic Goods Administration issued a safety alert on 4th November 2011 advising that citalopram should no longer be used at doses greater than 40mg per day.²⁰ The TGA also advised that people diagnosed with congenital long QT syndrome should not take citalopram, and for some patients, the maximum recommended dose is 20mg per day.²⁰

As a result of this information, the **maximum recommended dose of citalopram is now 40mg per day.**²⁰ The previous maximum recommended dose was 60mg per day.

A maximum daily dose of 20mg per day is now recommended for patients:

- Greater than 65 years of age
- With liver dysfunction
- With poor CYP2C19 activity or
- Taking concomitant CYP2C19 inhibitors (e.g. cimetidine or omeprazole)²⁰

These new dosage recommendations and contraindications arose following a recent study by the Forest Research Institute in the USA, which showed that higher doses of citalopram can cause abnormal changes in the electrical activity of the heart.²⁰ These electrical changes were prolongation of the QT interval of the electrocardiogram (ECG), which can lead to arrhythmias and Torsades de Pointes.²¹

Citalopram was found to cause a dose-dependent increase in the QT interval. The mean change from baseline QTc was 8.5msec with 20mg/day and 18.5msec with 60mg/day.²² From this data it is estimated that citalopram 40mg/day could increase QTc by approximately 12.6msec.²²

Does this affect escitalopram?

Escitalopram is the s-isomer of citalopram, and is also associated with dose-dependent QT interval prolongation.²³

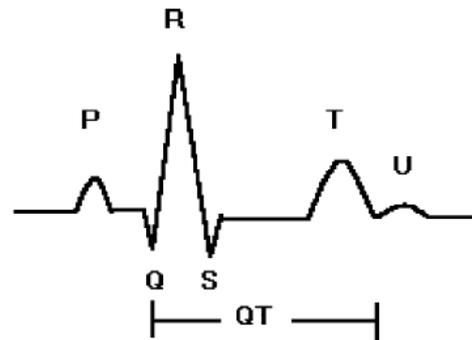
The maximum recommended daily dose of escitalopram is 20mg per day, and this has not been changed as a result of these findings. Escitalopram 20mg per day is approximately equivalent to citalopram 40mg per day.

Effect on QT interval

The QT interval on the ECG is measured from the beginning of ventricular depolarisation (Q wave) to the end of the ventricular repolarisation (end of the T wave),²⁴ as shown in figure 1. The QTc is the QT corrected for heart rate, as the QT interval shortens

with increasing heart rate, and lengthens with decreasing heart rate.²⁴

Figure 1: The QT interval on an ECG²⁴



The cardiac QTc interval is an indicator for the risk of torsades de pointes, a ventricular arrhythmia which is potentially fatal.²⁵

The normal upper limits for QTc are 440msec for men and 470msec for women. QTc values over 500msec have been clearly linked to an increased risk of arrhythmia.²⁵

For more detailed information on QT interval and psychotropics, refer to the Graylands Hospital Drug Bulletin 2010, number 2, available at <http://www.watag.org.au/wapdc/guidelines.cfm#Bulletin>

Recommendations

Frequent ECG monitoring should be considered for patients at higher risk of QT prolongation.²⁰ Hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment, and levels should be monitored periodically.

If citalopram is discontinued or the dose reduced, closely monitor the patient for re-emergence or worsening of any symptoms of depression.²⁰

This Drug Bulletin was written by Katie Walker and Darren Schwartz and was reviewed by the Graylands Pharmacy Department and Dr Sandy Tait

References available on request

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