

## Aripiprazole – a new class of antipsychotic?

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- ★ Aripiprazole (*Abilify<sup>TM</sup>*) is the latest antipsychotic to be registered in Australia for the treatment and maintenance therapy of schizophrenia. It is the first in a new emerging class of atypical antipsychotics known as the “dopamine system stabilisers”.
- ★ Whether the novel mode of action of aripiprazole will translate into significant clinical advantages is not yet apparent. Available data do not suggest any superiority over existing agents with regard to *efficacy* in schizophrenia.
- ★ Safety and tolerability data however suggest that aripiprazole may have some advantages when compared with other atypical antipsychotics. Unlike some of these agents, research indicates it does not cause hyperprolactinaemia, excessive weight gain or cardiac rhythm disturbance, nor is it associated with glucose or lipid changes.
- ★ If these initial observations are confirmed with widespread, long-term clinical use, aripiprazole could be a very promising addition to the range of antipsychotics currently available.
- ★ More research is needed to determine its efficacy and safety in refractory schizophrenia and special populations such as the elderly and children.
- ★ It is not yet available on the Pharmaceutical Benefits Scheme (PBS) or included on Graylands Hospital Formulary.
- ★ Price details are currently unavailable. However, the manufacturers indicate that it will likely be priced between risperidone and olanzapine at recommended daily doses.

### What is novel about aripiprazole's mode of action?

Similarly to existing antipsychotics, aripiprazole acts at dopamine D<sub>2</sub> receptors in the limbic system, but as a *partial agonist* rather than an *antagonist* <sup>(1)</sup>. A partial agonist will displace dopamine at receptors, as would an antagonist, but instead of completely blocking the receptor and preventing all activity, it behaves like a weaker version of dopamine itself. This does not result in any weaker action as an antipsychotic, but should

lead to improved tolerability. It can be compared to a “thermostat”, reducing dopaminergic neurotransmission in situations where dopamine activity is high (psychoses) and enhancing neurotransmission in situations where dopamine activity is low (negative / cognitive symptoms). It also simultaneously maintains a balance in other important areas of dopaminergic neurotransmission such as those that regulate motor function and prolactin. This should translate theoretically in clinical practice to a low incidence of

extrapyramidal symptoms (EPS) and prolactin elevation.

Aripiprazole combines this dopamine stabilising action with *partial agonism* at 5HT<sub>1A</sub> (theoretically decreased anxiety, depressive symptoms, improvement in negative symptoms) and similarly to other atypical antipsychotics, *antagonism* at 5HT<sub>2A</sub> receptors (theoretically decreased EPS, improvement in negative symptoms) (2).

### What is the pharmacokinetic profile of aripiprazole?

Aripiprazole is well absorbed, the peak plasma concentration occurring within 3-5hrs of dosing (3).

It is extensively metabolised by the liver via CYP450 3A4 & 2D6 to form an active metabolite (dehydro-aripiprazole). Clearance is primarily hepatic.

Once-daily dosing is possible due to its long elimination half-life (75 and 100hrs for aripiprazole and active metabolite, respectively).

Steady-state concentration is reached within two weeks of dosing. For this reason, dosage adjustments should be made not less than two weeks apart in order to fully assess patient response.

### Are there any unusual precautions associated with the use of aripiprazole?

No. Aripiprazole carries the usual standard warnings found on manufacturer's product information for antipsychotics.

As to be expected, there is currently insufficient data at present to recommend its use in pregnancy or lactation.

### How does aripiprazole's side-effect profile differ to existing atypical antipsychotics?

Similarly to existing atypicals, aripiprazole has a low propensity for extrapyramidal symptoms (EPS) (4).

Common Side Effects (4)	
Headache	Nausea
Insomnia	Vomiting
Agitation	Light-headedness
Anxiety	

However, unlike some of the atypical agents, research indicates it is associated with minimal prolactin, lipid, or glucose changes, significant weight gain or QTc prolongation (4,5). If these initial observations are confirmed following extensive use in general clinical practice, aripiprazole could be a very valuable addition to the range of antipsychotics currently available.

The only dose-related side effect was found to be sedation (most prominent at 30mg), the incidence of which seems to decrease with time.

### Does aripiprazole interact significantly with other medications?

Potent **CYP3A4/2D6 inhibitors** eg. ketoconazole, paroxetine, fluoxetine, may reduce aripiprazole clearance. The dose of aripiprazole should be reduced or started at 10mg. Less potent inhibitors of these enzymes that may also theoretically interact with aripiprazole, include fluvoxamine, nefazodone and erythromycin.

Potent **CYP3A4 inducers** eg. carbamazepine may lead to increased aripiprazole clearance. The dose of aripiprazole may have to be increased. Other inducers of this enzyme that may theoretically interact with aripiprazole include phenytoin and dexamethasone.

*NB. Dose adjustments may be necessary following withdrawal of the above interacting drugs.*

No interaction was found with lithium, valproate, warfarin or omeprazole (3).

### How much evidence is available to support its use in clinical practice?

#### Short-term efficacy

There are five (4 & 6 week) placebo-controlled trials in over 1500 inpatients with acute relapse of schizophrenia or

schizoaffective disorder <sup>(6-9)</sup>. Two trials are fully published <sup>(6,7)</sup>, the remainder being currently available only in abstract or poster (meta-analysis) format. Some improvements in symptoms were noted at week one with aripiprazole <sup>(8)</sup>.

In general, aripiprazole (15-30 mg) was more effective than placebo with regard to positive and negative symptom improvement (except one study, where 30mg aripiprazole was not found to be superior to placebo in the treatment of negative symptoms<sup>(7)</sup>).

The overall response in aripiprazole-treated patients was similar to that seen in patients receiving haloperidol (10 mg/day) or risperidone (6 mg/day).

#### **Long-term efficacy**

There are two trials (one fully published <sup>(10)</sup>) investigating maintenance and relapse prevention in chronic schizophrenia.

A 26-week trial found aripiprazole 15mg to be more effective than placebo in preventing relapse in stabilized patients with chronic schizophrenia. Reported adverse event rates were similar for each group <sup>(10)</sup>.

A 52-week trial showed aripiprazole to be more effective than haloperidol for the long-term maintenance treatment of schizophrenia. Significantly more patients had responded AND remained on treatment at endpoint (31% vs. 20% respectively). Study discontinuation rates for both drugs were high but not statistically different from each other (57% & 70% for aripiprazole and haloperidol respectively). Aripiprazole was superior in terms of negative symptom improvement <sup>(11)</sup>.

#### **Neurocognitive effects**

A 26-week open-label study versus olanzapine in chronic, stable schizophrenia or schizoaffective disorder suggested that aripiprazole may be superior in improving certain neurocognitive deficits, especially memory dysfunction <sup>(12)</sup>.

#### **Acute bipolar mania**

Aripiprazole is not yet licensed for this use. However, like other antipsychotics, it may also be useful in managing an acute manic episode.

One published, placebo-controlled study in approximately 250 patients is available. Twice as many patients in the aripiprazole group as in the placebo group responded to treatment (40% vs. 19%). Superior response rates with aripiprazole were evident by day 4 (mean dose 27.9mg) <sup>(13)</sup>.

No trials are available in the elderly, children or in first episode or treatment resistant schizophrenia as yet.

#### **What equivalence does aripiprazole have to chlorpromazine?**

This parameter is of controversial value for atypical antipsychotics. However, a recent article stated 7.5mg aripiprazole was equal to 100mg chlorpromazine (using the 2mg haloperidol equals 100mg chlorpromazine convention) <sup>(14)</sup>.

#### **What are the dosage recommendations?**

The recommended starting and maintenance dose is 15mg once daily, with or without food. Morning dosing may be more appropriate, as it is not sedating at recommended doses and insomnia is a possible side effect. Adjust the dose if necessary after two weeks. The range 15-30mg was found to be effective in clinical trials but the manufacturer states there is no evidence to support improved efficacy with doses higher than 15mg/day. No dosage adjustment is required in the elderly, hepatic or renal impairment or according to smoking status.

Due to aripiprazole's lack of sedative properties, it may be appropriate in the initial stages of therapy to use a benzodiazepine or sedative antipsychotic to help control symptoms of a very disturbed or aggressive patient.

## What is a suitable regimen for switching a patient from an existing oral antipsychotic to aripiprazole?

Data collected by the manufacturer found the following three methods to be equally safe and effective<sup>(15)</sup>.

- ☑ Stop current antipsychotic one day, start aripiprazole the next
- ☑ Start aripiprazole whilst simultaneously tapering down current antipsychotic over 2 weeks\*
- ☑ Taper down existing antipsychotic whilst at the same time titrating aripiprazole upwards from 10mg (over period of 2 weeks)

*\*Manufacturer suggests use of 2<sup>nd</sup> regimen as the risk of experiencing transient exacerbation of symptoms is reduced.*

### Presentation

Available as 10mg, 15mg, 20mg and 30mg tablets – all unscored.

### Sponsor

Bristol-Myers Squibb

## ARIPIPRAZOLE

### Suitable for use in which patients?

- ⊛ As there is little experience of its efficacy and safety to date, it should not be used as a first line antipsychotic.
- ⊛ It would be useful for patients in whom potential side effects such as significant weight gain and lipid/glucose disturbances would be *especially* detrimental.
- ⊛ There are no studies in treatment resistant schizophrenia as yet. Clozapine should still be used in preference to aripiprazole in this instance.

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This article was written by Kate Smith and reviewed by members of the Pharmacy Department. Comments are welcome at the e-mail address:

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