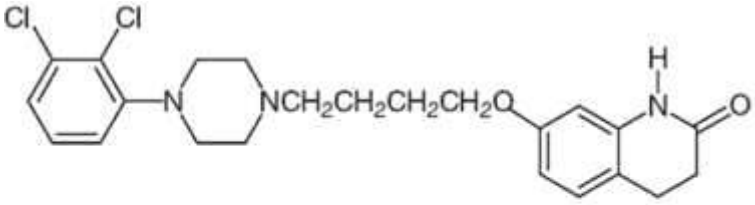
The Medicine Cabinet: Aripiprazole

Judy Longworth and Dr Kenneth Nunn

Senior Clinical Pharmacist and Psychiatrist,
Department of Psychological Medicine,
The Children's Hospital at Westmead



Aripiprazole

In November 2002, aripiprazole or OPC-4392, the first in a new class of atypical antipsychotics was approved by the US FDA for the treatment of schizophrenia for the pharmaceutical companies Otsuka/Bristol-Myers Squibb. US patent was to expire in October 2014 but has now 6 month extension due to the paediatric studies of use in bipolar and challenging behaviours in autism. Once the patent has expired then generic companies can develop generic equivalents and the price of the medication will fall for those paying premium due to inability to access the medication under the PBS. Aripiprazole was the largest selling medication in the world for the fourth quarter of 2013 according to Wikipedia.

According to the dopamine hypothesis, postulated by Avrid Carlsson (Nobel Prize, 2000) dopamine transmission inhibition by antipsychotics block the postsynaptic dopamine receptors leading to an improvement in positive schizophrenia symptoms. Positive symptoms are reported as the delusions, hallucinations, distortions or exaggerations in language and communication, disorganised speech and behaviour, catatonic behaviour and agitation. These were treated with typical antipsychotics such as haloperidol and chlorpromazine and lead to some permanent adverse effects such as tardive dyskinesia (a movement disorder of involuntary, repetitive tic-like movements) (from chronic blockade of D_2 receptors). About two decades ago, a new class of antipsychotics was released onto the market and these included Risperidone (see previous medicine cabinet Volume 2 Issue 1) and olanzapine. These were more favourable as they did not cause the debilitating tardive dyskinesia but have since found they have led to significant weight gain leading to metabolic problems in some patients (obesity medicine cabinet Volume 3, Issue 1). Finally, we have development of the next class of atypicals for which aripiprazole is the current only member in Australia but there are more on the way.

Aripiprazole works in a different way to the previous classes of antipsychotics. Antagonism of postsynaptic dopamine receptors, in particular the D_2 receptor seems to be an important factor for efficacy against positive symptoms of schizophrenia. Aripiprazole is described as a partial agonist of D_2 dopamine receptors. Partial agonism can be explained by being an agonist of dopamine autoreceptors and weak antagonist at postsynaptic D_2 receptors. It is also a partial antagonist of $5HT_{1A}$ receptors and antagonist for $5HT_{2A}$receptors.

As well as these principle receptors, there is also antagonist activity at serotonin $5HT_{2C}$, and $5HT_7$, dopamine D_3 and D_4, histamine H_1 and alpha 1 adrenergic receptors[1]. When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors (such as clarithromycin and fluoxetine) with aripiprazole occurs, the aripiprazole dose should be reduced as the inhibitors slow the metabolism of aripiprazole and more is free in the body leading to more adverse effects. When the concomitant administration of CYP3A4 inducers (such as St John 's Wort or carbamazepine and other antiepileptics) the dose of aripiprazole needs to be increased. This is due to the metabolism being sped up so there is not as much aripiprazole in the body. When the inducer is withdrawn, the dose of aripiprazole should be reduced again. This is why it is important for all prescribers to know about all the medications and complementary medicines being taken by a patient.

With the large scale studies about metabolic syndrome in adults the importance of having a medication that is weight neutral or causes small gains as opposed to larger gains in weight is preferable. Aripiprazole showed in adult trials against risperidone and olanzapine to be weight neutral and thus many patients who have gained significant amount of weight are being transferred to aripiprazole.

Aripiprazole has also shown not to increase serum prolactin as significantly as risperidone and paliperidone. Although uncertainty remains about the long term consequences for elevated serum levels of prolactin (hyperprolactinemia) when there is clinical signs there is probably a need to

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change medication or treat the elevated prolactin.

Aripiprazole trials for children and adolescents with ID/ASD
Marcus, Sikich, Owen *et al*, (2009) reported an 8 week trial of aripiprazole vs placebo for irritability in autistic children and was found to be efficacious and well tolerated with 83% of the aripiprazole group finishing compared to 70% of placebo group[2,3]. This trial then went onto a year long follow-on open trial that also showed efficacy and less overall weight gain.

Cochrane review of aripiprazole in treatment of irritability in autistic adolescents showed from 2 trials there was significantly less irritability, hyperactivity, and repetitive movements in children and youths with autism spectrum disorders although weight gain and neurological adverse effects occurred[9].

Ishitobi *et al,* (2013) had a 12 week switching open label trial of risperidone to aripiprazole in ASD children and adolescents aged 9-22 years. These patients were previously on risperidone 0.6± 0.4mg/d . Risperidone was abruptly ceased and aripiprazole initiated at dose of 2.7 ±_1.9mg/d for 2 weeks then increased slowly to mean maintenance dose of 4.8 ±_4.0mg/d. reasons for the switching included lack of efficacy, hyperprolactinemia, excessive appetite and long term safety. After the switch, clinical changes included reports of decreased irritability and impulsiveness, decreased prolactin levels as well as improvement in excessive appetite[4].

These multicentre trials led to the licensing of aripiprazole for use in ASD children and adolescents for irritability and challenging behaviours by USA's FDA.

Despite this there are some problems as follows;

- Acute difficulties – nausea, headache and dizziness due to lowering of blood pressure due to action of alpha receptors in brain
- Subacute difficulties – aripiprazole is metabolised by the same enzyme CYP $2D_6$ (which also has genetic variance) as risperidone and thus cross over from one to the other may be problematic
- Long term – need to stick with it as it will take 6-8 weeks for the binding to D_2 receptors to stabilise and thus have optimal effect. As there is very little sedative effect associated with aripiprazole a sedative agent maybe used concurrently initially with the aim of reducing it eventually. Optimal therapy is the least number of medications.

Most of these problems are transient or minor and can be helped by starting at a lower dose and slowly weaning the dose up to ensure the lowest effective dose is used. This can also be achieved as the tablets can be crushed and dispersed in water and a portion taken to ensure a smaller dose (don't rush to crush) as the liquid preparation is not available in Australia

Adverse effects reported in schizophrenia trial adolescent patients (13-17years) over 6 week period with ≥ 5% occurrence. Somnolence (sleepiness or hypersomnia), extrapyramidal disorder (movement disorder), fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness. So tips to help manage these are:-

- Akathsia (restlessness) feeling more on the edge - happier when moving around, try to relax by deep breathing – blowing bubbles or whistles and dressing in loose clothing
- Nausea (stomach upset) - usually transient at dose changes and will last for a few days but if ongoing consult your doctor
- Dizziness and light headness or unsteadiness - take time in standing up from lying position, rest by putting head on desk or lying down when these feelings happen.
- Salivary hypersecretion - if this is happening at night, a plastic cover over the pillow can help as well as additional medications can help alleviate the problem so mention this to the prescribing doctor.
- Constipation - increase fluid intake as well as fruit vegetables and cereals in the diet

So aripiprazole has some advantages over the other atypical antipsychotics especially long term with minimal weight gain but there are problems in introducing a partial agonist. From aripiprazole other medications are now being developed so some of these introduction problems might be eliminated.

References

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Aripiprazole: Parent /Client leaflet

What is aripiprazole used for?
Aripiprazole (also known by trade name Abilify®) is used to treat symptoms of psychosis, schizophrenia and mania. It has also been used to help in bipolar disorder, challenging behaviours and depression together with antidepressants. Aripiprazole currently is only available as tablets but these can be crushed and dispersed.

When should I take aripiprazole ?
Together with a glass of water at regular times each day according to the medicine label, there are no problems taking it with food if that helps remember to take it.

How long will aripiprazole take to work?
There maybe some response in a couple of days but for total effect to occur it may take a few months. Initially there might a feeling of being unsettled but this usually wears off in time.

How long will I need to take aripiprazole for?
This will depend in why you are taking it. It could be several months or years to ensure symptoms do not come back. Aripiprazole has not been shown to be addictive.

Can I stop taking aripiprazole suddenly?
It is unwise to cease suddenly as this can lead to rebound effects. When ceasing, the aripiprazole dose should be tapered and under the direction of the treating doctor.

What should I do if I forget to take a dose of aripiprazole?
Take the missed dose as soon as you remember, but if the missed dose is within 12 hours of the next dose just remember to take the dose as normal. Do not take catch up doses. If having problems remembering the dose please discuss with your community pharmacist or doctor.

Can I cycle, drive or operate a boat while taking aripiprazole?
If you feel light-headed when initially taking aripiprazole this should wear off before driving or cycling or operating machinery.

Will aripiprazole affect other medication?
There are a few interactions with other medications so make sure the prescriber knows what you are taking before prescribing.

What sort of side-effects might I get with aripiprazole?

- Akathisia (restlessness) feeling more on edge. You may sweat more; try to relax and take deep breaths Usually wears off in a few weeks
- Stomach upset feeling and being sick as well as diarrhoea usually wears off after few days if continuing see your doctor
- Constipation – ensure you are eating enough fibre, cereals and fruit as well as drinking water
- Headache ask about use of paracetamol of other pain medications
- Insomnia let your doctor know so the dose or timing of dose can be changed
- Blurred vision don't drive see your doctor if troublesome
- Tremor usually wears off after a few weeks; if persistent consult the doctor who may prescribe additional medication
- Hypotension do not stand up too quickly and try to lie down when feeling faint or dizzy
- Seizure or fit (convulsion) cease aripiprazole and see your doctor immediately
- Palpitations can be treated if worrisome

This is small list if side effects. Some people get no side effects whilst others may get some side effects that are not listed. If you think you have a side effect then contact your doctor and discuss the symptoms.