Graylands Hospital
Drug Bulletin

Aripiprazole long-acting injection – *A new formulation for schizophrenia*

North Metropolitan Health Service – Mental Health September 2014 Vol 21 No.3 ISSN 1323-1251

Introduction

Aripiprazole long-acting injection (Abilify Maintena®) is a new long-acting injectable (LAI) antipsychotic medication for the maintenance treatment of schizophrenia. Aripiprazole LAI was approved for use in the US in March 2013, Europe in November 2013 and launched in the UK in January 2014. Aripiprazole LAI was approved for use in Australia by the Therapeutic Goods Administration (TGA) in July 2014 and is currently under consideration for listing on the Pharmaceutical Benefits Schedule (PBS). In order to familiarise health professionals with this new product, this edition of the bulletin reviews the pharmacology, pharmacokinetics, efficacy, safety and administration of aripiprazole LAI and compares it to other available LAI antipsychotics.

Pharmacology

Aripiprazole is a partial agonist at dopamine D_2 receptors.[1] This means that aripiprazole binds to D_2 receptors and prevents attachment of endogenous dopamine but at the same time stimulates D_2 receptors (but to a lesser degree than by dopamine itself). When aripiprazole occupies 100% of D_2 receptors the overall effect is to reduce receptor-mediated activity by around 70%.[1]

Aripiprazole is also a partial agonist at 5-hydroxytryptamine 1A ($5HT_{1A}$) receptors, an action that may protect against dopamine-mediated adverse effects and provide anxiolytic activity.[2] It is also a potent antagonist at $5HT_{2A}$ receptors and so may, in theory, offer protection against extrapyramidal side effects (EPSEs). Aripiprazole has only moderate activity at alpha1-adrenergic receptors, histamine (H_1) receptors and serotonin $5HT_{2C}$ receptors. So, a low incidence of (respectively) postural hypotension, sedation and weight gain might be predicted.

Pharmacokinetics

Aripiprazole LAI is a lyophilized powder of unmodified aripiprazole, which is reconstituted in sterile water prior to intramuscular injection. Due to the low solubility of aripiprazole particles, following IM injection, aripiprazole is absorbed into the systemic circulation slowly, with the average absorption half-life of aripiprazole LAI being 28 days. Maximum plasma aripiprazole concentrations (C_{max}) are reached in approx. 5-7 days (median t_{max}). Steady state aripiprazole concentrations are reached by the fourth once-monthly dose. The elimination half-life of aripiprazole LAI is 29.9 days for a 300mg dose and 46.5 days for a 400mg dose.

Table 1 Affinity of aripiprazole for various receptors

Receptor	K_i	Affinity	Activity
Dopamine			
D_2	0.34	high	PA
D_3	0.8	high	PA
D_4	44	moderate	PA
Serotonin			
$5HT_{1A}$	1.7	high	PA
$5HT_{2A}$	3.4	high	antagonism
$5HT_{2C}$	15	moderate	PA
$5HT_7$	39	moderate	antagonism
$Alpha_1$	57	moderate	antagonism
Histamine	61	moderate	antagonism

K_i inhibition constant (nmol/L) PA: Partial agonism

Dosage

The recommended starting and maintenance dose is 400 mg, administered once-monthly (no sooner than 26 days after the previous injection). After the first injection, treatment with 10-20 mg oral aripiprazole should be continued for14 days to maintain therapeutic aripiprazole concentrations during initiation of therapy. If there are adverse reactions with the 400 mg dosage, a reduction to 300 mg once monthly should be considered.

Drug Interactions

Aripiprazole is metabolised by multiple enzymatic pathways involving the cytochromes CYP2D6 and CYP3A4. Inhibitors of either of these enzymes are known to decrease clearance of aripiprazole and to increase aripiprazole plasma levels. Therefore, dose adjustments are recommended in patients taking concominant strong CYP3A4 inhibitors (e.g. fluoxetine, paroxetine, ketoconazole) or CYP2D6 inhibitors (e.g. duloxetine, fluoxetine, paroxetine, bupropion, quinidine) for more than 14 days.

Summary of efficacy studies

The efficacy of aripiprazole LAI was established in 2 randomised controlled trials. The first study by Kane *et al*[3] compared aripiprazole 400 mg once-monthly injections with placebo. In the second study, Fleischhacker *et al*[4] compared aripiprazole once-monthly injections with oral aripiprazole 10–30 mg daily.

Kane *et al*

The study by Kane *et al*, was designed as a 52-week, randomized, placebo-controlled, double-blind trial in which patients were first stabilized on oral aripiprazole (10–30 mg/day for 4–6 weeks) and then on the LAI formulation (400 mg/4 weeks for 12 weeks). Patients who met stabilization criteria were then randomized in a 2:1 fashion to either continue on their stabilization dose of aripiprazole LAI (300 or 400 mg administered every 4 weeks) or be switched to placebo IM injections. The primary outcome measure was time to exacerbation of psychotic symptoms/impending relapse (events).

Efficacy

710 patients entered oral stabilisation, 576 progressed to aripiprazole LAI, and 403 were randomly assigned to double-blind treatment (aripiprazole LAI, n=269; placebo, n=134)). The study was terminated early because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 events).

Time to impending relapse was significantly delayed with aripiprazole LAI compared with placebo in both the interim analysis and the final analysis ($p<0.0001$). Relapse rates were also significantly lower with aripiprazole LAI than placebo at endpoint (80 events; 10.0% [n=27/269] vs 39.6% [n=53/134]; Hazard Ratio=5.03 (95% CI, 3.15 to 8.02). Improvements in CGI-S and PANSS total scores were maintained with aripiprazole LAI treatment but showed significant worsening with placebo.

Safety and tolerability

During double-blind treatment, the most common treatment emergent adverse events (AEs) were insomnia, headache and tremor. Overall discontinuations due to treatment-emergent AEs were low, occurring in 3.0% and 4.9% of subjects during oral and LAI stabilization, respectively. During double-blind treatment, 7.1% of aripiprazole LAI and 13.4% of placebo patients discontinued due to treatment-emergent AEs.

The incidence of prolactin elevation during double-blind treatment was lower with aripiprazole LAI than placebo (1.9 vs 7.1%). The incidence of potentially clinically relevant changes in vital signs, orthostatic hypotension and ECG parameters was similar between treatment groups during double-blind treatment, as was the mean change in QTc intervals. Akathisia occurred in 5.6% of aripiprazole LAI subjects in the double-blind treatment phase (vs 6.0% for placebo-treated subjects).

Fleischhacker *et al*

Fleischhacker *et al*[4] conducted a 38 week, randomised, double-blind, active-controlled study to evaluate the efficacy, safety and tolerability of aripiprazole LAI compared with oral aripiprazole and in comparison with a suboptimal dose of aripiprazole LAI (50mg).The aripiprazole LAI 50mg dose was included as a 'pseudo placebo' to test assay sensitivity for the non-inferiority design.

The study consisted of a screening phase and 3 treatment phases. In phase 1, patients were cross-titrated from other antipsychotic(s) to oral aripiprazole. In phase 2, patients were stabilised on oral aripiprazole (10–30 mg/day). In phase 3, patients were randomised 2:2:1 to aripiprazole once-monthly 400 mg, oral aripiprazole (10–30 mg/day) or aripiprazole once-monthly 50 mg. The primary efficacy endpoint was the proportion of patients in phase three of the trial with impending relapse by week 26 from the date of randomisation.

Efficacy

A total of 1118 patients were screened, and 662 responders to oral aripiprazole were randomised. The estimated impending relapse rates at week 26 were 7.12 % for aripiprazole LAI 400mg and 7.76 % for oral aripiprazole 10-30mg, with a treatment difference of -0.6 % (95 % CI: -5.26 to 3.99) demonstrating noninferiority.

Safety and tolerability

The most common AEs (at least 10% in any group for aripiprazole LAI 400 mg, oral aripiprazole and aripiprazole LAI 50 mg, respectively) were insomnia (11.7 vs 13.9 vs 13.7%), akathisia (10.6 vs 6.8 vs 8.4%), headache (9.8 vs 11.3 vs 5.3%), weight increase (9.1 vs 13.2 vs 5.3%) and back pain (3.8 vs 5.3 vs 11.5%). There was a statistically significant change in bodyweight from baseline to end point between aripiprazole LAI 50 mg (-1.6 kg) and aripiprazole LAI 400 mg (+0.1 kg; $p < 0.05$). Patients on oral aripiprazole gained 1.0 kg. The incidence of weight gain of at least 7% from baseline was 15.9% for

Table 2: An overview of aripiprazole LAI

Drug name	Abilify Maintena®
Approved name	Aripiprazole Long-acting injection
Therapeutic class	Second Generation Antipsychotic – Long Acting injection (SGA-LAI)
Indication	Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole
Receptor profile	Dopamine D_2 and Serotonin 5-HT_{1A} partial agonist & Serotonin 5-HT_{2A} antagonist
Available dosage strengths	300mg and 400mg
Starting dose	400mg. After the first injection, treatment with 10- 20mg oral aripiprazole should be continued for 14 days to maintain therapeutic aripiprazole concentrations during initiation of therapy
Max dose: interval: injection site	400mg: Monthly: Gluteal only
Pharmacokinetics	Time to peak concentration 5-7 days: Absorption half-life 28 days: Elimination half-life of 300mg & 400mg doses are 29.9 days & 46.5 days respectively.Time to steady state 4-5 months
Solubilisation and vehicle	Lyophilized powder reconstituted with sterile water to form injectable suspension
Metabolism	Metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Dose adjustments necessary in patients who are taking concomitant strong CYP2D6 and CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days
Renal & hepatic impairment	No dose adjustment necessary
Clinical effectiveness	Established in two double-blind RCTs. In the first (n=403) aripiprazole LAI statistically significantly delayed time to impending relapse compared with placebo ($p<0.0001$). In the second, aripiprazole LAI (n=662) was non-inferior to oral aripiprazole 10-30mg daily for proportion of participants experiencing impending relapse (7.12% and 7.76% respectively).
Safety	Overall adverse event profile of aripiprazole LAI was similar to that of oral aripiprazole, apart from injection-site reactions. Common adverse events in the RCTs included weight gain (9%), akathisia (7.9%); insomnia (5.8%) and injection site pain (5.1%)

aripiprazole LAI 400 mg, 16.2% for oral aripiprazole and 6.1% for aripiprazole LAI 50 mg. No potentially clinically relevant shifts in metabolic parameters were observed at end point.

Review of antipsychotic LAIs

With the introduction of aripiprazole LAI there are now 9 different antipsychotic LAIs available for use in Australia. Six of these are LAI preparations of First-Generation Antipsychotics (FGA-LAIs) and 4 are LAI formulations of the Second-Generation Antipsychotics (SGA-LAIs).

First Generation LAIs

There are few differences between individual FGA-LAIs, although a Cochrane review found that zuclopenthixol decanoate may be more effective in preventing relapses than other FGA- LAIs.[5] The use of FGA-LAIs is generally limited due to their propensity to cause Extrapyramidal Side Effects (such as dystonia, Parkinsonism, akathisia & tardive dyskinesia) and symptoms related to hyperprolactinaemia (such as amenorrhoea, galactorrhoea, gynaecomastia, sexual dysfunction, & osteoporosis). Pipotiazine may be associated with relatively less frequent EPSEs, and fluphenazine decanoate with relatively more EPSEs (but perhaps less weight gain).[6]

Second Generation LAIs

In recent years, formulations of SGA-LAIs have become available and have to some extent replaced the use of older FGA-LAIs. In this regard, the apparent preference for the use of SGA-LAIs is probably a result of their perceived lower incidence of EPSEs compared with older drugs in depot form.

Risperidone long-acting injection (Risperdal Consta®)

Risperidone was the first SGA to be made available as a LAI. It contains risperidone coated in polymer to form microspheres. These microspheres have to be suspended in an aqueous base immediately before use. The whole vial must be used which means there

is limited flexibility in dosing. In addition, the injection must be stored in a refrigerator, which may present practical issues for community-based staff with limited access to suitable storage.

Risperidone LAI must be given every 2 weeks. A test dose is not required. Instead, response and tolerability should normally be confirmed by a previous course of oral risperidone. Therapeutic plasma levels of risperidone will not normally be achieved until four or five weeks after the first injection. This means that it will not begin to exert a significant clinical effect before the third injection has been given. Patients should, if possible, continue to take oral risperidone for at least three weeks after receiving the first dose of risperidone LAI. This also means that at least three injections of a particular dose must be given before increasing that dose.

Risperidone LAI is associated with relatively low rates of EPSEs, although it is well known to increase plasma prolactin (similar to FGA-LAI).[7] Weight gain averages around 3kg in the longer term.[7]

Olanzapine long-acting injection (Zyprexa Relprevv®)

Olanzapine pamoate, which was launched in 2008, is available as a crystalline salt formulation of olanzapine and pamoic acid suspended in water. This salt slowly dissolves in solution, dissociates into separate molecular entities, and enters systemic circulation as olanzapine and pamoic acid.[8] Whilst a test dose is not required, patients should be successfully treated with oral olanzapine before receiving olanzapine LAI in order to establish tolerability and response.

Common side effects include weight gain, increased plasma triglycerides, sedation and increased appetite. The use of olanzapine LAI is limited by the development of post injection syndrome (PIS). PIS occurs after 0.07% of injections and is characterised by confusion, delirium and profound sedation. Because of the risk of PIS all patients should be observed in a healthcare facility for 2hours after administration.

Paliperidone long-acting injection (Invega sustenna®)

Paliperidone long-acting injection has been available in Australia since 2011. Paliperidone is the major active metabolite of risperidone: 9-hydroxyrisperidone. Following an IM injection, active paliperidone levels are seen within a day or so, therefore co-administration of oral paliperidone or risperidone during initiation is not required. Dosing consists of two initiation doses (deltoid) followed by monthly maintenance doses (deltoid or gluteal).

For many reasons, paliperidone LAI may be preferred to risperidone LAI: it acts acutely, can be given monthly, does not require cold storage and has a wider, more useful dose range. Further support for the use of paliperidone LAI comes from a recently published prospective study by Attard and colleagues.[9] They followed patients treated with paliperidone LAI for one year, and found that paliperidone LAI was effective and well tolerated with continuation rates as high as 80% after one year.

A Place for aripiprazole LAI?

The advent of aripiprazole LAI provides a different option from other available LAIs. In particular, aripiprazole LAI has a tolerability and safety profile quite different from the other SGA-LAI. Essentially free of prolactin-elevating effects (unlike risperidone and paliperidone LAIs) or major metabolic effects or PIS (unlike olanzapine LAI), aripiprazole LAI appears to be an attractive option.

However, as with risperidone LAI, aripiprazole LAI does require oral supplementation at the time of initiation, although only for 14 days compared with 21 days for risperidone LAI. In addition, switching to aripiprazole LAI may also be challenging if the patient has been chronically treated with potent dopamine D_2 receptor-blocking agents, and may require a slower cross titration.

Conclusion

Aripiprazole LAI is an effective and well tolerated LAI. If the initial data regarding efficacy and side effect profile is replicated, aripiprazole LAI might become an appealing alternative to currently available LAIs; all of which may be associated with either movement disorders, metabolic adverse effects, PIS or complications secondary to hyperprolactinaemia.

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