Aripiprazole (Abilify) for schizophrenia (ari-pip-rah-zol)

Summary

PBS listing: Authority required
Schizophrenia

Reason for listing: Listing was recommended on a cost-minimisation basis against olanzapine, suggesting similar benefits at similar or reduced cost to the PBS.

Place in therapy: There is presently no evidence to suggest that aripiprazole is more effective than existing antipsychotics in the treatment of schizophrenia but it offers prescribers another treatment option for this illness. Based on its tolerability profile, it can be considered another atypical antipsychotic.

Safety issues: The risk of extrapyramidal side-effects and hyperprolactinaemia appears low with aripiprazole at recommended doses. In clinical trials, weight gain was less than with olanzapine. Diabetes, hyperlipidaemia, tardive dyskinesia and QT prolongation have not been identified as problems in clinical trials but more post-marketing experience is needed to determine its long-term safety profile. The dose of aripiprazole may need to be adjusted if co-administered with carbamazepine, or inhibitors of enzymes CYP3A4 (e.g. ketoconazole, erythromycin) or CYP2D6 (e.g. fluoxetine, paroxetine).

Dosing issues: The recommended starting and maintenance dose is 15 mg once daily. The maximum approved dose is 30 mg daily, but there is no evidence that doses over 15 mg are more effective.
Aripiprazole is a new antipsychotic agent. There is presently no evidence to suggest that it is more effective than existing antipsychotics in the treatment of schizophrenia but it offers prescribers another treatment option for this illness. Its efficacy in treatment-resistant schizophrenia is not established; for these patients clozapine is generally considered the drug of choice.

Antipsychotic drugs are generally classified into two groups: the older or ‘conventional’ agents (e.g. haloperidol, chlorpromazine) and the newer or ‘atypical’ agents (amisulpride, clozapine, olanzapine, quetiapine and risperidone).

Conventional antipsychotics are effective at reducing positive symptoms of schizophrenia, such as hallucinations and delusions, but are commonly associated with distressing adverse effects such as extrapyramidal side-effects† and hyperprolactinaemia.

Atypical antipsychotics are at least as efficacious at treating positive symptoms as the conventional agents and may be more effective in managing negative symptoms2–4 (see Table 1). Atypical antipsychotics are less likely to cause extrapyramidal effects and hyperprolactinaemia, although both risperidone and amisulpride may induce these effects at higher doses.2,4

While aripiprazole has been described as a ‘novel antipsychotic agent’5 (a ‘dopamine system stabiliser’6), the clinical relevance of this mechanism of action is as yet unknown. Based on its tolerability profile it can be considered another atypical antipsychotic.7

Atypical antipsychotics are often preferred to conventional agents in the treatment of schizophrenia2,3 but the Therapeutic Guidelines: Psychotropic does not distinguish between the older and newer agents and argues that choice of antipsychotic drug and dose should be individualised to suit the patient.4

†includes Parkinsonism, dystonia, akathisia (restlessness) and tardive dyskinesia.

Table 1: Symptoms of schizophrenia2–4

<table>
<thead>
<tr>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
<th>Cognitive symptoms</th>
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<tbody>
<tr>
<td>• hallucinations</td>
<td>• blunted affect</td>
<td>• impaired planning</td>
</tr>
<tr>
<td>• delusions</td>
<td>• loss of sense of pleasure (anhedonia)</td>
<td>• problem-solving (executive function)</td>
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<td></td>
<td>• poor self-care</td>
<td>• impaired memory</td>
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<td></td>
<td>• impoverished speech</td>
<td>• impaired language</td>
</tr>
<tr>
<td></td>
<td>• apathy/lack of motivation</td>
<td>• processing</td>
</tr>
<tr>
<td></td>
<td>• attentional impairment†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• social withdrawal</td>
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</tbody>
</table>

*also considered a cognitive symptom.
Aripiprazole efficacy studies

Few published studies compare aripiprazole directly with other antipsychotics in the treatment of schizophrenia and it is difficult to draw conclusions about its relative efficacy, particularly compared with other atypical agents. Aripiprazole has been compared with olanzapine in clinical trials but, as yet, efficacy data have not been published.

A recent meta-analysis compared the efficacy of atypical and conventional antipsychotics. Of the atypicals, only clozapine, amisulpride, risperidone and olanzapine were found to be more effective than the older drugs, but the analysis of aripiprazole was based on limited data.

Aripiprazole 10–30 mg was significantly better than placebo in three short-term (4–6 week) double-blind trials in schizophrenia and schizo-affective disorder, although two earlier dose-ranging studies failed to demonstrate efficacy. Some studies included an active control (either haloperidol or risperidone) but were not powered to allow a direct comparison with aripiprazole.

Two long-term, double-blind, maintenance studies have been conducted. A 6-month comparison with placebo found that patients taking placebo relapsed significantly sooner and more frequently than those taking aripiprazole 15 mg. In a 52-week study of more than 1200 patients with acute relapse of chronic schizophrenia, aripiprazole was not superior to haloperidol in the primary efficacy endpoint, time-to-failure to maintain response, but was better tolerated.

Published studies exclude patients with treatment-refractory schizophrenia, a history of suicide attempts or ideation, and/or past or current substance abuse; results therefore cannot be generalised to these patient groups. Only one study enrolled patients aged over 65 years. Patients aged less than 18 years were excluded and the safety and effectiveness of aripiprazole in this age group is not established.

Efficacy was assessed using standardised instruments, including the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impression (CGI).

If switching patients to aripiprazole

An 8-week outpatient study found that any of the following methods could be used if switching patients from other antipsychotics to aripiprazole:

- Immediate initiation of aripiprazole and immediate cessation of current antipsychotic;
- Immediate initiation of aripiprazole and a 2-week taper of current antipsychotic;
- 2-week up-titration of aripiprazole with simultaneous taper of current antipsychotic.

Prescribing guidelines generally advocate a simultaneous taper method to minimise antipsychotic withdrawal effects.

Most patients in the study were taking either olanzapine or risperidone.

Safety issues

The risk of extrapyramidal side-effects and hyperprolactinaemia appears low with aripiprazole at recommended doses. In clinical trials weight gain was less than with olanzapine. Diabetes, hyperlipidaemia, tardive dyskinesia and QT prolongation have not been identified as problems in clinical trials but more post-marketing experience is needed to determine its long-term safety profile. The dose of aripiprazole may need to be adjusted if co-administered with potent CYP2D6 or CYP3A4 inhibitors or inducers (see Drug interactions).

Contra-indications and precautions

The general contra-indications, warnings and precautions for aripiprazole are similar to those of other atypical antipsychotics; refer to the Abilify product information.

Aripiprazole demonstrated developmental toxicity in animal studies and if possible should be avoided in pregnancy.

The UK Committee of Safety of Medicines (CSM) has recently warned that atypical antipsychotics (although not specifically aripiprazole) may increase the risk of stroke in elderly patients with dementia.
Adverse drug reactions

Weight gain can occur with most atypical agents but clozapine and olanzapine tend to cause the greatest short-term gains in weight. Long-term comparisons found aripiprazole was more likely than haloperidol (20% vs. 13%) to be associated with significant weight gain, but less likely than olanzapine (13% vs. 33%).

A recent consensus statement on antipsychotic drugs, obesity and diabetes concluded that aripiprazole was associated with little or no significant weight gain, diabetes or dyslipidaemia, with the caveat that it had not been used as extensively as other atypical agents. Nevertheless, the Food and Drug Administration (FDA) has requested that all atypical antipsychotics include a diabetes warning statement in US product information.

In short-term trials the incidence of extrapyramidal side-effects was similar to placebo, although akathisia was slightly more common with aripiprazole. In long-term comparisons the incidence of extrapyramidal effects was comparable to that with olanzapine but significantly less than with haloperidol.

QT prolongation can occur with some antipsychotic drugs and predispose patients to the potentially fatal arrhythmia, torsade de pointes. QTc prolongation has not been reported with aripiprazole at recommended doses but may be a potential problem in overdose.

Increased prolactin levels have not been reported with aripiprazole in clinical trials.

Orthostatic hypotension may occur.

Drug interactions

If potent inhibitors of enzymes CYP2D6 (e.g. fluoxetine, paroxetine) and CYP3A4 (e.g. ketoconazole, erythromycin) are co-administered the dose of aripiprazole may need to be reduced.

The potent CYP3A4 inducer, carbamazepine, increases the clearance of aripiprazole; if co-administered the dose of aripiprazole should be doubled.

Dosing issues

The recommended starting and maintenance dose is 15 mg once daily. The maximum approved dose is 30 mg daily but there is no evidence that doses over 15 mg are more effective.

For further information on dosing, drug interactions and adverse effects consult the Australian Medicines Handbook or the Abilify product information.

Information for patients

As with any antipsychotic therapy, many patients taking aripiprazole may relapse or discontinue therapy in the longer-term. Poor compliance and substance misuse are common triggers for relapse and patients and carers should be counselled about the dangers of these.

For more detailed information, suggest or provide the Abilify Consumer Medicine Information (CMI).
References

9. Davis JM, Chen N. Arch Gen Psychiatry 2003;60:553–564.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.