

Aripiprazole

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Aripiprazole is an atypical antipsychotic licensed for the treatment of schizophrenia. It has a different mechanism of action to other atypical drugs and is described as a dopamine system stabiliser.
- Short-term trials have shown it to have similar efficacy to haloperidol and risperidone for both positive and negative symptoms of schizophrenia. In a 52-week trial, aripiprazole was associated with a similar response rate to haloperidol but fewer discontinuations due to adverse events.
- Short-term comparison against risperidone showed a similar adverse event profile, although aripiprazole had less effect on prolactin. It appears to have little effect on prolactin, glucose and lipid levels and QT interval in short and long-term trials. Weight gain is similar to risperidone and less than olanzapine.
- The adverse event profile requires confirmation in further long-term and post-marketing studies. In particular, long-term comparisons against other atypical antipsychotics are needed.
- NICE guidance recommends atypical agents are considered for first line treatment for newly diagnosed schizophrenia or for those patients suffering unacceptable adverse events with typical agents. Where more than one atypical agent is appropriate, the drug with the lowest acquisition cost should be prescribed. Aripiprazole may be an option in patients suffering adverse events on other atypical antipsychotics.
- The cost of aripiprazole is similar to that of other atypical agents.

Introduction

Aripiprazole is a quinolinone derivative. It is a partial agonist at dopamine D₂ and 5-HT_{1A} receptors and is an antagonist at 5-HT₂ receptors. It has been described as a dopamine system stabiliser as, in high levels of dopamine production, it will act as an antagonist and where dopamine activity is low, it will act as an agonist.¹ This has theoretical advantages in schizophrenia where positive symptoms are thought to be related to excess dopamine and negative symptoms to dopaminergic hypofunction.²

Evidence

A 4 week, double-blind study randomised 414 patients with schizophrenia or schizoaffective disorder to placebo, aripiprazole 15mg or 30mg daily or haloperidol 10mg daily.³ Overall 55%, 67%, 59% and 60% of the groups respectively completed the study. Primary efficacy variables were PANSS total (Positive and Negative Syndrome Scores), PANSS positive subscale and CGI-S (Clinical Global Impressions- Severity of Illness) scores. Other efficacy variables included changes in PANSS negative subscale and CGI-I scores (Clinical Global Impressions- Global Improvement) and responder rates. Efficacy analysis was on an intention-to-treat (ITT) basis. Mean changes in PANSS total scores were statistically significantly greater in the active groups than placebo (P vs placebo <0.001, 0.009, 0.001 for the 15mg, 30mg and haloperidol groups respectively). However, confidence intervals were not quoted. No statistical comparison with haloperidol was made but improvements were numerically similar. Similar statistically significant improvements were seen with active treatment in the other primary efficacy variables.

A similarly designed trial randomised 404 patients to placebo, aripiprazole 20mg or

Brand Name, (Manufacturer): Abilify™ (Bristol-Myers Squibb/ Otsuka Pharmaceuticals)

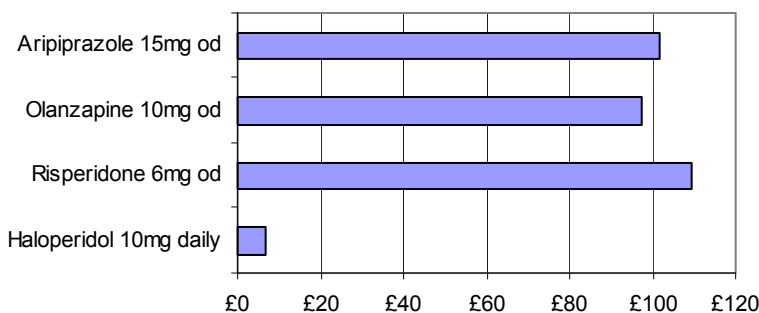
BNF Therapeutic Class: Antipsychotic drugs (section 4.2.1)

Licensed Indications: Treatment of schizophrenia

Dosage and Administration: 15mg once daily. Enhanced efficacy at doses higher than 15mg has not been demonstrated although individual patients may benefit from a higher dose. Patients taking certain concomitant enzyme inhibitors may require a dose of 10mg daily. Maximum daily dose 30mg.

Marketed: June 2004

Cost Comparisons: Cost for 28 days treatment [Drug Tariff -June 2004].



N.B. Doses shown for general comparison and do not imply therapeutic equivalence

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30mg or risperidone 6mg daily for 4 weeks.⁴ Overall 50%, 60%, 66% and 63% of the groups respectively completed the study. The higher drop-out rate with placebo was due to a higher rate of insufficient clinical response and adverse events.

Efficacy analysis was on an ITT basis. Mean changes in PANSS total scores were -5.0, -14.5, -13.9 and -15.7 for the placebo, 20mg, 30mg and risperidone groups respectively (P vs placebo 0.001, 0.003 and <0.001). Again, confidence intervals were not quoted. Similar statistically significant improvements were seen with active treatments in the other primary efficacy variables.

Long-term use has been studied in two trials (prospectively planned to be published as one merged set of results), which randomised a total of 1294 patients with chronic schizophrenia in acute relapse to aripiprazole 30mg or haloperidol 10mg daily for 52 weeks.⁵ The primary efficacy outcome was the time to failure to maintain response in responders. Overall 43% of aripiprazole and 30% of haloperidol patients completed the trial. This difference was primarily related to a statistically significantly lower rate of discontinuation for adverse events with aripiprazole. Overall, response rates were similar (72% vs 69% for aripiprazole and haloperidol respectively). Kaplan-Meier estimates for patients maintaining response at week 52 were 77% aripiprazole and 73% haloperidol.

A 26 week placebo-controlled study assessed aripiprazole 15mg daily for the prevention of relapse in 310 stabilised patients with schizophrenia.⁶ More patients relapsed with placebo than with aripiprazole (57% vs 34%).

A further study assessed methods of switching to aripiprazole from other antipsychotic agents.⁷ This 8 week study randomised 311 patients with chronic stable schizophrenia to one of three groups: initiation of aripiprazole with simultaneous discontinuation of current antipsychotic; initiation of aripiprazole with tapering of current antipsychotic or up-titrating aripiprazole with tapering of current antipsychotic. Overall, all strategies

were similar in terms of efficacy although group 3 had slightly fewer gastro-intestinal adverse events.

Safety

Pooled safety data from five short-term trials have shown the most common adverse events (AE) which occurred more frequently than with placebo were headache (31.7%), insomnia (24.1%), nausea and vomiting (12-14%) and light-headedness (11.4%).⁸ Aripiprazole showed a lower incidence of somnolence, akathisia and extra-pyramidal symptoms (EPS) than haloperidol (incidence of EPS haloperidol 43.5%, placebo 19.4% aripiprazole 21.1%). Aripiprazole was associated with similar weight gain as risperidone (0.8-1.5kg over 4 weeks)⁴ and less than olanzapine over 26 weeks.⁹ Aripiprazole had statistically significantly less effect on prolactin levels than haloperidol^{3,5}, risperidone⁴ and olanzapine⁹ in short and long-term trials. Aripiprazole had little effect on QT interval or on glucose and lipid levels in short-term trials.^{3,4,8} Other AE include tachycardia, blurred vision or orthostatic hypotension.¹⁰ Aripiprazole can interact with potent inducers or inhibitors of CYP3A4 and CYP2D6 enzymes, including carbamazepine, quinidine, phenytoin, rifampicin, St Johns wort, fluoxetine, paroxetine, ketoconazole.¹⁰ Caution should be taken with other sedating drugs and alcohol.¹⁰ Aripiprazole has the potential to enhance α -blocker anti-hypertensive agents.¹⁰

Place in Therapy

Aripiprazole has been shown to be as effective as haloperidol in one short-term³ and one long-term trial.⁵

Trials versus atypical agents are limited to one non-comparative short-term study against risperidone⁴ and one unpublished safety study against olanzapine.⁹ There is no evidence that aripiprazole is more effective than established agents for the treatment of positive or negative symptoms of schizophrenia.

The AE profile of antipsychotic drugs is of great importance and aripiprazole appears promising, although more long-term and post-marketing studies will be needed to

confirm this.

NICE guidance recommends atypical agents are considered in the choice of first-line treatments for patients newly diagnosed with schizophrenia or for those patients suffering unacceptable AE with typical agents.¹¹ Where more than one atypical agent is appropriate, NICE recommend that the drug with the lowest acquisition cost should be prescribed. Aripiprazole may be an option in patients suffering adverse events on other atypical antipsychotics.

Experience with aripiprazole in treatment-resistant schizophrenia is very limited and it is not licensed for this indication.¹²

The Future

Trials with aripiprazole have also been conducted in acute mania associated with bipolar disorder.¹³

Key Papers

- 3 Kane JM et al Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder J Clin Psychiatry 2002; **63**: 763-771
- 4 Potkin SG et al Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder Arch Gen Psychiatry 2003; **60**: 681-690
- 5 Kasper S et al Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia Int J Neuropsychopharmacol 2003; **6**: 325-337

Appendix I: Bibliography Appendix II: Table of Clinical Trials, Table of assessment tools

Risk Management Issues:

None identified



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by Vanessa Chapman, Trent Medicines Information Centre, Leicester. Tel 0116 258 6491

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Appendix I

Bibliography

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2. Taylor DM Aripiprazole: A review of its pharmacology and clinical use Int J Clin Pract 2003; **57**: 49-54
3. Kane JM, Carson WH et al Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder J Clin Psychiatry 2002; **63**: 763-771
4. Potkin SG, Saha AR et al Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder Arch Gen Psychiatry 2003; **60**: 681-690
5. Kasper S, Lerman MN et al Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia Int J Neuropsychopharmacol 2003; **6**: 325-337
6. Pigott TA, Carson WH et al Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: A placebo-controlled 26-week study J Clin Psychiatry 2003; **64**: 1048-56
7. Casey DE, Carson WH et al Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study Psychopharmacology 2003; **166**: 391-9
8. Marder SR, McQuade RD et al Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials Schizophrenia Research 2003; **19**: 1-14
9. McQuade RD, Jody DN et al Long-term weight effects of aripiprazole vs olanzapine Poster presented at the American Psychiatric Association, 156th Annual Meeting, San Francisco May 2003
10. Otsuka Pharmaceuticals Abilify Summary of Product Characteristics, June 2004
11. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia NICE Technology Appraisal Guidance No 43 June 2002
12. Kane JM, Carson WH et al Aripiprazole vs perphenazine in treatment-resistant schizophrenia Poster presented at the American Psychiatric Association, 156th Annual Meeting, San Francisco May 2003
13. Lyseng-Williamson KA & Perry CM Aripiprazole in acute mania with bipolar I disorder CNS Drugs 2004; **18**: 367-376
14. Lader M Rating scales in schizophrenia. A review of their usefulness for assessing atypical antipsychotics CNS Drugs 2000; **14**: 23-32
15. Assessment tools www.psychiatry-in-practice.com

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Appendix II

Table 1: Published comparative trials of aripiprazole

Ref No	Trial Design	Trial Population	Treatment	Efficacy Results (*primary efficacy parameters)																																			
3	4 week, double blind, active and placebo controlled trial in the US	414 patients with schizophrenia or schizoaffective disorder. Patients were eligible if they were hospitalised for an acute relapse and remained hospitalised throughout. Mean baseline PANSS total score 99.3	Aripiprazole 15mg (n=102) Aripiprazole 30mg (n=102) Haloperidol 10mg (n=104) Placebo (n=106)	<p>Mean changes from baseline to week four (all P values vs placebo):</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Placebo</th> <th style="text-align: center;">Ari 15mg</th> <th style="text-align: center;">Ari 30mg</th> <th style="text-align: center;">Haloperidol</th> </tr> </thead> <tbody> <tr> <td>PANSS total*</td> <td style="text-align: center;">-2.9</td> <td style="text-align: center;">-15.5 (P<0.001)</td> <td style="text-align: center;">-11.4 (P=0.009)</td> <td style="text-align: center;">-13.8 (P=0.001)</td> </tr> <tr> <td>PANSS positive*</td> <td style="text-align: center;">-0.6</td> <td style="text-align: center;">-4.2 (P<0.001)</td> <td style="text-align: center;">-3.8 (P=0.001)</td> <td style="text-align: center;">-4.4 (P<0.001)</td> </tr> <tr> <td>PANSS negative</td> <td style="text-align: center;">-1.2</td> <td style="text-align: center;">-3.6 (P=0.006)</td> <td style="text-align: center;">-2.3 (P=0.213)</td> <td style="text-align: center;">-2.9 (P=0.043)</td> </tr> <tr> <td>CGI-Severity*</td> <td style="text-align: center;">-0.1</td> <td style="text-align: center;">-0.6 (P<0.001)</td> <td style="text-align: center;">-0.4 (P=0.019)</td> <td style="text-align: center;">-0.5 (P=0.002)</td> </tr> </tbody> </table> <p>Mean values (all P values vs placebo):</p> <table style="width: 100%; border-collapse: collapse;"> <tbody> <tr> <td>CGI-Improvement</td> <td style="text-align: center;">4.3</td> <td style="text-align: center;">3.5 (P<0.001)</td> <td style="text-align: center;">3.8 (P=0.016)</td> <td style="text-align: center;">3.7 (P=0.002)</td> </tr> <tr> <td>Responder rate</td> <td style="text-align: center;">17%</td> <td style="text-align: center;">35% (P=0.002)</td> <td style="text-align: center;">28% (P=0.05)</td> <td style="text-align: center;">26% (P=0.089)</td> </tr> </tbody> </table>		Placebo	Ari 15mg	Ari 30mg	Haloperidol	PANSS total*	-2.9	-15.5 (P<0.001)	-11.4 (P=0.009)	-13.8 (P=0.001)	PANSS positive*	-0.6	-4.2 (P<0.001)	-3.8 (P=0.001)	-4.4 (P<0.001)	PANSS negative	-1.2	-3.6 (P=0.006)	-2.3 (P=0.213)	-2.9 (P=0.043)	CGI-Severity*	-0.1	-0.6 (P<0.001)	-0.4 (P=0.019)	-0.5 (P=0.002)	CGI-Improvement	4.3	3.5 (P<0.001)	3.8 (P=0.016)	3.7 (P=0.002)	Responder rate	17%	35% (P=0.002)	28% (P=0.05)	26% (P=0.089)
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5	Two 52 week double blind active controlled trials (one in the US, one worldwide). Results of the trials were pooled (prospectively planned)	1294 patients in acute relapse with chronic schizophrenia Primary efficacy outcome- time to failure to maintain response in responders. Response defined as a $\geq 20\%$ decrease from baseline in PANSS total score at a single time point. A more stringent criteria was also used, defined as a $\geq 30\%$ decrease from baseline in PANSS total score for at least 28 days.	Aripiprazole 30mg od (n=861) Haloperidol 10mg od (n=433) A one-time dose reduction to 20mg daily of aripiprazole and 7mg daily of haloperidol was allowed for tolerability.	Response rate $>20\%$ improvement in PANSS $>30\%$ improvement in PANSS over ≥ 28 days *Kaplan-Meier estimates for patients maintaining responses at week 52 Time to failure to maintain response	Aripiprazole 72% 52% Aripiprazole 77% 85%	Haloperidol 69% 44% Haloperidol 73% 79%	P value 0.362 0.003 Risk ratio 0.88 0.7 P value 0.427 0.098	

Table 2: Assessment tools used to monitor efficacy in trials

Assessment tool	Definition ^{16,17}
PANSS (Positive and negative syndrome scale)	30-item scale including 7 positive items, 7 negative items and a 16-item general psychopathology scale. Each item is rated on a 7-point scale (1=absent, 7=extreme). This gives a maximum score of 210 for PANSS total, 49 for PANSS positive and 49 for PANSS negative.
CGI (Clinical Global Impression)	Severity of illness (CGI-S)- this requires the clinician to rate the severity of the patient's illness on a seven-point scale (1=normal, 7=extremely ill) Global Improvement (CGI-I)- this requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state on a seven-point scale (1=very much improved, 7=very much worse)