

NEW DRUG EVALUATION

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ARIPIPRAZOLE

Aripiprazole is a new atypical antipsychotic drug licensed for the management of schizophrenia. In short term studies it shows similar efficacy to haloperidol but like other atypical antipsychotics, it is less likely to cause extrapyramidal effects. There are limited comparative data with higher doses of haloperidol or with other atypical antipsychotic drugs. There is currently no evidence that aripiprazole has any efficacy or safety benefits compared with other atypical agents.

What is it?

Aripiprazole (Abilify®, Bristol Myers Squibb and Otsuka) is a new atypical antipsychotic agent licensed for the treatment of schizophrenia.¹ Unlike other atypical antipsychotics, aripiprazole has partial agonist activity at dopamine-2 receptors.^{1,2} It was thought that this may result in a lower incidence of extrapyramidal side effects (EPS) and hyperprolactinaemia.³ The recommended dose is 15 mg once a day with an option to titrate up to 30 mg once a day.¹ This document reviews the place of aripiprazole in the management of schizophrenia.

How effective is it?

The efficacy of aripiprazole in schizophrenia has been evaluated in two fully published 4 week double-blind, placebo controlled trials in acutely relapsed inpatients.^{4,5} Both used improvement from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. Positive and negative PANSS scores were also pre-specified endpoints. Neither study was designed to directly compare the efficacy of aripiprazole with the active control.

In one study (n=414) improvements in PANSS total and positive scores were seen with aripiprazole 15 mg ($p < 0.001$) and 30 mg ($p < 0.009$) and with haloperidol 10 mg ($p < 0.01$) compared with placebo.⁴ Aripiprazole 15 mg ($p < 0.006$) and haloperidol ($p = 0.043$) but not aripiprazole 30 mg significantly improved PANSS negative scores compared with placebo.⁴

In the other study (n=404), statistically significant improvements in PANSS total, positive and negative scores were documented with aripiprazole 20 mg and 30 mg, as well as with risperidone 6 mg.⁵

No evidence was presented in any of the above studies to show that the groups treated with higher doses of aripiprazole showed any advantage over the lowest dose group.⁶

An 8-week switch study in patients with chronic stable schizophrenia receiving typical and atypical antipsychotics reported numerical improvements (not statistically significant) when patients were switched to aripiprazole 30mg.⁷ However few conclusions can be drawn as this was an open label, non-comparative study with ambiguous inclusion criteria using only the maximum dose of aripiprazole.

A 26-week, double-blind, placebo controlled study randomised 310 patients with schizophrenia to receive

aripiprazole 15 mg daily or placebo.⁸ The primary outcome measure was time to relapse following randomisation. The time to relapse following randomisation was significantly longer ($p > 0.001$) for aripiprazole compared to placebo, however the time to relapse was not stated. The probability of not experiencing a relapse before week 26 was 39% in the placebo group and 63% in the aripiprazole group ($p < 0.001$). A double-blind, controlled 52 week study, randomised 1294 patients with acute relapsed schizophrenia to receive aripiprazole 30 mg (n=861) or haloperidol 10mg (n=433).⁹ The primary endpoint was the time to failure to maintain response in responders ($\geq 20\%$ decrease in PANSS total score at any time). For this end point there were no differences between the two drugs (77% for aripiprazole and 73% for haloperidol $p = 0.427$) and both were associated with similar improvements in symptoms as measured by changes from baseline in PANSS total and positive subscales. Aripiprazole demonstrated a statistically significant improvement in the PANSS negative score compared with haloperidol ($p < 0.05$). In a trial published as an abstract (n=255) in clinically stable patients with schizophrenia aripiprazole 30 mg produced significant improvements in verbal memory compared to olanzapine 15 mg, but this was an open trial and the possibility of observer bias cannot be excluded.¹⁰

How safe is it?

The adverse effects most commonly reported ($> 1/100 < 1/10$) more frequently than with placebo were light-headedness, insomnia, akathisia, somnolence, tremor, blurred vision, nausea, vomiting, dyspepsia, constipation, headache and asthenia.¹ Aripiprazole is metabolised by the CYP2D6 and CYP3A4 isoenzymes.¹ The dose should be doubled in patients taking carbamazepine and other cytochrome enzyme inducers.¹ In patients taking enzyme inhibitors (e.g. ketoconazole, itraconazole and protease inhibitors) the dose of aripiprazole should be halved.¹ In a 52-week study significantly more patients reported EPS related event with haloperidol than with aripiprazole (58% vs. 27% $p < 0.001$).⁹ The mean weight gain was not significantly different between the two drugs and there were no significant differences in ECG effects.⁹ In the 4-week study that compared aripiprazole and risperidone with placebo the changes in serum prolactin levels were not significantly different between aripiprazole and placebo while risperidone produced a significantly greater

increase in prolactin levels than placebo ($p < 0.001$).⁵ The overall incidence of EPS related events was comparable in the aripiprazole 20 mg (32%) 30 mg (31%) and risperidone treated groups (31%).⁵ An unpublished study suggests less weight gain with aripiprazole (-1.3kg) compared with olanzapine (4.23kg) over 26 weeks.¹¹ This finding needs to be confirmed and comparisons with other atypical agents are also needed.

What other options are there?

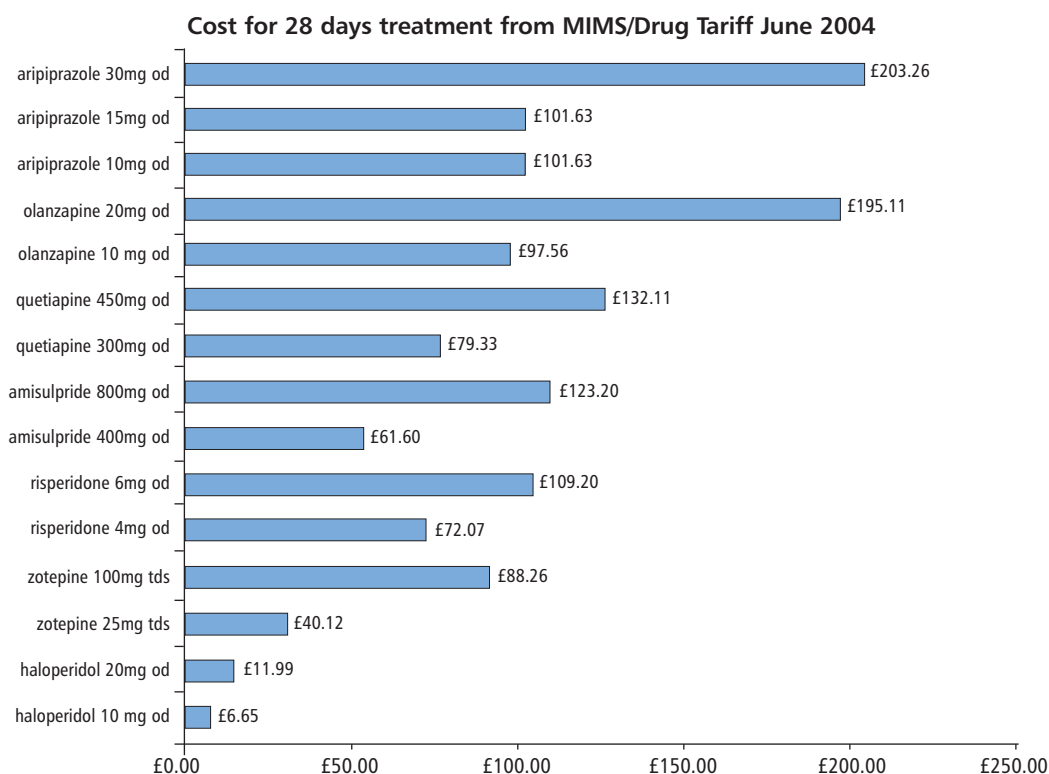
Following the publication of the NICE guidance on the use of newer atypical antipsychotics, oral atypical antipsychotics (amisulpride, olanzapine, quetiapine, risperidone or zotepine) are considered first line treatments for individuals with newly

diagnosed schizophrenia.¹² Oral atypical drugs should be considered as treatment options for individuals using typical antipsychotics who have unacceptable side effects. Individuals with treatment resistant schizophrenia should be prescribed clozapine.

When should it be used?

Aripiprazole appears to be similar in efficacy to haloperidol. Clinical comparisons with other atypical antipsychotics are lacking, there are currently no proven benefits in terms of efficacy or safety and there is also a lack of long term experience. The Cochrane collaboration recently concluded that, aripiprazole is effective for the treatment of schizophrenia, but it offers no proven advantage over other atypical antipsychotics.¹³

How much does it cost?



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, G-guideline, MA- meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

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