

Aripiprazole is effective against the symptoms of schizophrenia and schizoaffective disorder

Potkin SG, Saha AR, Kujawa MJ, *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**:681–90.

Q Is aripiprazole effective in people with schizophrenia or schizoaffective disorder?

METHODS

 **Design:** Randomised controlled trial.

 **Allocation:** Unclear.

 **Blinding:** Double blind (participants and assessors).

 **Follow up period:** Four weeks.

 **Setting:** Forty medical centres in the USA; September 1997 to October 1998.

 **Patients:** 404 people hospitalised with acute relapse of schizophrenia (n=289) or schizoaffective disorder (n=115), scoring ≥ 60 on the Positive and Negative Syndrome Scale (PANSS), and responsive to antipsychotics. Participants taking long acting neuroleptics were included if they were deteriorating clinically. Exclusions: other psychiatric disorder requiring pharmacotherapy; recent history of suicidal tendencies/attempts; violence; substance abuse; neurological abnormality (not tardive dyskinesia or extrapyramidal symptoms); treatment with investigational drug in the month preceding the washout phase; and acute or unstable medical comorbidity.

 **Intervention:** Four weeks of: 20 mg/day aripiprazole (n=101), 30 mg/day aripiprazole (n=101), 6 mg/day risperidone (n=99), or placebo (n=103). Participants were hospitalised for the entire study period.

 **Outcomes:** Changes in PANSS scores from baseline, change in Clinical Global Impression-Severity of Illness (CGI-S) subscale score.

 **Patient follow up:** Dropout rates: 50% with placebo v 40% with 20 mg/d aripiprazole v 34% with 30 mg/d aripiprazole v 37% with risperidone. Dropouts were due to worsening symptoms or lack of clinical improvement (10%), adverse effects (11%), or other reasons (19%).

MAIN RESULTS

Aripiprazole significantly improved overall PANSS score and CGI-S score compared with placebo (see web extra table 1).

CONCLUSIONS

Aripiprazole is the first non-dopamine D2 receptor antagonist shown to be effective against the positive and negative symptoms in schizophrenia and schizoaffective disorder.

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Commentary

Aripiprazole, as a partial agonist at D2 dopamine receptors, presents an intriguing new treatment approach for psychotic illness. Theoretical mechanisms of action of other antipsychotics have involved high D2 dopamine receptor blockade (for conventional agents) and high 5HT_{2A} serotonin: D2 dopamine blockade or fast dissociation from D2 dopamine receptors (for earlier atypical agents).¹

This important, large study provides the first substantial evidence that compared with a leading atypical antipsychotic, aripiprazole has similar efficacy and greater tolerability. Trials by Kane *et al*² and Daniel *et al*³ (reported in Kelleher *et al*⁴) of aripiprazole or haloperidol versus placebo provide related evidence. In those studies, aripiprazole had comparable efficacy and was at least as fast in onset as the conventional agent. It was also associated with less severe side effects.

The maximum dose⁵ of risperidone used in this trial is not typical of today's US practice, and titration may have been too rapid for some subjects. These factors may have influenced the results in aripiprazole's favour. Dosing of aripiprazole may have also been high. Doses over 15 mg/day have not generally been associated with increased efficacy.⁶ Finally, these data remind us that risperidone can cause QTc prolongation.

Evidence from a variety of studies suggests that aripiprazole can be recommended as a safe and effective treatment for schizophrenia. In addition to these findings, in preliminary studies aripiprazole has been beneficial for up to one year,⁷ and even at doses greater than 30 mg/day.^{8,9} Further comparisons with atypical antipsychotics, additional long term trials, and reports on use in combination with other psychotropics will ultimately define its best role. Aripiprazole is also a promising agent for the treatment of acute mania¹⁰ and possibly other illnesses. Its success could lead to the development of a new generation of antipsychotics.

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