

Aripiprazole is effective for relapse prevention in people with chronic stable schizophrenia

Pigott TA, Carson WH, Saha AR, *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.

Q Does maintenance aripiprazole prevent relapse in people with chronic schizophrenia with residual symptomatology?

METHODS

-  **Design:** Randomised controlled trial.
-  **Allocation:** Unclear.
-  **Blinding:** Double blinded.
-  **Follow up period:** 26 weeks; participants monitored daily.
-  **Setting:** 31 centres in the USA, Czech Republic, Poland, Russia, and Ukraine; 2000–01.
-  **Patients:** 310 adults with confirmed schizophrenia (DSM-IV) of at least 2 years' duration with residual symptomatology despite antipsychotic treatment. Main inclusion criteria: ongoing antipsychotic treatment to which they had shown some response; Positive and Negative Syndrome Scale (PANSS) score of ≥ 60 with score ≤ 4 on the hostility or uncooperativeness subscales; Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≤ 4 . Exclusions: acute relapse; psychiatric comorbidity; resistant to antipsychotics; alcohol or substance abuse or benzodiazepine dependency; recent use of fluoxetine, long acting antipsychotics, or electroconvulsive therapy; suicidality; pregnant or at risk of pregnancy; cognitive disorders such as dementia, delirium, or amnesia. Participants discontinued antipsychotic and psychotropic medication and underwent a three day washout period before randomisation.
-  **Intervention:** Aripiprazole (15 mg/day) or placebo.
-  **Outcomes:** Time to relapse (defined as an impending decompensation based on at least one of the following: CGI-Global Improvement (CGI-I) score ≥ 5 ; PANSS score ≥ 5 on the hostility or uncooperativeness subscales on two successive days; or PANSS total score increase $\geq 20\%$); symptom scores and incidence of adverse effects.
-  **Patient follow up:** 96% for efficacy outcome.

MAIN RESULTS

Aripiprazole significantly decreased relapse rate compared with placebo (Kaplan-Meier survival rates at week 26: 62.6% with aripiprazole *v* 39.4% with placebo; $p < 0.001$; RR for relapse 0.50, 95% CI 0.35 to 0.71). Aripiprazole significantly improved schizophrenic symptoms compared with placebo at 26 weeks (PANSS total score, CGI-S and CGI-I scales; see table). Both groups had a similar

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Commentary

Aripiprazole, an atypical antipsychotic, has a novel mechanism of action—dopamine partial agonism. Like most atypical antipsychotics it also has strong 5-HT_{2A} affinity. Currently available atypical antipsychotics are possibly more effective, and certainly better tolerated, than conventional treatment regarding motor side effects. However, problems with weight gain, type II diabetes, and long QTc syndrome have arisen with some atypical antipsychotics. Clozapine remains the only drug indicated for treatment resistant illness: recent UK government guidance has recommended a much lower threshold for its consideration than previously, despite its side effects.¹ Therefore, most clinicians would appreciate a drug effective in more severe schizophrenia, with good tolerance. Could aripiprazole fit the bill? The relapse rate in this study—27% over 6 months on aripiprazole—is relatively high compared with similar studies, although much better than placebo (49%). There were no direct measures of compliance—that is, serum assay, which makes true efficacy unclear. These patients' PANSS scores were relatively high, and improvements over six months on active treatment were clinically negligible. However, aripiprazole was as well tolerated as placebo.

In my experience, the best tolerated effective antipsychotic currently is quetiapine;² the main question regarding aripiprazole will be, can it provide additional advantages in efficacy or tolerability compared to quetiapine? If not, is it a "me too" antipsychotic? This study cannot answer these questions in full, but the placebo level side effect profile looks very promising. Furthermore aripiprazole, unlike quetiapine, does not require titration and dosing is simpler. Regarding efficacy, however, clinicians may be cautious about switching stable patients to a drug on which nearly one in three relapse within six months, even though these patients were far from well. Furthermore, the lack of clinically significant symptom remediation on aripiprazole detracts from its potential usefulness in more severely ill patients.

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- 1 National Institute for Clinical Excellence. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. London: NICE, 2002. NICE Technology Appraisal Guidance No: 43.
- 2 Dev V, Raniwalla J. Quetiapine: a review of its safety in the management of schizophrenia. *Drug Saf* 2000;**23**:295–307.

incidence of adverse effects (79.7% with aripiprazole *v* 77.1% with placebo).

CONCLUSIONS

Aripiprazole is effective for preventing relapse in people with chronic schizophrenia and residual symptomatology over a six month period.

Table Mean change in PANSS and CGI scores from baseline to week 26

	Aripiprazole	Placebo	p Value
PANSS total	-2.08	+4.50	≤ 0.01
PANSS positive subscale	+0.12	+2.37	≤ 0.01
PANSS negative subscale	-1.40	-0.54	NS
PANSS derived BPRS	-0.21	+1.17	≤ 0.01
CGI-S	+0.15	+0.40	≤ 0.05
CGI-I	+3.74	+4.47	≤ 0.01

BPRS, brief psychiatric rating scale; NS, not significant.