**Aripiprazole in the treatment of the psychosis prodrome**

**An open-label pilot study**

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**Background**  Research studies for the treatment of the putative prodromal phase of psychotic disorders have begun to appear.

**Aims**  To obtain preliminary evidence of the short-term efficacy and safety of aripiprazole treatment in people with the psychosis prodrome.

**Method**  Fifteen participants meeting prodrome criteria (mean age 17.1 years, s.d. = 5.5) enrolled in an open-label, single-site trial with fixed-flexible dosing of aripiprazole (5–30 mg/day) for 8 weeks.

**Results**  In the mixed-effects repeated-measures analysis, improvement from baseline on the Scale of Prodromal Symptoms total score was statistically significant by the first week. No participant converted to psychosis and 13 completed treatment. Neuropsychological measures showed no consistent improvement; mean weight gain was 1.2 kg. Akathisia emerged in 8 participants, but the mean Barnes Akathisia Scale score fell to baseline levels by the final visit. Adverse events were otherwise minimal.

**Conclusions**  Aripiprazole shows a promising efficacy and safety profile for the psychosis prodrome. Placebo-controlled studies are indicated.

**Declaration of interest**  S.W.W. has received grants from Bristol-Myers Squibb, Janssen, and Eli Lilly.

The prodromal phase of schizophrenic disorders has been recognised since the 19th century (Bleuler, 1911) and the possibility of treatment during the prodromal phase has a history almost as long (Sullivan, 1927). Although some studies have begun to investigate methods to prevent progression from the putatively identified prodromal phase to frank psychosis (Falloon, 1992; McGorry et al., 2002; Morrison et al., 2004; McGlashan et al., 2006), fewer have focused on the acute treatment effects on current symptoms (Woods et al., 2003). Aripiprazole is a relatively new antipsychotic medication with limited liability for weight gain (Marder et al., 2003), whose mechanism of action differs from other antipsychotics in that it is a partial agonist rather than a full antagonist at dopamine D2 receptors (Burris et al., 2002). The overall goal of the present pilot study was to obtain preliminary information about the efficacy and safety of aripiprazole in relieving symptoms that may be prodromal for schizophrenia.

**METHOD**

**Sample**

Adult participants gave written informed consent and minors gave written informed assent with consent from a parent or guardian. Participants were included if they were treatment-seeking out-patients of 13–40 years of age who met diagnostic criteria for a possible prodromal syndrome. People were excluded for any of the following reasons: (a) past or current DSM-IV criteria (American Psychiatric Association, 1994) for any lifetime psychotic disorder; (b) they were judged clinically to have a psychiatric disorder (e.g. mania, depression, attention-deficit hyperactivity disorder) which could account for the symptoms; (c) they presented with symptoms occurring primarily as sequelae to drug or alcohol use; (d) alcohol or drug misuse or dependence in the past 3 months; (e) use of antipsychotic medication in the previous 3 months; (f) change in dosage of any antidepressant within 6 weeks, stimulant medication within 4 weeks, or mood stabiliser within 4 weeks.

The Criteria of Prodromal Syndromes (COPS; Woods et al., 2001) were used to identify those possibly prodromal. The COPS are based on sub-threshold levels of positive symptoms and operationally define three prodromal syndromes (Yung et al., 1998): attenuated positive symptom syndrome, brief intermittent psychotic syndrome, and genetic risk and recent functional decline syndrome. The COPS and the three syndromes are described in detail elsewhere (Woods et al., 2001; Miller et al., 2003a). Individuals were assessed to determine whether the COPS were met by using the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 1999).

Reliability of the COPS diagnosis of possible prodrome has been excellent when using the SIPS (Miller et al., 2002, 2003a), and patients thus diagnosed are symptomatic (Miller et al., 2003b), functionally impaired (Miller et al., 2003b), cognitively impaired (Hawkins et al., 2004a) and treatment-seeking (Peda et al., 2002).

**Study design**

Participants were enrolled between October 2004 and February 2006. The Yale Human Investigation Committee Institutional Review Board approved the protocol. The trial is registered with ClinicalTrials.gov (NCT00237874). This was an open-label study at one site for 8 weeks, followed by an open-label extension phase with monthly follow-up visits to 52 weeks. Findings from the extension phase will be reported subsequently.

**Procedure**

During the 1–2 weeks prior to beginning study medication, participants underwent eligibility and neuropsychological examinations. After beginning study medication, participants were scheduled for eight weekly visits.

Dosing followed a fixed-flexible schedule. Initial doses were 5 mg/day aripiprazole; after 1 week, the dose was scheduled for increase to 10 mg/day and after 2 weeks to 15 mg/day, unless adverse effects dictated a slower titration schedule. After the third week, the dose could be increased further to 20 mg/day and if needed to...
30 mg/day should the person not be responding. Aripiprazole was prescribed as a single daily dose unless there was a reason to divide the dose. The number of milligrams prescribed and the number taken were recorded each day; these data were used to calculate the percentage adherence since the previous visit. Drowsiness was managed initially by switching the timing of the daily dose to bedtime or by dividing the dose. Insomnia was managed initially by switching the timing of the daily dose to early morning. Lorazepam was used to treat insomnia or agitation. Lorazepam or the anticholinergic benztropine was permitted for extrapyramidal symptoms (EPS). Participants continued doses of antidepressant, mood stabiliser, or stimulant medication prescribed before consent but were not permitted to begin or increase dosage of these medications after consent. Individual and family psychosocial interventions with supportive and psychoeducational components were available to each participant.

**Assessments**

The primary efficacy measure for the analysis of acute treatment was change over time in the total score of the Scale of Prodromal Symptoms (SOPS; Miller et al., 1999), a 19-item scale with items scored 0–6. The interrater reliability has been excellent (Miller et al., 2003a). Factor analysis supports the validity of the SOPS subscales (Hawkins et al., 2004b). Treatment response was defined as all five SOPS positive symptom items being rated below the prodromal range (i.e., ≤2).

Secondary efficacy assessments included the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990), the Young Mania Rating Scale (YMRS, Young et al., 1978), the Beck Anxiety Inventory (BAI; Beck et al., 1988), the Global Assessment of Functioning Scale (GAF; Hall, 1995), the Heinrichs–Carpenter Quality of Life role functioning sub-scale (HCRF; Heinrichs et al., 1984), and the Social Functioning Scale (SFS; Birchwood et al., 1990).

Neuropsychological assessments included tests of attention and working memory: the Continuous Performance Test (CPT; Cornblatt et al., 1988), identical pairs version, letter number sequencing, N-back, Trails A and B; Stroop Color Word Test for processing speed; Auditory Verbal Learning Task (AVLT; Rey, 1964), using alternate forms for verbal memory; and the Wisconsin Card Sort Test (WCST; Heaton et al., 1993), semantic (category) fluency, and Controlled Oral Word Association (FAS; Spreen & Benton, 1969) test of phonemic fluency for executive functioning.

Abnormal involuntary movements and EPS were assessed by observation and administration of the Simpson–Angus Scale (SAS; Simpson & Angus, 1970), the Barnes Akathisia Scale (BAS; Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS; Branch, 1975). Safety was also assessed by analysing treatment-emergent adverse events (Systematic Assessment For Treatment–Emergent Events, SAFTEE, specific inquiry method; Levine & Schooler, 1986), vital signs and weight. Treatment-emergent adverse events were defined as those first occurring or worsening after baseline. All of the above measures were assessed at baseline and weekly thereafter.

**Statistical analyses**

For the present report, the time frame was the first 8 weeks after beginning study medication, and the principal outcome measure was the SOPS total score. Analyses were based on the intent-to-treat (ITT) principle. All participants were included in the analysis. The principal outcome measure was addressed using a mixed-effects likelihood-based repeated measures linear model (MRRM, as implemented in SAS PROC MIXED) on post-baseline change scores, using baseline scores as a covariate. For other measures we used t-test end-point models at 8 weeks, carrying forward the last observation (LOCF).

**RESULTS**

**Participants**

A total of 15 participants were enrolled. Demographic and treatment characteristics at baseline are shown in Table 1. All were diagnosed with the common attenuated positive symptom syndrome putative prodrome subtype according to the COPS and none also qualified for either of the other two less common COPS prodromal syndromes. All but two had never received antipsychotic medication prior to participating. One participant had received antipsychotic for 5 weeks 5 years earlier, and the other for 6 months ending 17 months before baseline, both for indications other than psychosis. Scores for severity of illness at baseline are shown in Table 2. Although there are a dearth of age-specific normative data (our sample with test-retest data has a mean age of 15.5 years, s.d.=1.3), baseline data (Table 3) suggest mild neuropsychological impairment similar to that observed in our previous prodromal sample (Hawkins et al., 2004a). A higher mean AVLT total score was reported for a younger sample by Spreen & Strauss (1998) and substantially better Trail-Making Part A and Part B performances were reported for a healthy sample aged 15–17 years from Fromm-Auch & Yeudall (1983).

Thirteen participants completed the 8-week study (87%). Of the two drop-outs, one completed 48 days on aripiprazole and dropped out because of improvement, feeling medication was no longer needed. The other completed only 8 days on medication and left the study primarily because of sedation after the first 10 mg dose, after having concluded that 5 mg was ineffective after the first week.

**Medication**

Prescribed mean (s.d.) aripiprazole doses at weeks 1, 2, 3, 4, 5, 7 and 8 were 5 (0), 9 (2), 11 (5), 11 (7), 11 (6), 13 (6), 14 (8), and 15 (7) mg/day, respectively. Final prescribed doses were 5 mg/day (n=1 participant), 10 mg/day (n=3), 15 mg/day (n=6), 20 mg/day (n=4) and 30 mg/day (n=1). Reported mean (s.d.) percentage adherence with prescribed aripiprazole doses was 94 (13), 92 (22), 98 (4), 96 (8), 97 (7), 95 (10), 98 (5), and 94 (9) at weeks 1, 2, 3, 4, 5, 6, 7 and 8 respectively. New concomitant medication used after

![Fig. 1 Change in Scale of Prodromal Symptoms (SOPS) total score from baseline with aripiprazole treatment. Mixed-effect repeated-measures model-derived mean and standard error are shown for each time point. *P<0.05, **P<0.001.](image-url)
and BAI scales, as well as significantfunc-
tion from baseline on the YMRS, CDSS
disorganisation and general symptom sub-
point for each of the positive, negative,
SOPS was statistically significant at end-
cant at each time point (Fig. 1). The LOCF
s98
Efficacy
enrollment included benzodiazepine in
hallucinogens and others.
2. Includes alcohol, sedatives, opioids, cocaine,
these medications.
stabilisers, or stimulants were permitted to continue

Table 1: Demographic and treatment data at
baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>17.1 (5.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Single, n (%)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>First-degree family history, n (%)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Non-psychotic major depression</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Non-psychotic bipolar disorder</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Medication use at baseline, n (%)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Benzodiazepines/hypnotics</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Mood stabilisers</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Lifetime substance</td>
<td></td>
</tr>
<tr>
<td>misuse/dependence, n (%)</td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Other (except nicotine)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

1. Patients taking antidepressants, antianxiety, mood stabilisers, or stimulants were permitted to continue
these medications.
2. Includes alcohol, sedatives, opioids, cocaine, hallucinogens and others.

enrollment included benzodiazepine in
three participants (20%) and anticholinergic medication in 5 participants (33%).

Table 2: Baseline and change from baseline in severity of illness scores of participants treated with
aripiprazole

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean</th>
<th>Change from baseline Mean</th>
<th>t (14) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOPS Total</td>
<td>43.3 (15.0)</td>
<td>−29.1 (12.3)</td>
<td>−9.2 &lt; 0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>13.6 (3.7)</td>
<td>−10.0 (4.1)</td>
<td>−9.4 &lt; 0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>12.9 (6.9)</td>
<td>−8.2 (6.5)</td>
<td>−4.9 &lt; 0.001</td>
</tr>
<tr>
<td>Disorganisation</td>
<td>7.1 (3.8)</td>
<td>−4.8 (3.3)</td>
<td>−5.6 &lt; 0.001</td>
</tr>
<tr>
<td>General</td>
<td>9.7 (4.2)</td>
<td>−6.1 (2.6)</td>
<td>−9.1 &lt; 0.001</td>
</tr>
<tr>
<td>YMRS total</td>
<td>4.7 (3.7)</td>
<td>−3.9 (3.6)</td>
<td>−4.3 &lt; 0.001</td>
</tr>
<tr>
<td>CDSS total</td>
<td>4.6 (4.5)</td>
<td>−3.8 (4.2)</td>
<td>−3.4 0.005</td>
</tr>
<tr>
<td>BAI total</td>
<td>14.9 (12.3)</td>
<td>−13.1 (11.2)</td>
<td>−9.5 &lt; 0.001</td>
</tr>
<tr>
<td>Current GAF</td>
<td>41.5 (6.4)</td>
<td>9.2 (5.3)</td>
<td>6.7 &lt; 0.001</td>
</tr>
<tr>
<td>HCRF</td>
<td>14.2 (4.7)</td>
<td>3.2 (5.1)</td>
<td>2.3 0.044</td>
</tr>
<tr>
<td>SFS</td>
<td>118 (20)</td>
<td>−2 (21)</td>
<td>−0.3 0.734</td>
</tr>
</tbody>
</table>

SOPS, Scale of Prodromal Symptoms; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale for
Schizophrenia; BAI, Beck Anxiety Inventory; GAF, Global Assessment of Functioning; HCRF, Heinrichs–Carpenter
Quality of Life role functioning sub-scale; SFS, Social Functioning Scale.
1. Last-observation-carried-forward values at 8 weeks.
2. n=14, d.f.=13 for CDSS; n=13, d.f.=12 for HCRF and SFS.

Efficacy
In the mixed-effects model, the effect of
time for the SOPS total score change from
baseline was statistically significant (F
(7)=9.2, P <0.001. The reduction in the
SOPS total score was statistically signifi-
cant at each time point (Fig. 1). The LOCF
analyses revealed that improvement on the
SOPS was statistically significant at end-
point for each of the positive, negative,
disorganisation and general symptom sub-
scales (Table 2). The LOCF analyses also
revealed significant symptomatic improve-
ment from baseline on the YMRS, CDSS and
BAI scales, as well as significant func-
tional improvement on the GAF and HCRF
scales (Table 2).

A total of 11 participants met response
criteria (73%) at week 2 (n=1), 3 (n=2), 4
(n=1), 6 (n=4), 7 (n=1) and 8 (n=2).
Response was sustained thereafter until end-
point in all but one participant. No
participant converted to psychosis. Two
non-responders who completed the 8-week
course elected not to continue aripiprazole
after 8 weeks; the remaining 11 who
completed 8 weeks elected to continue on
aripiprazole into the extension phase.

Table 3 shows the results of the neuro-
psychological testing. Participants improved
as a group on two tests of attention and
working memory at the significant or trend
level (2-digit CPT reaction time, 2-back
number correct) but worsened on one other
(2-digit CPT performance). They improved
as a group on a test of executive function
(WCST perseverative errors) but worsen-
on one other (semantic fluency). Scores on the remaining 15 tests of atten-
tion, working memory, executive function-
ning, processing speed and verbal memory
did not change significantly.

Safety
One participant discontinued aripiprazole
because of adverse events (sedation after 8
days). As determined by the SAFTEE, there
were few adverse events of more than mild
severity (Table 4). Complaints of adverse
events tended to remit over time. Other
than the participant who took medication
for only 8 days, at the final evaluation an
emergent SAFTEE complaint of moderate
or greater severity was present in only one
participant (nasal congestion).

During treatment, eight participants
experienced emergent akathisia dem-
strated by increases from baseline on the
BAS. Emergent akathisia was managed by
slowing dose titration (1), prescribing
anticholinergic medication (2), slowing
dose titration and prescribing anticholin-
ergic medication (2), slowing dose titration
and prescribing benzodiazepine (2) and pre-
scribing anticholinergic medication and
then adding benzodiazepine (1). In the con-
text of these management efforts, all par-
ticipants experiencing emergent akathisia
completed treatment, and the emergent
akathisia remitted by the final evaluation
in six participants. Mean BAS total scores
consequently returned to baseline by the
e-end point evaluation (Table 5). Four parti-
cipants continued to receive medication for
akathisia at the 8-week evaluation.

Little change from baseline to end-point
was observed for blood pressure (Table 5).
Pulse increased 6 beats per minute on aver-
age. There were no significant differences
from baseline to end-point on the SAS or
AIMS scales (Table 5). Patients gained a
mean of 1.2 kg in weight (Table 5).

DISCUSSION
The principal finding of the present study
was that those meeting criteria for a schizo-
phrenic prodromal syndrome who were
treated with aripiprazole improved to a
significant degree over an 8-week period
on the SOPS and other rating scales. Ad-
verse effects were generally mild and
manageable. Important limitations, how-
ever, are the small sample size and the use
of an uncontrolled, open-label design.
Improvements observed could have been a result of placebo effects or simply the passage of time.

Other studies
No participants converted to psychosis during the 8-week trial. We would have expected two or three conversions without treatment, based on the placebo group in our previous study (McGlashan et al., 2006). Caution is indicated in comparing our current findings with our historical placebo group, however, because it is possible that people volunteering for an open-label trial could differ from those volunteering for a placebo-controlled study (Woods et al., 2005).

This is the second report to our knowledge to focus on an acute pharmacological treatment of symptoms that can be prodromal for schizophrenia. Our findings can be compared with those from the acute phase of our previous placebo-controlled trial of olanzapine (Woods et al., 2003), but again one must allow for the different study designs. Participants with established schizophrenia improved less from baseline to end-point on active medication when placebo-controlled designs were used (Woods et al., 2005). It is not known whether this same effect of design occurs with putatively prodromal subjects. However, improvement in prodromal symptoms and treatment completion rates in participants assigned to aripiprazole compared favorably with these indices in participants randomised to olanzapine in our previous study. Participants were slightly more severely ill at baseline in the current sample according to the SOPS total score, although GAF scores at baseline and sample demography were similar. Improvement on GAF, as well as on mania and depression measures, was also more robust in the open-label study of aripiprazole than we had previously observed in a marked study of olanzapine.

Weight gain with aripiprazole also compared favourably with our previous experience with olanzapine. Participants treated with olanzapine gained a mean of 4.5 kg over 8 weeks in LOCDF analyses, whereas the aripiprazole mean weight gain in this study was 1.2 kg (Table 5) despite being exposed to drug for a higher proportion of the 8 weeks. This degree of weight gain was comparable to that observed in previous short-term studies of aripiprazole (mean 0.71 kg v. no change for placebo; Marder et al., 2003).

Akathisia, on the other hand, was more problematic with aripiprazole than it had been with olanzapine, leading to higher rates of benzotropine prescription. However, benzotropine, or in some cases slowing of dose titration or benzodiazepine prescription, was effective in managing this adverse effect, so that by the final evaluation the net effect of treatment on akathisia ratings was similar to what we had observed with olanzapine.

Adherence with prescribed doses was relatively high in this short-term analysis as measured by participant report at each visit. Adherence was similar to or higher than with olanzapine in our masked study, although the latter used a somewhat more...
rigorous pill-count method of monitoring adherence (Woods et al, 2003). As for most studies, surreptitious non-adherence cannot be excluded. Future studies should continue to assess adherence in this population.

Our neuropsychological findings show little consistent effect of aripiprazole over 8 weeks. Among the 20 results reported, a few tests did show improvement, but others showed a decline, with most suggesting little change. Considering tests that did change, within domain of function there appeared to be little consistency in direction. Certainly the limited sample size would have predisposed our study to low power to detect possible real effects; on the other hand, some gains would be expected on the basis of prior test exposure. In the only previous study, to our knowledge, on neuropsychological effects of aripiprazole (Kern et al, 2006), 169 participants with chronic schizophrenic psychosis underwent neuropsychological examinations before and 8 weeks after random assignment to aripiprazole or olanzapine. Aripiprazole-treated participants improved significantly over 8 weeks on a general cognitive factor on which loaded our letter number sequencing, verbal fluency and trail-making tasks. Our failure to find consistent improvement on these measures could relate to our small sample or to our participants being less impaired and having less room to improve. Aripiprazole-treated participants improved significantly in the previous study (Kern et al, 2006) on a verbal learning factor on which loaded a test similar to our AVLT but without use of alternative forms. Our failure to find consistent improvement on verbal memory could relate to the small sample, studying prodromal, chronic illness, or, our use of a counterbalanced alternate form for the repeat verbal learning list, which may have prevented the confounding of measurement of new verbal learning by familiarity with the word list carried over from the baseline testing (practice effect; Hawkins & Wexler, 1999; Hawkins et al, 2004c). In the previous study (Kern et al, 2006) aripiprazole-treated participants improved but not significantly on an executive functioning factor on which loaded our WCST tasks. These findings were similar to ours with WCST perseverative errors.

Dosing
We paid close attention to the dosing of aripiprazole in the current study. Although some investigators have emphasised that patients meeting prodrome criteria can be managed with antipsychotic doses which are lower than those used in chronic schizophrenia (Fallon, 1992; McGorry et al, 2002), there had been some evidence in our previous study that olanzapine had been used at too low a dose, especially in the first month (McGlashan et al, 2006). In the present study we employed a recommended fixed dose titration by the end of the second week to 15 mg/day, the minimal consistently effective aripiprazole dose for patients with chronic schizophrenia (Woods, 2003), unless the prescriber had a specific reason to deviate from this schedule. The 15 mg/day dose was also that most commonly employed in a recent pilot study of aripiprazole in first-episode schizophrenia (Brown et al, 2003). Initial doses were 5 mg/day, in keeping with guidelines for initiation of aripiprazole in adolescents/children who weigh 50–70 kg (Findling et al, 2004).

Implications
Our current findings are relevant to discussions of the ethics of intervention research in people who appear prodromal. Pro-drome research studies thus far have primarily focused on preventing the development of psychosis. Although this is certainly an important goal, ethical issues are raised because some participants will be false-positives who have no personal opportunity to benefit if benefit is defined solely as prevention. The current data suggest that people carrying a risk of progression to psychosis can receive not only the possibility of a preventive benefit but also a treatment benefit ‘on average’ from intervention. The prospect of treatment benefit on average is generally considered sufficient to justify exposure to some treatment risk in other illnesses. Thus the current data strengthen the argument that intervention studies can be ethical with people who appear prodromal.

Although our findings suggest that people who meet prodrome criteria benefit when prescribed aripiprazole, the present results contribute to what is only the beginning of the process of establishing a standard of care for such people. The sample size in our study was small and we had no control group, placebo or otherwise. Future placebo-controlled studies with more participants are needed before recommendations can responsibly be made regarding routine treatment. The present findings suggest that aripiprazole is a promising candidate for such studies.

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REFERENCES


