Effectiveness of aripiprazole *v.* haloperidol in acute bipolar mania

Double-blind, randomised, comparative 12-week trial

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on behalf of the Aripiprazole Study Group

Background Despite several treatment options, adherence to therapy is poor in patients with bipolar disorder.

Aims A double-blind, controlled comparison of aripiprazole and haloperidol in patients with bipolar I disorder experiencing acute manic or mixed episodes.

Method Patients (n=347) were randomised to receive aripiprazole or haloperidol in this 12-week, multicentre study. The primary outcome measure was the number of patients in response (≥50% improvement from baseline in Young Mania Rating Scale score) and receiving therapy at week 12.

Results At week 12, significantly more patients taking aripiprazole (49.7%) were in response and receiving therapy compared with those taking haloperidol (28.4%; $P<0.001$). Continuation rates differed markedly between treatments (week 12: aripiprazole, 50.9%; haloperidol, 29.1%). Extrapyramidal adverse events were more frequent with haloperidol than aripiprazole (62.7% *v.* 24.0%).

Conclusions Aripiprazole showed superior levels of response and tolerability to haloperidol in the treatment of an acute manic episode for up to 12 weeks.

Declaration of interest This study was sponsored by Bristol-Myers Squibb Company, Princeton, New Jersey, USA, and Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan.

The goal of effective treatment in acute mania is to provide acute symptom improvement and continued efficacy and safety of treatment in the long term. Despite effective treatment options, adherence to therapeutic regimens remains poor in patients with bipolar disorder, with studies reporting partial or total non-adherence rates of 40–60% (Colom & Vieta, 2002). Aripiprazole is a novel psychotropic agent with a distinctly different mechanism of action from currently available antipsychotics. It has been shown to be effective for acute and long-term treatment of schizophrenia and the treatment of acute mania, and is associated with minimal potential for extrapyramidal symptoms, weight gain and hyperprolactinaemia (Kasper *et al*, 2003; Keck *et al*, 2003; Marder *et al*, 2003; Pigott *et al*, 2003). This 12-week study compared the effectiveness of aripiprazole with haloperidol for treatment of an acute manic or mixed episode, based on patients remaining on treatment and in response at week 12.

METHOD

Patient selection

Patients eligible for enrolment in the study were men and women aged 18–65 years, with a DSM–IV diagnosis of bipolar I disorder (American Psychiatric Association, 1994), receiving in-patient or out-patient treatment for an acute manic or mixed episode. All patients were required to have a Young Mania Rating Scale (YMRS; Young *et al*, 1978) baseline score of 20 or above.

Exclusion criteria were the presence of rapid-cycling bipolar I disorder; duration of the current manic episode of more than 4 weeks; proven substance misuse; patient considered unresponsive to antipsychotics; patient at significant risk of suicide; recent treatment with a long-acting antipsychotic, lithium or divalproate; use of psychotropic medications (other than benzodiazepines) within 1 day of randomisation; fluoxetine treatment in the past 4 weeks; and previous enrolment in an aripiprazole clinical study.

Written informed consent was obtained from the patient or a legally acceptable representative. The study protocol, procedures and consent statement were approved by the institutional review boards of all participating sites.

Study design

In this 12-week, multicentre, double-blind comparative trial, patients were randomised to receive either aripiprazole or haloperidol, using a fixed randomisation schedule allocating patients between the two treatment arms in a 1:1 ratio.

Phase 1 (weeks 1–3)

Following a wash-out period of 1–3 days, patients fulfilling the entry criteria were randomised to receive aripiprazole 15 mg per day or haloperidol 10 mg per day. At the end of week 1 or 2, patients showing a poor response to therapy, measured using the Clinical Global Impression (Spearing *et al*, 1997) and defined as a Clinical Global Impression – Bipolar Disorder (CGI–BP) Improvement (mania) score of 3 or above, could have their daily dosage increased to aripiprazole 30 mg or haloperidol 15 mg. Patients intolerant of the higher dosage could return to the initial lower dosage. Patients unable to tolerate 15 mg aripiprazole or 10 mg haloperidol discontinued the trial.

At the end of this 3-week period, patients with a CGI–BP Severity (mania) score of 4 or more (moderately ill or worse) or a Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery–Åsberg, 1979) score of 18 or more discontinued the trial.

Phase 2 (weeks 4–12)

Patients remaining in the study throughout weeks 4–12 continued with the treatment and dose regimen prescribed in week 3. The dosage of study medication could be decreased from 30 mg to 15 mg per day for aripiprazole and from 15 mg to 10 mg per day for haloperidol if necessary for tolerability, but not increased. If this lower dosage was not tolerated, the patient was withdrawn from the study.

Patients were also withdrawn if there was a lack of maintained effect (originally observed at week 3), or intolerance as

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indicated by any of the following: increase in CGI–BP Severity (mania) score from previous assessment, confirmed on two consecutive visits; hospitalisation for manic or depressive symptoms; need for additional or increased doses of psychotropic medications; MADRS score of 18 or more; or need for concomitant medication for symptomatic treatment of side-effects.

Efficacy assessments

The primary efficacy outcome was an effectiveness measure of response. Responders were defined as patients who remained in therapy at week 12 and had a 50% or greater improvement from baseline in YMRS total score. Assessments (YMRS, CGI–BP and MADRS) were made at baseline, days 4, 7, 10 and 14, then weekly until week 6 and every 2 weeks during weeks 6–12. Secondary efficacy measures included the response rate at week 3 (i.e. remaining in treatment with a 50% or greater improvement in YMRS total score from baseline) and time to discontinuation for any reason.

Safety and tolerability assessments

Adverse event reports were gathered throughout the study and evaluated by investigators for severity and likely relationship to study medication. Extrapyramidal symptoms were evaluated using the Simpson–Angus Scale (SAS; Simpson & Angus, 1970), the Barnes Akathisia Scale (BAS; Barnes, 1989) and the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1975), administered at baseline and at weeks 1 (except for AIMS), 2, 3, 6 and 12.

Patients' vital signs were measured at screening and each assessment visit during the study. Electrocardiograms, serum prolactin concentrations, routine laboratory tests, body weight measurements and physical examinations were performed at screening and at weeks 3, 8 (except physical examinations) and 12.

Concomitant medications

The following medications were prohibited during the study: antipsychotic agents, mood stabilisers/anti-epileptics, lithium, benzodiazepines (except lorazepam 4 mg per day or oxazepam 60 mg per day during days 1–4, and lorazepam 2 mg per day or oxazepam 30 mg per day during days 5–10), antidepressants and all other psychotropic drugs. Anticholinergic agents were not permitted for symptomatic or prophylactic treatment of extrapyramidal symptoms during the study, because of their potential to mask differences in treatment tolerability between the two agents.

Statistical methods

The primary outcome measure (number of patients on treatment and in response at week 12) was evaluated by the Cochran–Mantel–Haenszel test (unstratified) using the safety sample (patients randomised to treatment and who took at least one dose of study medication). Patients who discontinued the study during the 12-week phase and patients without a 50% or greater improvement in YMRS total score at week 12 were considered to be non-responders. Response rates at week 3 were also evaluated using the Cochran–Mantel–Haenszel test. Change from baseline measures were evaluated by analysis of covariance (ANCOVA) with treatment as main effect and baseline value as covariate. All efficacy analyses were performed on the last observation carried forward (LOCF) and observed cases data-sets. Time to discontinuation was evaluated using the log rank test.

RESULTS

Patient characteristics

The study was conducted at 76 international centres. A total of 347 patients were randomised to medication (aripiprazole, n=175; haloperidol, n=172). Of those, 344 received at least one dose of study medication (safety sample); 338 patients received study medication and had at least one post-baseline efficacy rating (efficacy sample). The progress of participants through the trial is illustrated in Fig. 1. Most randomised patients were

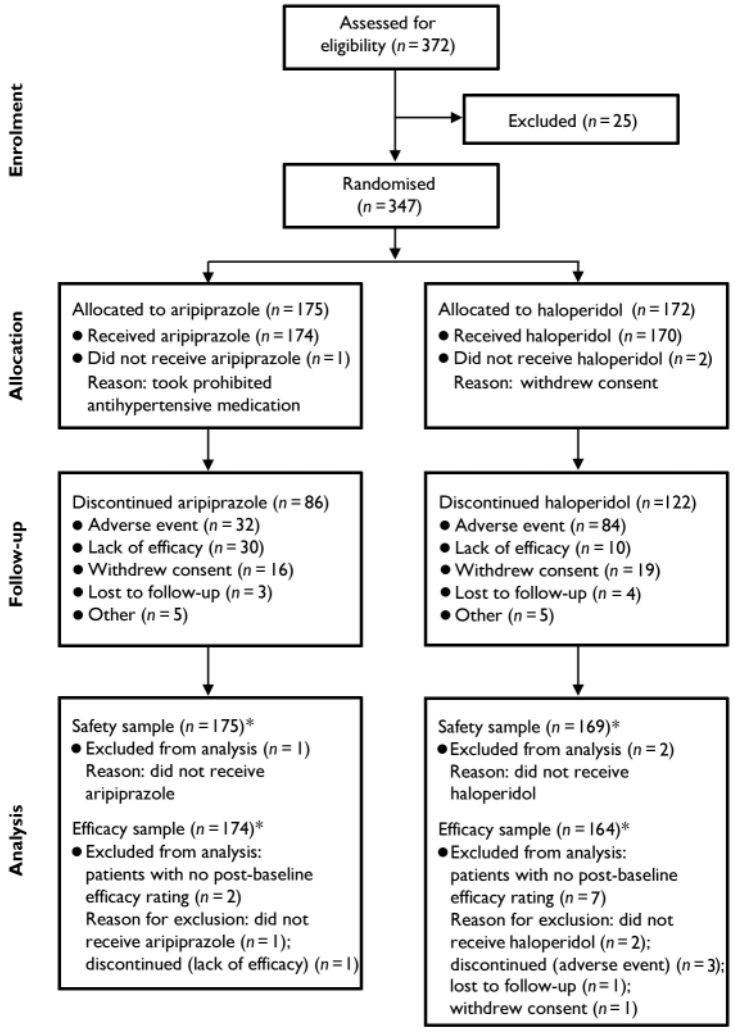

Fig. 1 CONSORT diagram showing progress of participants through the trial. *One patient was randomised to haloperidol but treated with aripiprazole.

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Table 1 Baseline demographic characteristics of randomised patients

	Aripiprazole group	Haloperidol group	Total
Patients, *n*	175	172	347
Male/female, *n*/*n*	76/99	57/115	133/214
Age, years: mean (s.e.)	42.6 (0.9)	41.0 (0.9)	41.8 (0.6)
Body weight, kg: mean (s.e.)[1]	74.6 (1.1)	72.3 (1.1)	73.5 (0.8)
Current episode, *n* (%)			
Manic	161 (92)	148 (86)	309 (89)
Mixed	14 (8)	24 (14)	38 (11)
YMRS total score: mean (s.e.)	31.1 (0.5)	31.5 (0.6)	31.3 (0.4)
CGI–BP Severity (mania) score: mean (s.e.)[2]	5.0 (0.1)	4.9 (0.1)	5.0 (0.0)
MADRS total score: mean (s.e.)[2]	9.2 (0.4)	9.9 (0.4)	9.6 (0.3)

CGI–BP, Clinical Global Impression – Bipolar Disorder; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.
1. Haloperidol, *n*=169; total, *n*=344.
2. Aripiprazole, *n*=174; haloperidol, *n*=171; total, *n*=345.

female (62%) and the majority of patients presented with a manic index episode (89%). Mean baseline YMRS and CGI–BP Severity (mania) scores were similar in the two treatment arms (Table 1). At week 3, the average daily dosage of aripiprazole was 22.6 mg and of haloperidol was 11.6 mg. At week 12, average daily dosages were 21.6 mg for aripiprazole and 11.1 mg for haloperidol.

Patient disposition

Overall, 229 randomised patients (66.0%) completed the first 3 weeks of treatment: 134 (76.6%) of the 175 patients receiving aripiprazole and 95 (55.2%) of the 172 patients receiving haloperidol ($P<0.001$) – a difference of 21.3% (95% CI 11.4–30.9). At the end of the second phase, 89 (50.9%) and 50 (29.1%) patients had completed 12 weeks of aripiprazole or haloperidol treatment, respectively ($P<0.001$; difference 21.8%, 95% CI 11.4–31.7).

Efficacy

At week 12, aripiprazole showed significantly greater response rates compared with haloperidol (Fig. 2). In the aripiprazole group, 49.7% of patients continued to respond to therapy, whereas the response rate in the haloperidol arm was 28.4% ($P<0.001$). Both aripiprazole and haloperidol treatment produced marked improvements in mean YMRS total scores from baseline (Fig. 3). At week 12, YMRS total scores showed mean reductions of 19.9 with aripiprazole and 18.2 with haloperidol from baseline (LOCF analysis; $P=0.226$). Among patients remaining in therapy, aripiprazole produced a significantly greater mean reduction in YMRS total score at week 12 than haloperidol (−29.0 *v.* −27.4; $P=0.044$). The proportion of patients in remission (YMRS total score <12) at week 12 was significantly higher in the aripiprazole group than in the haloperidol group (50% *v.* 27%; $P<0.001$).

Treatment with aripiprazole and haloperidol was associated with marked mean reductions in CGI–BP Severity (mania) scores (Fig. 4). Over the 12-week study, aripiprazole and haloperidol reduced CGI–BP Severity (mania) scores by 2.58 and 2.27 points, respectively (LOCF analysis; $P=0.095$). Mean decreases in CGI–BP Severity (mania) scores were also similar in the two groups using observed cases analysis (aripiprazole −3.71, haloperidol −3.55). Other efficacy measures showed similar changes in the aripiprazole and haloperidol groups with both LOCF and observed cases analyses (Table 2).

At week 3 of the first phase, 50.9% of aripiprazole-treated patients responded to treatment compared with 42.6% of haloperidol-treated patients ($P=0.126$; RR=1.19, 95% CI 0.95–1.50) (see Fig. 2). An initial rapid reduction in YMRS was noted in the first 3 weeks of therapy (aripiprazole −15.7, haloperidol −15.7; LOCF), with responses sustained and

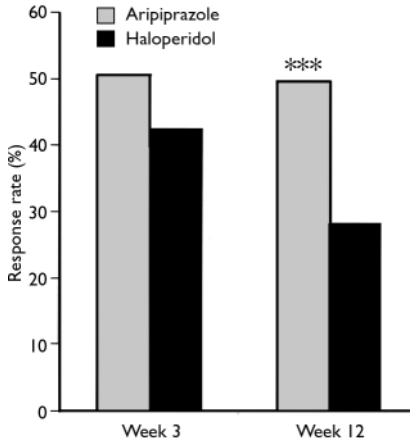

Fig. 2 Response rates to treatment with aripiprazole and haloperidol at weeks 3 and 12 (***$P<0.001$ *v.* haloperidol).

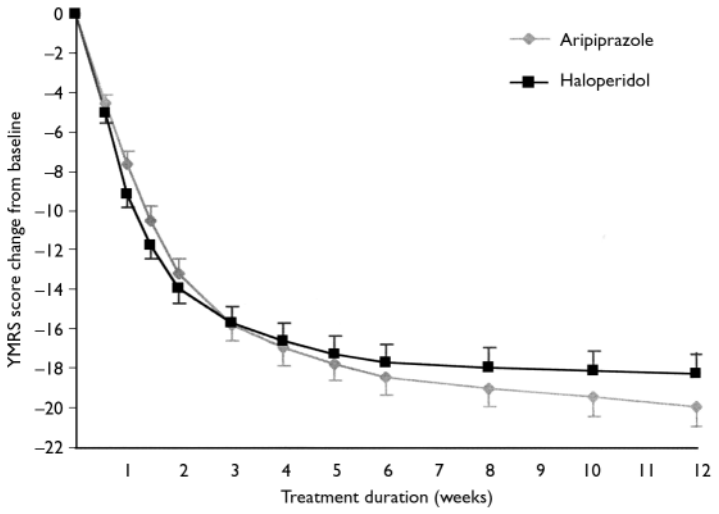

Fig. 3 Change in Young Mania Rating Scale (YMRS) scores from baseline to week 12 (last observation carried forward analysis): means and standard errors. Mean scores at baseline were 31.1 (s.e.=0.6) for the aripiprazole group and 31.5 (s.e.=0.6) for the haloperidol group.

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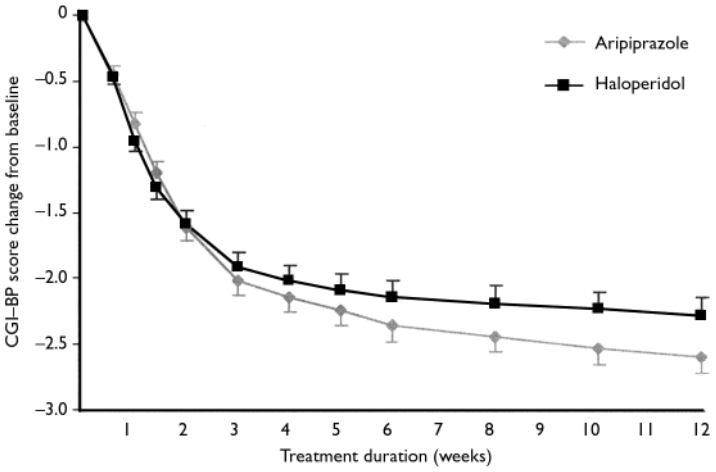

Fig. 4 Change in Clinical Global Impression – Bipolar Disorder (CGI–BP) Severity (mania) score from baseline (last observation carried forward analysis): means and standard errors. Mean scores at baseline were 4.96 (s.e.=0.07) for the aripiprazole group and 4.94 (s.e.=0.07) for the haloperidol group.

Table 2 Mean change in Young Mania Rating Scale and Clinical Global Impression – Bipolar Disorder Severity of Illness scores from baseline at week 12

Assessment	Data-set[1]	Aripiprazole Mean (s.e.)	Haloperidol Mean (s.e.)
YMRS total	LOCF	−19.93 (0.98)	−18.22 (1.02)
	OC	−28.98 (0.45)*	−27.44 (0.60)
CGI–BP Severity (mania)	LOCF	−2.58 (0.13)	−2.27 (0.13)
	OC	−3.71 (0.08)	−3.55 (0.10)
CGI–BP Severity (depression)	LOCF	0.20 (0.07)	0.27 (0.08)
	OC	−0.02 (0.06)	0.16 (0.08)
CGI–BP Severity (overall)	LOCF	−2.01 (0.12)*	−1.60 (0.12)
	OC	−3.09 (0.09)	−2.91 (0.11)

CGI–BP, Clinical Global Impression – Bipolar Disorder; LOCF, last observation carried forward; OC, observed cases; YMRS, Young Mania Rating Scale.
1. LOCF: aripiprazole n=173 (YMRS, n=174), haloperidol n=164 (YMRS, n=162); OC: aripiprazole n=89 (YMRS, n=90), haloperidol n=50.
*$P<0.05$ *v.* haloperidol.

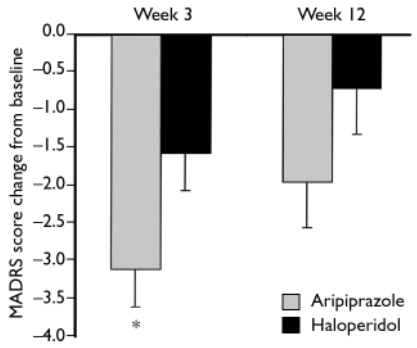

Fig. 5 Change in Montgomery–Åsberg Depression Rating Scale (MADRS) total scores from baseline at weeks 3 and 12 (last observation carried forward analysis): means and standard errors.
*P=0.027 *v.* haloperidol.

improving over subsequent weeks of treatment. Marked reductions in CGI–BP Severity scores for mania (aripiprazole −2.0, haloperidol −1.9; LOCF) and overall bipolar illness (aripiprazole −1.6, haloperidol −1.4; LOCF) were also observed at week 3 with both treatments, whereas CGI–BP depression scores showed minimal change from baseline in either group (aripiprazole 0.0, haloperidol 0.1; LOCF). The proportion of patients in remission (YMRS total score <12) was 35% with aripiprazole and 31% with haloperidol treatment at week 3. Differences between the groups were not statistically significant for any of these assessments.

Depression ratings

Mean baseline MADRS total scores were similar in both treatment groups (aripiprazole 9.24, haloperidol 9.75; LOCF). Significantly more patients demonstrated a 50% or greater decrease in MADRS total score from baseline with aripiprazole than with haloperidol at week 3 (51% *v.* 37%; P=0.007) and week 12 (51% *v.* 33%; P=0.001). Aripiprazole treatment produced significantly greater reductions in depressive symptoms compared with haloperidol, as measured by the mean change in MADRS total score at week 3 (aripiprazole −3.1, haloperidol −1.6; P=0.027; LOCF) (Fig. 5). Statistically significant ($P<0.05$) differences between the groups were observed at weeks 3 through 6, and the week 8 results approached significance (P=0.051). Improvements in depressive symptoms with aripiprazole were sustained at week 12, but did not reach significance compared with haloperidol (aripiprazole −2.0, haloperidol −0.7; P=0.150; LOCF).

Patients experiencing a switch to depression were defined *post hoc* as those whose CGI–BP depression sub-scale scores worsened by ⩾2 points (CGI–BP depression scores were available for 337 of the participants). Of 173 patients treated with aripiprazole, 19 (11.0%) switched to depression; of 164 on haloperidol, 29 (17.7%) switched to depression (RR=1.61, 95% CI 0.94–2.76; P=0.079).

Safety

Adverse events

The most frequently reported adverse events during the study are shown in Table 3. The most frequent adverse events leading to discontinuation (⩾10% in at least one of the two treatment arms) were extrapyramidal symptoms (haloperidol, n=32 (18.9%); aripiprazole, n=5 (2.9%)), and akathisia (haloperidol, n=24 (14.2%); aripiprazole, n=9 (5.1%)). Overall, 18 patients had a serious adverse event during the study or within 30 days of discontinuation (aripiprazole, n=6; haloperidol, n=12). In general these were related to the underlying diagnosis. One patient in the haloperidol group discontinued treatment because of liver damage considered possibly related to study medication.

Patient discontinuations

Overall, 208 patients (59.9%) discontinued treatment during the 12-week study: haloperidol, n=122 (70.9%); aripiprazole,

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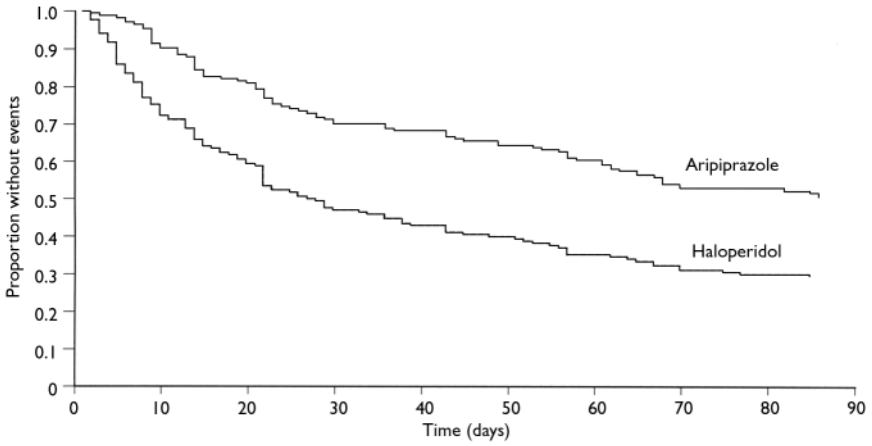

Fig. 6 Time to discontinuation of aripiprazole and haloperidol therapy for all reasons. Data are expressed as proportion of patients without events over time and numbers of patients at risk per time point are provided together with hazard ratio evaluation (unstratified log rank, $P<0.001$).

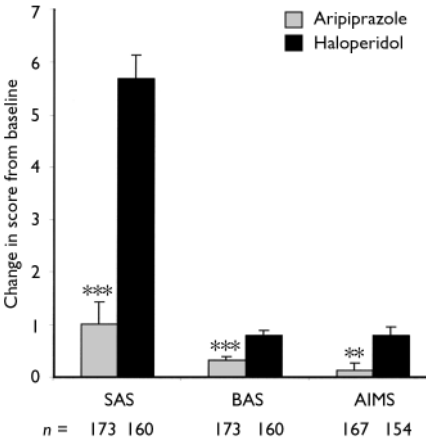

Fig. 7 Change in extrapyramidal symptom rating scale scores from baseline at week 12 (last observation carried forward analysis) on the Simpson–Angus Scale (SAS; ***$P<0.001$ *v.* haloperidol), the Barnes Akathisia Scale (BAS; ***$P<0.001$ *v.* haloperidol) and the Abnormal Involuntary Movement Scale (AIMS; **$P=0.002$ *v.* haloperidol).

Table 3 Incidence of treatment-emergent adverse events (⩾10% in either treatment arm)

Adverse event	Aripiprazole ($n=175$) %	Haloperidol ($n=169$) %
Insomnia	13.7	7.1
Akathisia	11.4	23.1
Depression	11.4	14.2
Headache	10.9	11.8
Extrapyramidal syndrome	9.1	35.5
Tremor	6.9	10.1

$n=86$ (49.1%). During the study, time to discontinuation for any reason was significantly greater for patients receiving aripiprazole than those receiving haloperidol ($P<0.001$) (Fig. 6). The hazard ratio for discontinuation of haloperidol over aripiprazole was 1.96 (95% CI 1.48–2.59). In addition, 13 patients (aripiprazole, $n=5$; haloperidol, $n=8$) who completed the first 3 weeks of treatment did not enter the second phase of the study (weeks 4–12).

In weeks 1–3 of the study, 118 patients (34.0%) discontinued treatment: haloperidol, $n=77$ (44.8%); aripiprazole, $n=41$ (23.4%). The most common reason for discontinuation was experiencing adverse events (20.2%), which showed a marked difference in incidence between the groups (aripiprazole, 9.7%; haloperidol, 30.8%). Other reasons for discontinuation included patient withdrawal of consent (6.1%) and lack of efficacy (5.2%). In weeks 4–12 of the study, 77 patients (22.2%) discontinued treatment: haloperidol, $n=37$ (21.5%); aripiprazole, $n=40$ (22.9%). The most common reason for discontinuation was experiencing adverse events (overall, 11.5%; aripiprazole, 8.6%; haloperidol, 14.5%). Other reasons for discontinuation were similar in incidence to those in weeks 1–3.

Extrapyramidal adverse events

The incidence of extrapyramidal adverse events in the haloperidol group (62.7%) was more than double that in the aripiprazole group (24.0%). Extrapyramidal syndrome and akathisia were the most frequently reported of these adverse events, and were much more frequent with haloperidol than with aripiprazole (see Table 3). The SAS, BAS and AIMS scores all showed minimal changes from baseline to end-point with aripiprazole. Significantly greater mean increases (i.e. worsening) in scores were observed with haloperidol compared with aripiprazole ($P\leqslant0.002$) (Fig. 6). Rating scale scores at week 3 also showed minimal mean changes from baseline with aripiprazole treatment, and larger mean increases with haloperidol treatment (SAS: aripiprazole 0.65, haloperidol 4.85; BAS: aripiprazole 0.15, haloperidol 0.57; AIMS: aripiprazole 0.04, haloperidol 0.50; observed cases analysis).

Body weight

The mean change in weight from baseline at week 12 (LOCF) was not significantly different between the aripiprazole (+0.27 kg) and haloperidol (−0.10 kg) groups. Small mean changes in weight were also observed from baseline to week 3 (observed cases) with both aripiprazole (−0.08 kg) and haloperidol (+0.28 kg).

When stratified by mean body mass index (BMI) at baseline, patients with a relative high baseline BMI (>27 kg/m^2) lost weight during aripiprazole treatment (−0.86 kg), compared with an increase in weight with haloperidol treatment (0.41 kg). Patients with the lowest baseline BMI (<23 kg/m^2) showed increases in weight with both aripiprazole (+1.38 kg) and haloperidol (+0.64 kg) treatment (observed cases analyses).

Serum prolactin levels

Serum prolactin levels showed a mean decrease from baseline in the aripiprazole group (−13.4 ng/ml, −284.1 mU/l), and a mean increase in the haloperidol group (7.7 ng/ml, −163.2 mU/l) at week 12; this difference was statistically significant ($P<0.001$). Similar changes in prolactin levels were observed at week 3 (aripiprazole −12.5 ng/ml (−265 mU/l), haloperidol 15.5 ng/ml (328.6 mU/l); observed cases analysis). In the haloperidol group, 57.1% of patients experienced serum prolactin levels above the upper limit of

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normal compared with 14.1% in the aripiprazole group.

Electrocardiography

Electrocardiogram (ECG) analysis showed an on-treatment QT_c value of 450 ms or more and a 10% or greater increase from baseline for 4 patients (2.7%) in the haloperidol group and 5 patients (3.0%) in the aripiprazole group, calculated using Bazett's (1920) formula, and no patient in either group using the Food and Drug Administration (2000) Neuropharmacological Division formula. There was no discontinuation owing to ECG abnormalities.

Vital signs and laboratory analyses

No clinically meaningful difference was detected in vital sign measurements, laboratory abnormalities or cholesterol levels between the aripiprazole and haloperidol treatment groups.

DISCUSSION

The results of this study demonstrate that aripiprazole offers superior effectiveness to haloperidol in the treatment of patients with acute mania for up to 12 weeks. Aripiprazole demonstrated similar efficacy, together with improved sustained response rates and tolerability, compared with haloperidol, indicative of improved effectiveness.

Haloperidol was chosen as an active comparator in this study because of the extensive study of this drug as an effective treatment of the manic symptoms, including psychosis, of acute mania (Garfinkel *et al*, 1980). Several atypical antipsychotic studies examining treatment of acute mania in patients with bipolar disorder have used haloperidol as an active control (Segal *et al*, 1998; Tohen *et al*, 2003; McIntyre *et al*, 2005; Smulevich *et al*, 2005). In these studies, haloperidol-treated patients showed similar improvements in mania rating scale scores to those receiving atypical (olanzapine or risperidone) therapy (Segal *et al*, 1998; Tohen *et al*, 2003), and remission rates were similar at week 6 and week 12 with olanzapine and haloperidol in the comparison study (Tohen *et al*, 2003).

Treatment effectiveness

The primary outcome measure in our study showed that a significantly greater number of aripiprazole-treated patients continued to respond to treatment at week 12, as measured by a 50% or greater improvement in YMRS total score from baseline and remaining in therapy, compared with patients treated with haloperidol (49.7% *v.* 28.4%, $P<0.001$). This outcome measure is affected by both efficacy and tolerability, and was chosen to reflect the combination of efficacy, safety and tolerability required for a treatment to be effective in clinical practice.

Analysis of YMRS and CGI measures showed similar efficacy improvements with both aripiprazole and haloperidol treatment. Total YMRS scores showed marked improvements with both aripiprazole and haloperidol, which were sustained over the 12-week study. Both treatments provided rapid control of manic symptoms, with marked decreases in YMRS scores from baseline observed with aripiprazole and haloperidol at week 3. The improvements in YMRS scores seen with aripiprazole therapy in our study are comparable with those observed in 12-week comparison studies of haloperidol with olanzapine (Tohen *et al*, 2003), risperidone (Smulevich *et al*, 2005) and quetiapine (McIntyre *et al*, 2005). Reductions in YMRS scores with aripiprazole at week 3 were also similar to those observed with olanzapine in a 3-week comparison with divalproex (Tohen *et al*, 2002) and a 4-week, risperidone *v.* haloperidol study (Segal *et al*, 1998).

The similar improvements in efficacy scores observed with aripiprazole and haloperidol treatment in this study are consistent with findings from comparison studies with olanzapine (Tohen *et al*, 2003) and risperidone (Segal *et al*, 1998), which also showed similar improvements with haloperidol and atypical therapy. The difference between the efficacy and effectiveness results observed in our study highlights the impact that tolerability has on overall treatment effectiveness. The superior maintained response observed with aripiprazole at week 12 reflects the increased ability of patients to continue taking aripiprazole compared with haloperidol, which is a pragmatic outcome measure with high external validity.

Depressive symptoms

It has been suggested that the use of typical antipsychotic therapy might worsen or induce depression in this patient population (Vieta, 2003). In this study, fewer patients receiving aripiprazole experienced a switch to depression compared with those receiving haloperidol (11.0% *v.* 17.7%), although this did not reach statistical significance. Similar findings have been reported in studies with olanzapine and quetiapine (Brecher & Huizar, 2003; Tohen *et al*, 2003), suggesting that atypical antipsychotics may offer benefits over typical agents in preventing or delaying the switch to depression in patients with bipolar disorder.

Aripiprazole was associated with significant improvements in depressive symptoms over the course of the study. Significantly more patients demonstrated a 50% or greater decrease in MADRS total score from baseline with aripiprazole than with haloperidol at week 3 and week 12. Reductions in MADRS total scores from baseline occurred rapidly after the start of aripiprazole therapy, with significant differences from haloperidol observed at week 3, although statistical significance was not maintained at week 12.

Treatment adherence

Full adherence to treatment is associated with improved long-term patient outcome (Tsai *et al*, 2001); higher recovery rates and shorter time to recovery (Keck *et al*, 1998); and reduced hospitalisation rates, days in hospital and treatment costs (Svarstad *et al*, 2001). Treatment discontinuation is often the result of unacceptable side-effects associated with therapy (Sachs & Rush, 2003). Treatment safety and tolerability are, therefore, key factors in patient outcome. In this study, the time to discontinuation for any reason was significantly greater for patients receiving aripiprazole than for those treated with haloperidol ($P<0.001$). Hazard ratio calculations suggest that patients given haloperidol were almost twice as likely to discontinue therapy as those given aripiprazole ($P<0.001$), adverse events being the most frequent reason for discontinuation.

Adverse events

Extrapyramidal syndrome, akathisia and tremor are common in patients receiving typical antipsychotic agents. In this study, patients taking haloperidol reported a four-fold increased incidence of extrapyramidal symptoms compared with patients taking aripiprazole (36% *v.* 9%). Although anticholinergic therapy was not allowed in this study, a greater percentage of patients taking haloperidol received

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concomitant medications for treatment of extrapyramidal symptoms. Despite this prohibition, the rate of such symptoms with haloperidol was comparable with rates reported for lower doses of haloperidol in other 12-week acute mania trials which allowed concomitant anticholinergic use (Tohen *et al*, 2003; McIntyre *et al*, 2005; Smulevich *et al*, 2005).

The reduced potential for extrapyramidal symptoms observed with aripiprazole is consistent with effects seen in previously published trials in schizophrenia and acute mania (Kasper *et al*, 2003; Keck *et al*, 2003; Marder *et al*, 2003; Pigott *et al*, 2003). This, and the lack of hyperprolactinaemia observed with aripiprazole in this study, may be explained by this drug's unique mode of action as a dopamine D_2 partial agonist (Lieberman, 2004); these agonists act as functional antagonists in areas of high dopamine concentrations but not in areas of normal dopamine levels, such as the nigrostriatal and tubero-infundibular pathways, thus reducing symptoms without producing movement disorders or elevated prolactin levels. In regions of low dopamine concentration, a D_2 partial agonist will show functional agonist activity.

Minimal mean changes in body weight were observed with both aripiprazole and haloperidol over the 12-week study. Lack of weight gain is an important treatment consideration, given the adverse effects of weight gain on treatment adherence and its implications for long-term patient health. Weight gain and obesity are established risk factors for cardiovascular disease and diabetes, and are associated with dyslipidaemia (National Institutes of Health, 1998). Clinical experience with other atypical antipsychotics has shown that the likelihood of weight gain differs markedly between different agents (American Diabetes Association *et al*, 2004). In addition, among the atypical antipsychotics, some have been attributed with an increased risk of diabetes (American Diabetes Association *et al*, 2004).

Study limitations

The findings of this study should, however, be considered in the light of the following limitations. The overall study completion rates could limit the generalisability of the results. The lack of anticholinergic medication use specified by the study protocol and the limited dose range permitted for haloperidol could have affected the results through a possible impact on the ability of patients to tolerate haloperidol. It may also limit the extent to which the haloperidol findings can be generalised to clinical practice. However, extrapyramidal symptom rates with haloperidol were similar to those reported in other 12-week studies that evaluated lower doses of haloperidol and permitted the use of anticholinergic medications to manage these symptoms (Tohen *et al*, 2003; McIntyre *et al*, 2005; Smulevich *et al*, 2005). The use of an atypical antipsychotic as a comparator in future studies would be expected to overcome the tolerability limitations associated with haloperidol, and reflect the increasingly widespread use of atypicals for the treatment of mania (Vieta, 2003).

CLINICAL IMPLICATIONS

- Aripiprazole provided improvements in efficacy sustained over 12 weeks in patients with bipolar I disorder presenting with a manic or mixed episode.
- Higher adherence rates and better tolerability compared with haloperidol suggest aripiprazole treatment may be well tolerated during prolonged treatment.
- Significantly greater sustained response rates and tolerability observed with aripiprazole suggest it may offer a more effective treatment option than haloperidol.

LIMITATIONS

- The overall study completion rates could limit the generalisability of the results.
- The protocol-specified lack of anticholinergic medication use and the limited dosage range permitted for haloperidol could limit the applicability of haloperidol findings to clinical practice.
- Low tolerability, and hence a large attrition rate, limits the usefulness of haloperidol as comparator.

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