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ARTICLE

Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia

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Abstract

Aripiprazole is a novel atypical antipsychotic for the treatment of schizophrenia. It is a D_2 receptor partial agonist with partial agonist activity at 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. The long-term efficacy and safety of aripiprazole (30 mg/d) relative to haloperidol (10 mg/d) were investigated in two 52-wk, randomized, double-blind, multicentre studies (using similar protocols which were prospectively identified to be pooled for analysis) in 1294 patients in acute relapse with a diagnosis of chronic schizophrenia and who had previously responded to antipsychotic medications. Aripiprazole demonstrated long-term efficacy that was comparable or superior to haloperidol across all symptoms measures, including significantly greater improvements for PANSS negative subscale scores and MADRS total score ($p < 0.05$). The time to discontinuation for any reason was significantly greater with aripiprazole than with haloperidol ($p = 0.0001$). Time to discontinuation due to adverse events or lack of efficacy was significantly greater with aripiprazole than with haloperidol ($p = 0.0001$). Aripiprazole was associated with significantly lower scores on all extrapyramidal symptoms assessments than haloperidol ($p < 0.001$). In summary, aripiprazole demonstrated efficacy equivalent or superior to haloperidol with associated benefits for safety and tolerability. Aripiprazole represents a promising new option for the long-term treatment of schizophrenia.

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Key words: Aripiprazole, atypical antipsychotic, dopamine partial agonist, long-term treatment, schizophrenia.

Introduction

Schizophrenia is a chronic illness requiring lifelong treatment. Approximately 50% of patients with schizophrenia will suffer a psychotic relapse within a year of discontinuing previously effective pharmacotherapy (Crow et al., 1986; Kane et al., 1982; Weiden and Glazer, 1997). Antipsychotic medication represents the cornerstone of current therapeutic interventions for schizophrenia. Specific antipsychotic selection for the treatment of schizophrenia is an individualized risk–benefit decision based on both short-term and long-term issues, including relative clinical efficacy, safety, and tolerability of available antipsychotic medication (Kasper, 1999; Kasper et al., 1999a). The selection of an antipsychotic agent and its dose represents a critical influence on the subsequent prognosis, complications, and compliance for patients with schizophrenia (Kasper, 1998; Sussman, 2001).

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Positive symptoms are more likely to improve than are the negative symptoms of schizophrenia during treatment with typical antipsychotic medication. In addition, typical antipsychotic agents are often associated with limited tolerability due to their propensity to elicit acute and chronic dystonic reactions as well as side-effects related to hyperprolactinaemia. In contrast, treatment with atypical agents has been associated with additional benefits including enhanced improvement in negative symptoms and potential amelioration of the neurocognitive deficits that are characteristic of schizophrenia (Kasper, 2000). The atypical antipsychotics also have consistently demonstrated less propensity for extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) in comparison to typical agents. Yet some potentially serious adverse events (AEs) have been linked to treatment with currently available atypical antipsychotics including enhanced weight gain, hyperprolactinaemia, and an apparently adverse impact on lipid and glucose metabolism (Kasper et al., 1999a). Additional AEs seen with certain atypical antipsychotics include QT_c prolongation, potentially leading to torsade de pointes, a rare but potentially fatal ECG abnormality.

Existing typical and atypical antipsychotic agents are all dopamine D_2 receptor antagonists. While D_2 antagonist activity is likely to be critical in conveying antipsychotic efficacy in the treatment of the positive symptoms associated with schizophrenia, D_2 receptor occupancy is also implicated in the emergence of many of the adverse effects associated with antipsychotic administration (Kasper et al., 1999b). The considerable safety and tolerability liabilities associated with D_2 receptor antagonism led to the investigation of partial D_2 agonists as a potential strategy for preserving antipsychotic efficacy yet attenuating and perhaps abolishing some of the AEs elicited by full D_2 receptor antagonism (Iyer et al., 1998; Lahti et al., 1998; Sramek et al., 1998). In the presence of low dopaminergic tone, a partial agonist at the D_2 receptor will act as a functional agonist, whereas when high dopaminergic tone exists, a partial D_2 agonist will act as a functional antagonist at the receptor site.

Aripiprazole is a novel antipsychotic agent distinguished from other atypical antipsychotics by its unique mechanism of action. While typical agents and other atypical agents act as antagonists at dopamine D_2 receptors, aripiprazole exhibits partial agonist activity at D_2 receptors (Burris et al., 2002). In addition, aripiprazole acts as a partial agonist at serotonin 5-HT_{1A} receptors (Jordan et al., 2002) and as an antagonist at 5-HT_{2A} receptors (McQuade et al., 2002). As a D_2 partial agonist, aripiprazole acts as a functional antagonist in areas of high dopamine levels, such as the mesolimbic pathway, but not in areas of normal dopamine levels, like the nigrostriatal and tuberoinfundibular pathways. Thus aripiprazole is expected to reduce the positive symptoms of schizophrenia without producing movement disorders or elevated prolactin levels. In regions of low dopamine concentration, such as the mesocortical pathway, aripiprazole acts as a functional agonist. Partial agonist activity at 5-HT_{1A} receptors has been linked to anxiolytic properties (Glennon and Dukat, 1995), and may also be associated with an improvement in depressive, cognitive, and negative symptoms in patients with schizophrenia (Millan, 2000). It is also thought that 5-HT_{2A} receptor antagonist activity is linked with favourable effects on negative symptoms of schizophrenia (Leysen et al., 1993; Rao and Möller, 1994), and may improve cognition and depressive symptoms (Kasper et al., 1999b). Aripiprazole's unique pharmacodynamic profile appears to be most consistent with functional stabilization of the dopamine and serotonin systems (Carlsson et al., 2000), acting as a dopamine–serotonin system stabilizer. As such, aripiprazole would be expected to be efficacious in treating a broad range of schizophrenic symptoms, yet also provide a potentially superior tolerability and safety profile in comparison to other available antipsychotic agents. Previous studies have demonstrated the efficacy of aripiprazole in the acute (up to 6 wk) treatment of schizophrenia with a low risk of treatment-emergent side-effects (Kane et al., 2002; Potkin et al., 2003). The current studies investigated the relative efficacy, safety, and tolerability of aripiprazole and haloperidol during long-term maintenance treatment of patients with chronic schizophrenia after the occurrence of an acute relapsing episode.

Patients and methods

Patients

The studies were conducted in accordance with Good Clinical Practice, US Food and Drug Administration (FDA) regulations, and the Declaration of Helsinki. All patients provided written informed consent for study participation; in addition, written informed consent for study participation was also obtained by the next of kin or caregiver if required by the local Institutional Review Board.

Men and non-pregnant, non-lactating women aged between 18 and 65 yr who met DSM-IV criteria for schizophrenia (APA, 1994) and who were experiencing an acute relapse were eligible for enrolment in the

studies. Additional primary enrolment criteria for the studies included: (a) history of previous response to antipsychotic medication (other than clozapine) and not considered refractory to typical antipsychotic medication; (b) history of continuous treatment on an outpatient basis for at least one 3-month period during the previous year; and (c) a total score $\geqslant 60$ on the Positive and Negative Syndrome Scale (PANSS) with a score $\geqslant 4$ (moderate) on any two of the four PANSS items that constitute the PANSS psychotic items subscale at the time of the baseline (week 0) study visit.

Subjects receiving oral antipsychotic medication at the time of the screening appointment were to complete at least a 5-d placebo washout period prior to the baseline study visit. For patients receiving depot antipsychotic therapy prior to study entry, a washout period of at least one depot cycle plus 1 wk after the administration of the last depot injection was necessary prior to the baseline study visit. If clinically indicated (e.g. in cases of clinical deterioration judged detrimental to the patient's well-being), a shorter washout period was permitted. Potential subjects were also required to be considered medically stable as determined by the results from a physical examination, ECG and routine laboratory testing (including serum chemistry, urine toxicology, and pregnancy test) completed during the screening and washout period prior to entry into the double-blind phase of the study.

Study exclusion criteria included: (a) presence of suicidal ideation or considered to be at significant suicide risk by the investigator; (b) initial episode of schizophrenia; (c) presence of a psychiatric disorder other than schizophrenia that required pharmacotherapy; (d) presence of any significant neurological condition (other than medication-induced EPS or TD) that required intermittent or maintenance concomitant treatment; (e) considered likely to require prohibited concomitant medication and/or medication that might interfere with the analysis or metabolism of the study drug during the double-blind phase of the study; and/or (f) currently or recently (<1 month) meeting DSM-IV criteria for psychoactive substance dependence. Patients who had participated in a previous aripiprazole study or who had used an investigational medication within 4 wk of the screening study visit were also excluded from the study.

Study design

These two active-controlled, randomized, double-blind studies were prospectively designed for pooled data evaluation. Study 1 was conducted at 33 centres in the USA and Study 2 at 137 centres worldwide.

Patients meeting DSM-IV criteria for schizophrenia and in acute relapse who initially met all of the inclusion and none of the exclusion criteria for study entry were enrolled in the placebo washout period ($\geqslant 5$ days) of the study. Patients who successfully completed the washout period were re-evaluated at the baseline visit and, if still eligible for further study participation, were randomly assigned in a 2:1 ratio to aripiprazole (30 mg) or haloperidol (5 mg, days 1–3; 10 mg, day 4 onwards). The study medication was administered orally once daily after breakfast. After completion of the first week of the double-blind, acute treatment phase, a one-time dose reduction was permitted as determined by clinical judgement (20 mg for aripiprazole or 7 mg for haloperidol). Symptoms and safety assessments were serially obtained at screening, baseline (visit 1, at the end of the washout period) and throughout the double-blind treatment phase (visits 2–21 over a 52-wk period). After randomization to the aripiprazole or haloperidol treatment arm, patients were followed for a maximum of 52 wk (or until early discontinuation) during the study.

Efficacy evaluations

The primary efficacy outcome was the time to failure to maintain response in responders. The response criteria specified in the protocol required a $\geqslant 20\%$ decrease from baseline in PANSS total score at any single time-point, provided that the patients did not concurrently have: (1) a Clinical Global Impression – Global Improvement (CGI-I) score of 6 or 7, or (2) an AE of worsening schizophrenia, or (3) a score of 5, 6 or 7 in at least one of the four PANSS psychotic subscale items. This definition of response does not, however, require that subjects meet these requirements for any length of time (i.e. clinically stable response), so a subject could potentially have met response criteria on one day and not the next, yet would still have been considered a responder. Furthermore, this definition of response is not consistent with response criteria in other long-term clinical trials of antipsychotics in patients with schizophrenia or schizoaffective disorder, in which response is defined as a symptomatic improvement maintained over time (Glick and Berg, 2002; Tran et al., 1997).

The following additional criteria were developed to better characterize a clinically meaningful response which requires both a greater degree of clinical improvement and that the clinical improvement is maintained over time. The additional response criteria require a $\geqslant 30\%$ decrease from baseline in PANSS total score provided that the patients did not

concurrently have: (1) a CGI-I of 6 or 7, or (2) an AE of worsening schizophrenia, or (3) a score of 5, 6 or 7 in at least one of the four PANSS psychotic subscale items. Patients were required to have at least one follow-up evaluation at which all of the above criteria were met, and no evaluation within 28 d at which the above criteria were not met. An analysis of the primary endpoint, time to failure to maintain response, is presented for both the initial and additional response criteria.

Other efficacy measures included mean change in scores from baseline to study endpoint for the PANSS (total, and positive and negative subscales), the Montgomery–Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression – Severity of Illness (CGI-S) and CGI-I scales during aripiprazole vs. haloperidol treatment. Each scale was administered at baseline (week 0) and then at each subsequent scheduled study visit during the double-blind phase of the study (weeks 1–8, 10, 12, 14, then every 4 wk to week 52). Whenever possible, the same assessor administered the scales for a given patient throughout the study.

Patients were considered to meet criteria for failure during this study if any of the following were present during the double-blind phase of the study: (1) a CGI-I score of 6 or 7; or (2) a score of 5, 6 or 7 on one or more of the four items comprising the PANSS psychotic subscale at two consecutive study visits; or (3) an AE of worsening schizophrenia. Time to failure to maintain response in responders was considered the primary outcome measure and was evaluated for both the initial and revised response criteria. Other efficacy measures analysed included percentage of patients on treatment and maintaining response (based on revised response criteria) as well as time to discontinuation due to any reason, and time to discontinuation due to lack of response or AE (based on all randomized patients).

Safety and tolerability evaluations

Serial safety and tolerability assessments were also obtained at each study visit including self-report instruments, standard clinical assessments, and standardized vital sign and movement assessments and measurements.

In addition to self-report, direct clinical observation, and specific inquiries, EPS were also evaluated at every study visit using the Simpson–Angus scale (SAS), Abnormal Involuntary Movement scale (AIMS), and the Barnes Akathisia Rating scale (BAS).

Vital signs and body weight were measured at baseline and at weeks 1, 4, 8 (vital signs, weeks 1–8), 12, 26, 38 and 52 (or study endpoint) of double-blind treatment. ECG recordings and routine laboratory tests (haematology, serum chemistry, and urinalysis) were also performed at screening, and then during the double-blind treatment phase at weeks 2, 8, 18 (not ECG), 26, 38 and 52 (or study endpoint). Physical examinations were performed at screening and repeated at weeks 8, 26 and 52 (or study endpoint). Determinations of plasma prolactin levels were only performed in Study 1 at baseline, and at weeks 2, 8, 18, 26, 38 and 52.

Concomitant medications

Psychotropic drug administration, other than the prescribed study medication, was prohibited throughout the study except for benzodiazepines prescribed for anxiety or insomnia, or intramuscular benzodiazepines administered for emerging agitation as deemed necessary by the investigator. The maximum daily benzodiazepine dose was not to exceed the equivalent of 4 mg/d of lorazepam during the time of participation in the study. Anticholinergic drugs for EPS were not allowed during the placebo washout phase but were permissible during the double-blind phase of the study (<6 mg/d benztropine) if clinically indicated in the judgement of the investigator. Other concomitant, non-psychotropic medications were administered at the investigator's discretion for the management of non-psychiatric conditions that emerged or changed during the time of study participation. All concomitant medication use was recorded.

Statistical procedures

A sample size of 1000 (later increased to 1300), randomized in a 2:1 ratio (aripiprazole:haloperidol), was calculated as the target sample size. This target sample size provides (a) 80% power to detect a difference of 12 percentage points in the rate of maintenance of response (using the original protocol-derived response criteria) at week 52 at a significance level of 0.05 (two-tailed) and (b) 90% power to detect a difference of 6 points in the mean change in PANSS total score at week 8, using a two-sided test at a significance level of 0.05.

Changes from baseline in PANSS (total, and positive and negative subscales), CGI-S, and MADRS scores, were compared by analysis of covariance (ANCOVA) with the baseline value as covariate and the protocol as a classification factor. Mean CGI-I score was analysed using the Cochran–Mantel–Haenszel (CMH) test stratified by protocol. Time-to-response, time-to-discontinuation, and time-to-failure analyses were

Table 1. Patient demographics (randomized population)

	Aripiprazole[a] ($n=861$)	Haloperidol ($n=433$)	Total[b] ($n=1294$)
Mean age (yr) ± S.E.	37.3 ± 0.4	36.8 ± 0.5	37.1 ± 0.3
Men	511 (59%)	247 (57%)	758 (59%)
Women	350 (41%)	186 (43%)	536 (41%)
Mean weight (kg) ± S.E.	74.5 ± 0.6	73.1 ± 0.8	74.0 ± 0.5
Schizophrenia type			
Disorganized	54 (6%)	30 (7%)	84 (7%)
Catatonic	10 (1%)	4 (1%)	14 (1%)
Paranoid	703 (82%)	353 (82%)	1056 (82%)
Residual	25 (3%)	12 (3%)	37 (3%)
Undifferentiated	68 (8%)	34 (8%)	102 (8%)
Not applicable[c]	1 (<1%)	0	1 (<1%)
Mean age at first episode (yr) ± S.D.	24.9 ± 8.0	25.5 ± 8.5	25.1 ± 8.1
Mean number of hospitalizations ± S.D.	5.5 ± 5.9	6.1 ± 8.1	5.7 ± 6.7
Mean number of weeks since current relapse began ± S.D.	3.3 ± 3.4	3.3 ± 2.9	3.3 ± 3.2
Mean length of treatment for current relapse (weeks) ± S.D.	1.5 ± 1.5	1.5 ± 1.3	1.5 ± 1.4

[a] $n=858$ for weight.
[b] $n=1291$ for weight.
[c] Not applicable refers to instances where the investigator's diagnosis did not match any of the diagnoses provided on the case report form.

plotted using Kaplan–Meier curves and analysed with the Cox proportional hazard regression model using baseline PANSS total score as a covariate and the study protocol as a stratification factor. The CMH test was used to analyse and compare the proportion of patients who were on treatment and in response (weeks 8, 26 and 52) during double-blind treatment. ANCOVA was used to evaluate changes in safety measures from baseline during double-blind treatment, as measured by the EPS scales (SAS, AIMS, BAS), vital-sign measurements (weight, blood pressure, pulse), ECG findings (QT_c interval) and serum prolactin determinations.

Results

Patients

A total of 1294 patients with schizophrenia completed the placebo washout period and were randomly assigned to double-blind treatment (aripiprazole, $n=861$; haloperidol, $n=433$) during the two studies. There were no significant differences in baseline demographic characteristics between the two treatment groups (Table 1). The two treatment groups were also comparable in terms of various psychiatric and medical characteristics at the time of the baseline study visit (week 0).

Data from 11 patients were excluded from the efficacy sample (aripiprazole, $n=8$; haloperidol, $n=3$) because they lacked a post-randomization efficacy evaluation. Four patients (two from each group) were excluded from the safety sample because they did not receive study medication.

The mean daily dose received during the acute treatment phase was 29.01 mg for aripiprazole and 8.90 mg for haloperidol.

Overall, 38% ($n=495$) of patients completed the entire 52-wk double-blind study. The completion rate was significantly higher for patients assigned to the aripiprazole group (43%, $n=367$) compared to the haloperidol group (30%, $n=128$; $p<0.001$). The difference in completion rate was primarily due to a significantly lower discontinuation rate for AEs (other than worsening schizophrenia) in the aripiprazole group compared to the haloperidol group (8% vs. 19%, $p<0.001$). Other reasons for discontinuation are shown in Table 2. Aripiprazole use was associated with a significantly greater time to discontinuation for all reasons compared to haloperidol ($p=0.0001$; Figure 1). The risk of discontinuation due to lack of response or AE was 31% lower with aripiprazole than

Table 2. Completion rates and reasons for discontinuation (randomized sample)

Status	Number of patients (%)			*p* value
	Aripiprazole ($n=861$)	Haloperidol ($n=433$)	Total ($n=1294$)	
Completed double-blind treatment	367 (43%)	128 (30%)	495 (38%)	0.0001
Reason for discontinuation				
Insufficient clinical response	63 (7%)	38 (9%)	101 (8%)	ns
Adverse event of worsening schizophrenia[a]	143 (17%)	58 (13%)	201 (16%)	ns
Adverse event other than worsening schizophrenia	70 (8%)	80 (19%)	150 (12%)	<0.001
Non-compliance	25 (3%)	17 (4%)	42 (3%)	ns
Other[b]	193 (22%)	112 (26%)	305 (24%)	ns

[a] Defined by the modified COSTART dictionary terms 'psychosis' and 'schizophrenic reaction', the majority of these events represent a relapse of the primary disease and are not considered attributable to study medication.
[b] Lost to follow-up, patient withdrew consent, protocol violation, patient met withdrawal criteria or study participation terminated by sponsor.

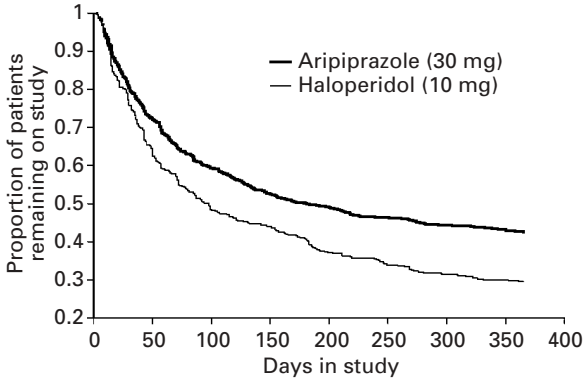

Figure 1. Time to discontinuation for all reasons (all randomized patients). Log rank *p* value = 0.0001.

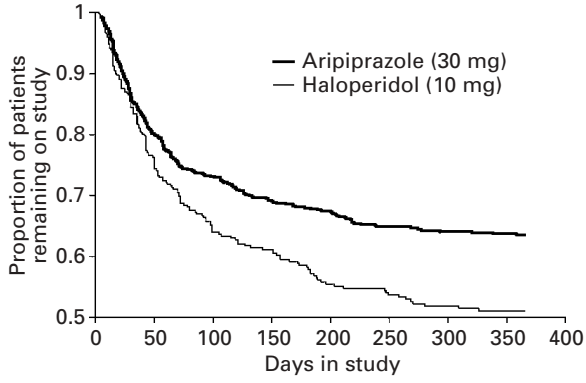

Figure 2. Time to discontinuation due to lack of response or adverse event (all randomized patients). Cox proportional hazard regression *p* value = 0.0001.

haloperidol (Figure 2; relative risk ratio = 0.692; 95% CI = 0.573–0.837; $p=0.0001$).

Efficacy data

Using the ⩾20% improvement in PANSS total score response criteria, the response rate was 72% in the aripiprazole group and 69% in the haloperidol group ($p=0.362$, Table 3). Based on a ⩾30% improvement in PANSS total score maintained for at least 28 d and one additional visit, aripiprazole produced a significantly higher response rate than haloperidol [52% (447/853) vs. 44% (189/430), $p<0.003$]. Time to failure to maintain response is also presented using both response criteria (Table 3); there was a 30% reduction in time to failure to maintain response with aripiprazole vs. haloperidol when response was characterized by the ⩾30% improvement criteria (risk ratio = 0.70; 95% CI = 0.45–1.07; $p=0.098$) (Figure 3). As illustrated by Figure 4, a significantly greater percentage of the patients randomized to aripiprazole treatment were still receiving study medication and maintaining response at weeks 8, 26 and 52 compared to those assigned to haloperidol (Figure 4; $p \leqslant 0.012$). Significant differences in favour of aripiprazole over haloperidol were also observed for time to failure (defined as time to failure to maintain the 30% response for responders or discontinuation from the study for those not meeting response criteria) (risk ratio = 0.737; 95% CI = 0.635–0.855; $p=0.0001$).

Aripiprazole and haloperidol were associated with similar improvements in symptoms as measured by changes from baseline on the total PANSS score, the PANSS positive symptoms subscale, and the CGI-S and CGI-I scores. However, aripiprazole was superior

Table 3. Response rates (efficacy sample) and time to failure to maintain a response (responders)

Response criteria[a]	Aripiprazole ($n=853$)	Haloperidol ($n=430$)	p value	
Response rate				
⩾20% improvement in PANSS (at a single time-point)[a]	72%	69%	0.362	
⩾30% improvement in PANSS (maintained for ⩾28 d plus one additional visit)[b]	52%	44%	0.003	
	Kaplan–Meier estimates for patients maintaining response at week 52			
Response criteria	Aripiprazole	Haloperidol	Risk ratio[d]	p value[d]
Time to failure to maintain response[c]				
⩾20% improvement in PANSS (at a single time-point)[a]	77%	73%	0.88	0.427
⩾30% improvement in PANSS (maintained for ⩾28 d plus one additional visit)[b]	85%	79%	0.70	0.098

[a] The response criteria specified in the protocol required a ⩾20% decrease from baseline in PANSS total score at any single time-point, provided that the patients did not concurrently have: (1) a CGI-I score of 6 or 7, or (2) an adverse event (AE) of worsening schizophrenia, or (3) a score of 5, 6 or 7 in at least one of the four PANSS psychotic subscale items.
[b] The revised response criteria require a ⩾30% decrease from baseline in PANSS total score provided that the patients did not concurrently have: (1) a CGI-I score of 6 or 7, or (2) an AE of worsening schizophrenia, or (3) a score of 5, 6 or 7 in at least one of the four PANSS psychotic subscale items. Patients were required to have at least one follow-up evaluation at which all of the above criteria were met, and no evaluation within 28 days at which the above criteria were not met.
[c] Regardless of response criteria, patients were considered to have failed if they were found to have any of the following: (1) a CGI-I score of 6 or 7, or (2) a score of 5, 6 or 7 in at least one of the four PANSS psychotic subscale items at two consecutive evaluations, or (3) an AE of worsening schizophrenia.
[d] Risk ratio and p values are from Cox Proportional Hazard Regression Model.

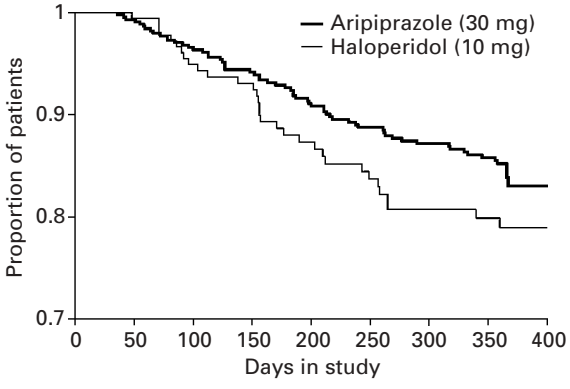

Figure 3. Time to failure to maintain response (responders only): based on a 30% decrease in PANSS and confirmed. Risk ratio = 0.697; CI = 0.454–1.069; Cox proportional hazard regression p value = 0.0982.

to haloperidol in improving the negative symptoms of schizophrenia as measured by changes from baseline on the PANSS negative subscale (LOCF analysis, $p<0.05$) (Figure 5a). Aripiprazole treatment was also more effective than haloperidol treatment in reducing depressive symptoms, as demonstrated by significantly greater improvement on the MADRS total score from baseline (LOCF analysis, $p<0.05$) (Figure 5b).

Safety and tolerability

AEs

Aripiprazole was well tolerated in this study. Most AEs were mild to moderate in intensity. The most commonly reported AEs are shown in Table 4. AEs that occurred in ⩾5% of patients during the first 8 wk decreased substantially, rarely exceeding 2% after 26 wk, and produced no evidence of new or late-emerging AEs for patients with extended exposure to aripiprazole.

The time to discontinuation due to AEs was significantly shorter with haloperidol than aripiprazole ($p=0.0004$; Figure 6). In all, 27% of patients (351/1290) discontinued due to an AE during the double-blind phase of the study [32% (138) in the haloperidol group and 25% (213) in the aripiprazole group]. The most

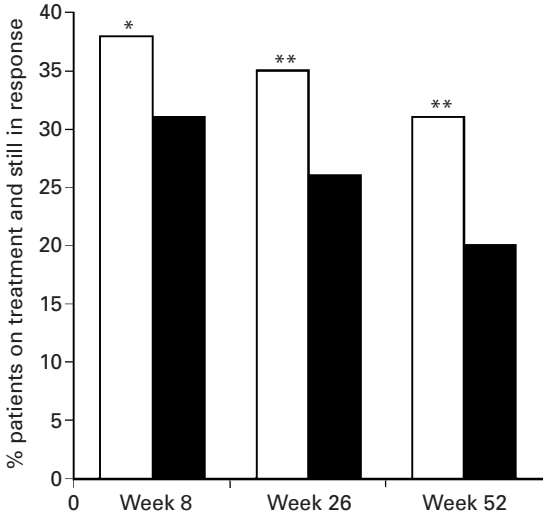

Figure 4. Percentage of patients on treatment and still in response: based on a 30% decrease in PANSS and confirmed. □, Aripiprazole ($n=861$); ■, haloperidol ($n=433$). * $p=0.012$; ** $p=0.001$, significantly more aripiprazole patients still on treatment and still in response. Responders exhibited ⩾30% improvement in PANSS total score, maintained for 28 d.

commonly reported AE associated with discontinuation was psychosis (aripiprazole, 14%; haloperidol, 12%); the majority of these reports represent a relapse of the underlying disease (schizophrenia) and are not considered attributable to the study drug.

Five deaths occurred during the study: 4 out of 861 (0.5%) in patients in the aripiprazole group, and 1 out of 433 (0.2%) in patients in the haloperidol group. None of the deaths were considered to be related to the study medication. Four of the deaths during the study were suicides; one aripiprazole-treated patient died from a cardiac arrest considered to be secondary to ischaemic heart disease rather than the study medication. During the course of the study, six patients attempted suicide. Four of the six patients committed suicide (1 in the haloperidol group; 3 in the aripiprazole group). Details of previous suicide attempts prior to study randomization are not available. Three of the four patients did not have suicidal ideation at the time of their last visit. One of the four patients committing suicide had attempted suicide unsuccessfully during the study and attempted suicide again 5 days later which led to death. No potentially clinically significant vital signs, ECGs, or laboratory studies were reported for these patients. Information on side-effects at the time of suicide was not captured by the investigators.

There was no difference in the occurrence of serious adverse events (SAEs) between the two treatment

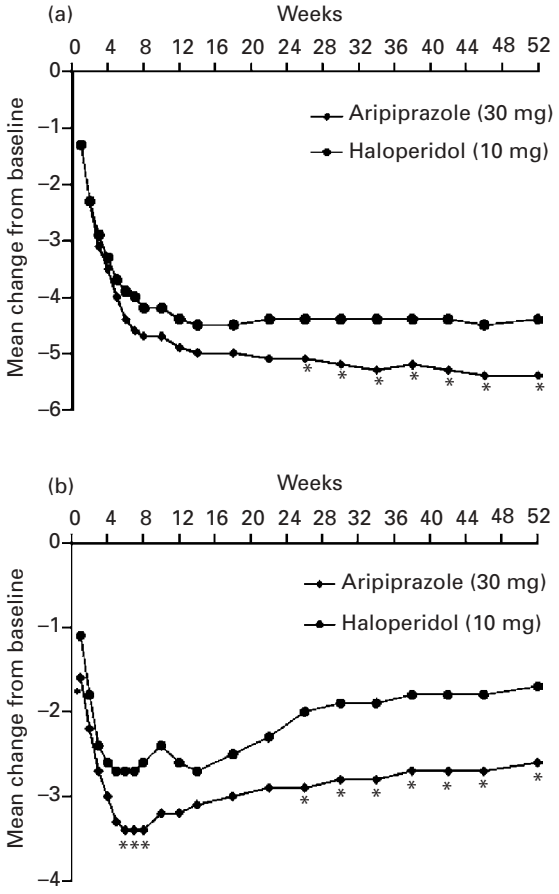

Figure 5. (a) Mean change from baseline in PANSS negative score, by week (LOCF). * Aripiprazole significantly greater improvement: $p<0.05$ (ANCOVA). Baseline scores: aripiprazole, 24.7 ($n=853$); haloperidol, 24.7 ($n=430$). (b) Mean change from baseline in MADRS total score, by week (LOCF). * Aripiprazole significantly superior to haloperidol: $p<0.05$. Baseline scores: aripiprazole, 12.5 ($n=851$); haloperidol, 12.8 ($n=427$).

groups [haloperidol, 75/431 (17%); aripiprazole 156/859 (18%)]. Nearly all of the SAEs were considered related to the underlying disease (schizophrenia), rather than attributable to study medication. The majority of SAEs were considered by the investigators to constitute a relapse of the primary disease (schizophrenia).

EPS

Overall, 37% (481) of patients reported an EPS-related AE during the double-blind treatment phase of the study. Significantly more ($p<0.001$) of the haloperidol-treated (58%) than aripiprazole-treated (27%) patients reported an EPS-related AE during the study. The incidence of early (<week 8 of treatment) EPS-related

Table 4. Adverse events with an incidence of ⩾5% of patients in either treatment group (safety sample)

	Aripiprazole ($n=859$) (%)	Haloperidol ($n=431$) (%)
Any adverse event	671 (78%)	377 (87%)
Body as a whole		
Headache	65 (8%)	38 (9%)
Metabolic/nutritional system		
Weight gain	44 (5%)	14 (3%)
Nervous system		
Insomnia	185 (22%)	88 (20%)
Psychosis	156 (18%)	70 (16%)
Akathisia	111 (13%)	108 (25%)
Anxiety	108 (13%)	50 (12%)
Extrapyramidal syndrome	84 (10%)	130 (30%)
Agitation	53 (6%)	30 (7%)
Somnolence	43 (5%)	32 (7%)
Tremor	34 (4%)	41 (10%)

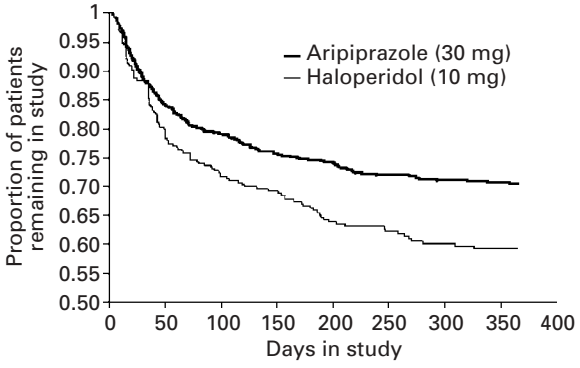

Figure 6. Time to discontinuation due to adverse event (safety sample). Kaplan–Meier curve of patients in the safety sample showing statistical difference at all time-points between treatment groups in time to discontinuation due to adverse events. Haloperidol was significantly more likely to be discontinued due to an adverse event. p value = 0.0004.

AEs was also significantly greater with haloperidol (55%) treatment than with aripiprazole (23%) treatment ($p<0.001$). As illustrated in Table 5, aripiprazole was associated with significantly less abnormal involuntary movement than haloperidol throughout the duration of double-blind treatment (at weeks 8, 26 and 52) as measured by changes from baseline on the EPS scales (SAS, BAS and AIMS).

More than half (57%) of the patients in the haloperidol group received anticholinergic medications for potential treatment of EPS, compared to 23% of those in the aripiprazole group. The most frequently used concomitant medication during the double-blind phase of the study was the anticholinergic biperiden (haloperidol, 31%; aripiprazole, 12%). The anticholinergic benztropine was administered to 10% of the patients assigned to haloperidol in comparison to 4% of those receiving aripiprazole treatment during the study.

Table 5. Extrapyramidal symptom scores. Mean change from baseline (LOCF analysis)

Test	Aripiprazole ($n=851$)	Haloperidol ($n=428$)	p value
Simpson–Angus scale score[a]			
Mean baseline	12.0	12.0	
Mean change at week 8	−0.3	1.8	<0.001
Mean change at week 26	−0.3	1.7	<0.001
Mean change at week 52	−0.2	1.9	<0.001
Abnormal Involuntary Movement scale score			
Mean baseline	1.1	1.1	
Mean change at week 8	−0.3	0.2	<0.001
Mean change at week 26	−0.3	0.2	<0.001
Mean change at week 52	−0.3	0.2	<0.001
Barnes Akathisia Rating scale score			
Mean baseline	0.3	0.3	
Mean change at week 8	0.0	0.4	<0.001
Mean change at week 26	0.0	0.4	<0.001
Mean change at week 52	0.0	0.4	<0.001

[a] $n=847$ (aripiprazole); $n=424$ (haloperidol).

Body weight

The mean change in weight from baseline to study endpoint (LOCF) was not significantly different between the aripiprazole [1.05 kg (±0.20 S.E.)] and the haloperidol [0.39 kg (±0.28 S.E.)] treatment groups. When stratified by mean body mass index (BMI) at the baseline study visit, only the patients with the lowest baseline BMI (<23 kg/m²) experienced a significantly greater weight gain during aripiprazole than haloperidol treatment. Patients with a relatively high BMI (>27 kg/m²) at baseline lost weight during both aripiprazole (−1.23 kg) and haloperidol (−0.78 kg) treatment (Figure 7). (Patients with a BMI of ⩾25 kg/m² are considered overweight; NHLBI, 1998.)

Prolactin

Serum prolactin samples were only collected in the first (the USA study) of the two combined studies. In the USA study, aripiprazole was associated with a significant decrease from baseline in prolactin levels, vs. haloperidol [aripiprazole −8.1 ($n=96$) vs. haloperidol +34.2 ($n=46$), $p<0.001$]. However, the

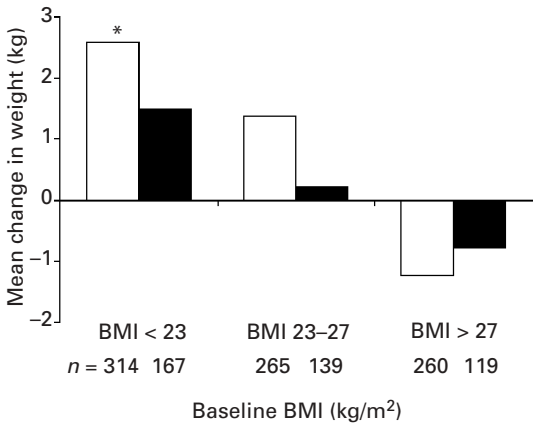

Figure 7. Mean change in weight, stratified by baseline BMI. □, Aripiprazole (30 mg); ■, haloperidol (10 mg). * Aripiprazole significantly different from haloperidol: $p \leqslant 0.05$ (ANCOVA).

prolactin values for most patients remained within normal limits. In addition, significantly fewer patients on aripiprazole (3.4%) had prolactin elevations greater than the upper limit of normal, regardless of baseline prolactin levels, vs. haloperidol (61%).

ECG

There was no significant difference in ECG findings between the aripiprazole and haloperidol treatment groups during the study. There were no significant increases from baseline on the QT_{cN} interval (calculated using the FDA Neuropharmacological Division formula, $QT_{cN} = QT/RR^{0.37}$) during either aripiprazole or haloperidol treatment. In fact, the mean change in the QT_c interval from baseline to study endpoint decreased during both aripiprazole (−7.8 ms) and haloperidol (−4.3 ms) treatment. In the aripiprazole group, only 2/810 (0.2%) patients had a $QT_c \geqslant 500$ ms during the study; in both of these patients, the QT_c exceeded 500 ms at only a single isolated time-point and no clinical sequelae were observed in either patient.

Laboratory analyses and vital signs

There were no clear differences in the incidence of potentially clinically significant laboratory abnormalities or vital-sign abnormalities between the two groups. Five (0.6%) aripiprazole-treated patients were discontinued due to a laboratory abnormality. Three patients were discontinued due to abnormal vital signs, two (0.2%) from the aripiprazole group and one (0.2%) from the haloperidol group.

Discussion

These results indicate that aripiprazole demonstrated sustained long-term efficacy, with favourable safety and tolerability during maintenance treatment of patients with acute relapse of chronic schizophrenia.

Extended treatment with aripiprazole at a starting dose of 30 mg was superior to haloperidol on a number of treatment issues. First, patients receiving aripiprazole remained in the study significantly longer than patients receiving haloperidol. Discontinuations due to lack of response or AEs occurred at a significantly lower rate in the aripiprazole group than in the haloperidol group. In addition, response rates demonstrating 30% improvement in PANSS total score were significantly higher with aripiprazole than with haloperidol, and the percentage of patients on treatment and maintaining a response at weeks 8, 26 and 52 was significantly higher for the aripiprazole group than the haloperidol group. The higher response rate and higher percentage of patients remaining on treatment and in response observed with aripiprazole may translate into potential for decreased utilization of healthcare resources (Launois et al., 1998).

Aripiprazole showed comparable long-term efficacy to haloperidol in improving PANSS total and positive scores, and CGI-S and CGI-I scores, and demonstrated long-term superiority to haloperidol in treating both the negative and depressive symptoms of schizophrenia as indicated by improvements in PANSS negative score and MADRS total score respectively. Improvement in both negative and depressive symptoms can have a significant impact on patients' lives. Negative symptoms have been correlated with social and occupational impairments, as well as persistent cognitive defects. Such impairments can prevent patients from leaving hospital and becoming integrated in society. Depressive symptoms are associated with compromised quality of life and an increased risk of psychotic relapse and suicide (Buchanan et al., 1996; Keck et al., 2000). Aripiprazole's efficacy in treating these symptoms may be related to its stabilizing effect on both the dopamine and serotonin systems. The unique combination of activities of aripiprazole – potent partial agonist activity at D_2 dopamine and 5-HT_{1A} serotonin receptors associated with 5-HT_{2A} antagonist activity – may underlie the differential effects of aripiprazole on negative and depressive symptoms.

Aripiprazole demonstrated superior safety and tolerability to haloperidol in several important factors. The discontinuation rate due to AEs (other than worsening of schizophrenia) was significantly higher ($p < 0.001$) in the haloperidol group (19%) than the

aripiprazole group (8%), supporting aripiprazole's suitability for long-term treatment. By comparison, a recently published long-term study comparing risperidone and haloperidol in stable schizophrenia patients demonstrated similar rates of discontinuation due to AEs for risperidone (12.4%) and haloperidol (15.4%) (Csernansky et al., 2002).

Both self-reports and standardized rating instruments for EPS and abnormal involuntary movements demonstrated that aripiprazole was superior to haloperidol treatment. EPS-related AEs reported during haloperidol treatment were more than double those reported during aripiprazole treatment. Aripiprazole was superior to haloperidol on the standardized movement scales that measure parkinsonian side-effects (SAS), akathisia (BAS), and abnormal involuntary movements (AIMS). Over twice as many patients in the haloperidol group than in the aripiprazole group received concomitant medication for potential treatment of EPS. EPS and abnormal movement remained unchanged or improved slightly with aripiprazole, while deteriorating with haloperidol. The reductions in EPS and related abnormal movements associated with aripiprazole were evident as early as week 1 and were maintained throughout treatment with aripiprazole. Antipsychotic-induced movement disorders are among the most common AEs encountered during antipsychotic treatment and are commonly implicated in poor treatment compliance (Casey, 2001); this finding has important implications for long-term treatment and outcome in patients with schizophrenia.

Somnolence, another side-effect of many antipsychotics, can negatively impact mental and social functioning and treatment compliance (Fleischhacker et al., 1994). In the current study, the incidence of somnolence was low for both agents (aripiprazole 5%, haloperidol 7%) (Table 4).

Weight gain is a common side-effect of antipsychotics, particularly atypical agents (Allison and Casey, 2001). Increases in body weight can have serious implications for general health (including increased risk of cardiovascular disease and the development of diabetes mellitus), can cause significant social stigma, and are associated with decreased treatment adherence (Sussman, 2001). Mean weight changes were small throughout the study. Furthermore, the weight gain observed in patients was predominantly associated with those with low baseline BMI. In contrast, in patients with high baseline BMI (i.e. $>27\ kg/m^2$), both drugs were associated with weight loss. Analysis of weight changes based on baseline BMI values suggests that the effects of aripiprazole on weight are better correlated with baseline BMI than with clinical improvement. In this sense, aripiprazole appears to be associated with weight gain in patients who are underweight, with minimal weight change in patients with normal weight, and weight loss in patients who are overweight.

Prolonged QT_c interval is a potentially fatal electrocardiographic change that has been observed on rare occasions in patients during treatment with antipsychotic medications (Gury et al., 2000). In the current study, the QT_c interval appeared to decrease with both aripiprazole and haloperidol. These data suggest that prolongation of the QT_c interval with aripiprazole and haloperidol is not likely to be a clinically important consequence of treatment with these drugs. The results observed in the current study are consistent with previous studies demonstrating minimal effect on the QT_c interval with haloperidol or aripiprazole (Kane et al., 2002; Potkin et al., 2003).

The current study is the first clinical report demonstrating long-term efficacy, safety, and tolerability for a dopamine partial agonist. Aripiprazole's unique mechanism of action (dopamine–serotonin system stabilizer) may be linked to the drug's efficacy and its low liability for side-effects. This study extends the findings of previous 4- to 6-wk studies (Carson et al., 2002; Marder et al., 2003) and demonstrates that aripiprazole has sustained efficacy in the overall treatment of schizophrenia with an excellent safety and tolerability profile. This clinical profile may lead to increased treatment adherence and decreased relapse rates, and suggests that aripiprazole represents an important new option for both acute and long-term treatment of schizophrenia.

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