Patient-Centered Outcomes with Aripiprazole Once-Monthly for Maintenance Treatment in Patients with Schizophrenia: Results From Two Multicenter, Randomized, Double-Blind Studies

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Abstract

Objectives: To further characterize the clinical profile of long-term treatment with aripiprazole once-monthly 400 mg (AOM 400) by examining patient-centered outcomes in adults with schizophrenia. **Methods:** Data are from 2 separate studies: a 52-week, multicenter, randomized, double-blind, placebo-controlled study and a 38-week, multicenter, randomized, double-blind, active-controlled study that evaluated the clinical profile of AOM 400 as maintenance treatment in patients with schizophrenia. The studies were conducted from July 2008 through February 2011 and from September 2008 through August 2012, respectively. Both studies included the Drug Attitude Inventory (DAI), the Medication Adherence Questionnaire (MAQ), the Patient Satisfaction with Medication Questionnaire, and a resource utilization and hospitalization form as prespecified patient-centered endpoints. **Results:** A total of 710 patients entered the oral stabilization phase in the 52-week study, and 403 patients were randomized to double-blind treatment. The corresponding sample sizes in the 38-week study were 842 and 662, respectively. In both studies, mean DAI and MAQ scores remained stable across all treatment phases; mean changes from baseline during the double-blind phase were not significantly different between treatment arms. Treatment satisfaction remained high throughout both studies, and most patients reported no or fewer side effects with AOM 400 relative to their prior medication. Most patients did not have unscheduled outpatient visits or hospitalizations throughout the studies. **Conclusions:** Data from 2 randomized, double-blind studies indicated that patient perceptions about treatment satisfaction, side effects, and medication adherence were maintained in patients with schizophrenia receiving maintenance treatment with AOM 400. **Trial Registration:** ClinicalTrials.gov: NCT00705783, NCT00706654.

Key Words: Aripiprazole Once-Monthly, Long-Acting Injectable Antipsychotic Agents, Schizophrenia, Medication Adherence, Treatment Satisfaction

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Introduction

The chronic nature of schizophrenia often requires long-term therapy with antipsychotic medication to achieve treatment goals, including relapse prevention, maintenance of functioning, and quality-of-life optimization (1). Relapse prevention may reduce the likelihood of cognitive and functional deterioration over the course of the illness (2). Discontinuation of antipsychotic treatment has been identified as the strongest predictor of relapse (3) and nonadherence the only significant predictor of relapse (4) in patients with schizophrenia.

Clinical Implications

Patients with schizophrenia who had previously responded to and tolerated oral aripiprazole maintained positive perceptions of their antipsychotic therapy after being switched to aripiprazole once-monthly 400 mg (AOM 400) for maintenance treatment, according to patient-centered outcomes from 2 long-term clinical trials. These positive perceptions were maintained without experiencing increased resource utilization. In both studies, mean Drug Attitude Inventory (DAI) scores improved during stabilization on oral aripiprazole and remained stable and positive across subsequent monthly dosing phases. Mean Medication Adherence Questionnaire (MAQ) scores indicated that, on average, patients reported that they were adherent to their medication throughout the trial. Patient Satisfaction with Medication Questionnaire (PSMQ)-Modified scores indicated that most patients were extremely or very satisfied with AOM 400. Results were consistent across all study phases, including the critical period when patients were switched from oral aripiprazole to AOM 400. Maintenance of treatment satisfaction and positive perceptions of tolerability after long-term therapy with AOM 400 were supported by low rates of treatment discontinuation (24.9%–26.0% for any reason in double-blind phases). These findings are important because they demonstrate for clinicians that switching patients from an oral to a long-acting injectable formulation of aripiprazole maintains patients' positive perceptions of their antipsychotic therapy, which may foster continued adherence and subsequently support long-term effectiveness and patient functioning.

Long-acting injectable (LAI) antipsychotics offer a treatment option for achieving the goals of long-term therapy for schizophrenia (5, 6). International treatment guidelines acknowledge the effectiveness of LAIs in preventing relapse and recommend them as maintenance therapy (1, 7).

Aripiprazole once-monthly 400 mg (AOM 400) is a long-acting injectable formulation of aripiprazole for the treatment of schizophrenia—400 mg is the recommended starting and maintenance dose (8). Data from two randomized, double-blind, placebo- or active-controlled studies demonstrated that AOM 400 delayed impending relapse and was well tolerated in patients with schizophrenia (9, 10). Given the challenges of maintaining medication adherence in patients with schizophrenia, the objective of the current analyses was to further characterize the clinical profile of long-term treatment with AOM 400 using patient-centered outcomes and to demonstrate stability in patient-centered outcomes when transitioning from oral aripiprazole to AOM 400.

Methods

Patients and Study Designs

Data are from 2 separate multicenter, international, randomized, double-blind studies: a 52-week, placebo-controlled study and a 38-week, active-controlled study that evaluated the clinical profile of AOM 400 as maintenance treatment in patients with schizophrenia. The studies were conducted from July 2008 through February 2011 and from September 2008 through August 2012, respectively. Details regarding study designs and patient inclusion/exclusion criteria were previously described (9, 10). Briefly, adults aged 18 to 60 years with a duration of schizophrenia of ≥3 years that was consistent with criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, a history of symptom exacerbation or relapse when not taking antipsychotic therapy, and who, in the investigators' opinion, would benefit from treatment with AOM 400, were eligible for study inclusion (9, 10). Key exclusion criteria included a *DSM-IV-TR* diagnosis other than schizophrenia, a history of refractoriness to antipsychotic treatment, and abnormal laboratory or electrocardiogram results at screening. Patients who were hospitalized for >30 days during the 90 days prior to study entry were also excluded from study enrollment (9, 10).

In the 52-week study, eligible patients entered 4 treatment phases. In the oral conversion phase (phase 1, 4–6 weeks), patients who were not already treated with oral aripiprazole were cross-titrated from their previous antipsychotic treatment to oral aripiprazole as previously described (9). During the oral stabilization phase (phase 2), patients were assessed biweekly and stabilized on oral aripiprazole. Patients who met predefined, previously described (9) stability criteria for 4 consecutive weeks entered the AOM stabilization phase (phase 3), in which they continued oral aripiprazole for the first 2 weeks after the initiation of AOM 400. During phase 3, patients who met previously described (9) stability criteria for 12 consecutive weeks entered phase 4, the randomized (2:1), double-blind, placebo-controlled phase in which patients continued AOM 400 or were switched to placebo intramuscular injection (9). Patients randomized to the AOM 400 treatment groups could have their AOM dose decreased on a single occasion to 300 mg for tolerability reasons and then increased to 400 mg for symptom management (9).

In the 38-week study, eligible patients entered 3 treatment phases. In the oral conversion phase (phase 1), patients who were not already treated with oral aripiprazole were

cross-titrated from their previous antipsychotic treatment to oral aripiprazole as previously described (10). During the oral stabilization phase (phase 2), patients were assessed biweekly and stabilized on oral aripiprazole. Patients who met predefined stability criteria (identical to the 52-week study) for 8 consecutive weeks entered the double-blind, active-controlled phase (phase 3, up to 38 weeks) and were randomized 2:2:1 to AOM 400, oral aripiprazole 10–30 mg, or AOM 50 mg (subtherapeutic active control) (10). Patients randomized to the AOM 400 treatment group could have their AOM dose decreased on a single occasion to 300 mg for tolerability reasons and then increased to 400 mg for symptom management. Patients in the AOM 50-mg treatment group could have their doses decreased to 25 mg and then subsequently increased to 50 mg if needed.

In both studies, AOM 400 delayed the time to impending relapse during the double-blind maintenance phase (9, 10). Moreover, the 52-week study was terminated early because efficacy was demonstrated in the preplanned interim analysis conducted after 64 relapses (9).

Assessments

Drug Attitude Inventory

The Drug Attitude Inventory (DAI) (11) is a validated, self-reported questionnaire that assesses patients' attitudes toward their treatment. The scale has 30 questions and consists of 7 subscales: a) subjective positive feelings, b) subjective negative feelings, c) health, d) confidence in the physician, e) control, f) prevention, and, g) harm. Possible total scores range from -30 to 30. Positive total scores indicate a positive attitude, and a negative total score indicates a negative attitude toward treatment (11).

Medication Adherence Questionnaire

The Medication Adherence Questionnaire (MAQ) (12) is a validated, self-reported questionnaire that assesses reasons for nonadherence (forgetfulness, carelessness, stopping the drug when feeling better or when feeling worse). The scale has 4 questions with possible answers of "yes" or "no." Possible total scores range from 0 to 4, with higher scores indicating greater treatment nonadherence (12).

Patient Satisfaction with Medication Questionnaire-Modified

The Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-Modified) (13) is a self-reported questionnaire that assesses patient satisfaction with treatment and frequency of side effects using a 6-point rating scale (extremely satisfied, very satisfied, somewhat satisfied, somewhat unsatisfied, very unsatisfied, and extremely unsatisfied). Patients also compared side effects of their current treatment with their pretrial antipsychotic medication using a 6-point rating scale (no side effects, much less side effects, less side effects, the same as previous medications, a little more side effects, and much more side effects). Patients were also asked whether they preferred their current medication or their pretrial antipsychotic medication, whether a caretaker commented on any differences that they observed in the patient when comparing the current medication versus the pretrial antipsychotic medication, and whether the patient had any additional comments (13).

Resource Utilization and Hospitalization Form

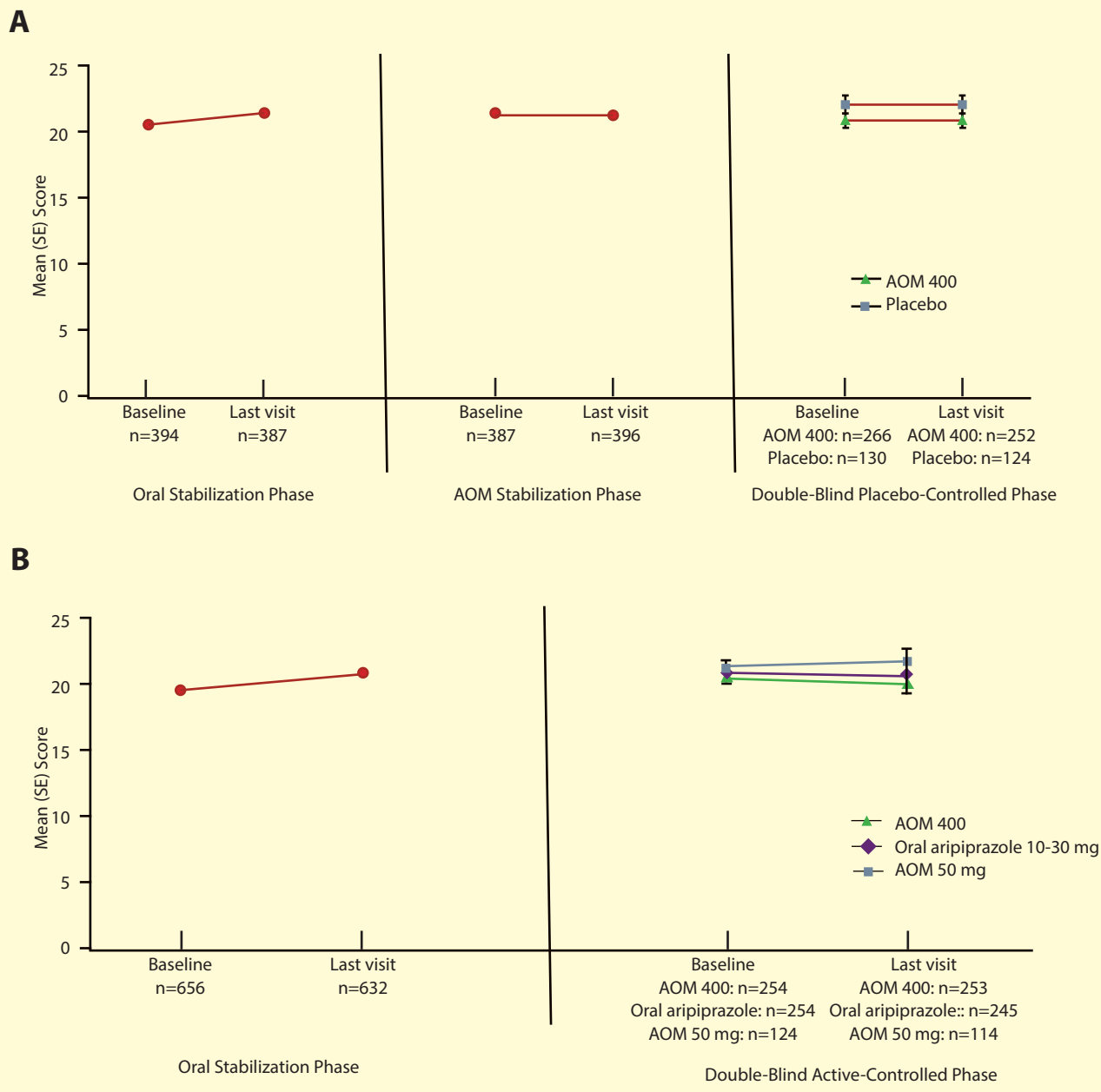
A resource utilization and hospitalization form that consisted of 3 questions was developed to obtain information about healthcare utilization (i.e., unplanned outpatient visits, hospitalizations) and employment status during the clinical trials.

Statistical Analyses

In the 52-week study, DAI and MAQ changes from baseline were computed for the oral stabilization phase (baseline=Week 6/end of conversion phase); the AOM stabilization phase (baseline=Week 12/end of oral stabilization phase); and, the double-blind, placebo-controlled phase (baseline=Week 36/end of AOM stabilization phase). In the 38-week study, DAI and MAQ changes from baseline were computed for the oral stabilization phase (baseline=Week 6/end of the conversion phase) and the double-blind, active-controlled phase (baseline=Week 28/end of oral stabilization phase). In both studies, DAI and MAQ changes from baseline were calculated for the double-blind efficacy sample (intent-to-treat data set), which consisted of all patients who were randomized to the double-blind, placebo- or active-controlled treatment phases. Analyses of covariance were computed for the double-blind phase only, with treatment as a factor and baseline value as a covariate.

Data collected from the PSMQ-Modified and the resource utilization and hospitalization form were analyzed using descriptive statistics. Specifically, in the 52-week study, frequency distributions using the PSMQ-Modified were calculated for treatment satisfaction, side effects, and treatment preference from the AOM stabilization phase and the double-blind, placebo-controlled phase using the double-blind efficacy sample. In the 38-week study, these frequency distributions were calculated for the double-blind, active-controlled phase using the double-blind efficacy sample. In the 52-week study, descriptive statistics (observed cases) collected using the resource utilization and hospitalization

Figure 1 **Mean (SE) DAI Total Score Across Study Phases in (A) the 52-Week Study (Last Observation Carried Forward) and (B) the 38-Week Study (Last Postbaseline Evaluation)**



AOM=aripiprazole once-monthly; DAI=Drug Attitude Inventory; PBO=placebo. Last visit data represent the last postbaseline evaluation.

form included the proportion of patients with outpatient visits; the proportion of patients hospitalized for worsening psychotic reasons; and, employment information during the oral stabilization phase, the AOM stabilization phase, and the double-blind, placebo-controlled phase. In the 38-week study, these descriptive statistics (observed cases) were evaluated during the oral stabilization phase and the double-blind, active-controlled phase.

Results

Patient Disposition and Characteristics

For both studies, patient disposition, characteristics, and treatment exposure were described in detail previously (9, 10). Briefly, 710 patients entered the oral stabilization phase in the 52-week study, and 403 patients were randomized to double-blind treatment. The corresponding sample sizes in the 38-week study were 842 and 662, respectively.

Table 1 Medication Adherence Questionnaire (Double-Blind Phase Efficacy Samples)

	52-Week Study				38-Week Study			
	Oral Stabilization	AOM Stabilization	Double-Blind, Placebo-Controlled Phase		Oral Stabilization	Double-Blind, Active-Controlled Phase		
	Oral ARI 10–30 mg	AOM 400 mg	AOM 400 mg	Placebo	Oral ARI 10–30 mg	AOM 400 mg	Oral ARI 10–30 mg	AOM 50 mg
MAQ Score								
Baseline*, *n*	399	389	264	131	658	257	253	125
Mean (SD)	0.70 (0.95)	0.57 (0.89)	0.58 (0.93)	0.37 (0.73)	0.88 (1.03)	0.72 (0.96)	0.64 (0.91)	0.70 (0.96)
Last visit†, *n*	389	395	258	126	635	256	247	115
Mean (SD)	0.57 (0.89)	0.51 (0.87)	0.53 (0.91)	0.49 (0.94)	0.68 (0.94)	0.66 (0.91)	0.64 (0.87)	0.63 (0.95)
Mean change, *n*	386	381	253	123	631	248	236	110
Mean (SD)	-0.13 (0.90)	-0.04 (0.93)	-0.04 (0.80)	0.12 (0.90)	-0.21 (1.02)	-0.08 (0.99)	-0.02 (0.94)	-0.07 (0.90)
P value‡				0.3341			0.8793	0.9911

AOM=aripiprazole once-monthly; ARI=aripiprazole; MAQ=Medication Adherence Questionnaire.
*Baseline data in the oral stabilization phase are the values at the end of the conversion phase for patients who were cross-titrated during the conversion phase or the baseline visit of the oral stabilization phase. †Last visit data represent the last postbaseline evaluation. ‡Versus AOM 400.

In both studies the majority of patients were male and white (mean age at randomization to double-blind maintenance phase, 40.6 and 41.2 years in the 52-week and 38-week studies, respectively) with a mean age at first diagnosis of 26.0 and 27.3 years, respectively. In the 52-week study, discontinuation rates (excluding those who discontinued because the sponsor stopped the study early) were 12.5%, 13.0%, and 15.1% in phases 1, 2, and 3, respectively, and 24.9% for AOM 400 in the double-blind phase (9). In the 38-week study, discontinuation rates were 13.4% and 21.4% in phases 1 and 2, respectively, and 26.0% for AOM 400 and 33.1% for oral aripiprazole in the double-blind phase (10). In both studies, the majority of patients in the AOM 400 treatment group who initiated AOM 400 had no dose change (93.3% and 92.8% in the 52- and 38-week studies, respectively) (9, 10). Also, in the 38-week study, 99.2% of patients randomized to AOM 50 mg did not require a change in dose (10).

Drug Attitude Inventory

Mean change in DAI total scores from baseline to last visit of the double-blind, controlled phase was comparable between placebo and AOM 400 (p=0.4019) in the 52-week study and between AOM 400 and oral aripiprazole (p=0.6034) and AOM 400 and AOM 50 mg (p=0.5168) in the 38-week study (see Figure 1 [A & B]). In both studies across treatment groups, mean DAI scores showed modest increases (i.e., improvement) during the oral aripiprazole stabilization phases (range, 0.80–1.34) and remained stable during the double-blind controlled phase (range, -0.56–-0.10).

Medication Adherence Questionnaire

Mean MAQ scores remained low (range, 0.49–0.68) and demonstrated minimal change over the entire duration of both trials (range, -0.21–0.12; see Table 1). Mean change in MAQ scores from baseline to last visit of the double-blind controlled phase was comparable between AOM 400 and placebo (p=0.3341) in the 52-week study. In the 38-week study, mean changes in MAQ scores were also comparable between AOM 400 and oral aripiprazole (p=0.8793) and AOM 400 and AOM 50 mg (p=0.9911) (see Table 1).

Patient Satisfaction with Medication Questionnaire-Modified

Descriptive statistics showing number and percentage of patients responding to each PSMQ-Modified question are presented for both studies in Table 2. No comparative statistical analyses were conducted. In the double-blind phase of the 52-week study, the percentage of patients who were extremely satisfied was lower in the AOM 400-mg group than in the placebo group at baseline and higher in the AOM 400-mg group than in the placebo group at last visit (see Table 2). Similarly, the percentage of patients who were extremely satisfied at baseline in the double-blind phase of the 38-week study was lowest for the AOM 400-mg group; at last visit, it was highest for the AOM 400-mg group (see Table 2). None of these differences were statistically significant. At each visit that evaluated side effects with the PSMQ-Modified, a majority of patients in each group reported none, much less, or less side effects relative to their previous medication (see Table 2).

Table 2 Patient Satisfaction with Medication Questionnaire-Modified (Double-Blind Phase Efficacy Samples)

	52-Week Study			38-Week Study		
	AOM Stabilization	Double-Blind, Placebo-Controlled Phase		Double-Blind, Active-Controlled Phase		
	AOM 400 mg	AOM 400 mg	Placebo	AOM 400 mg	Oral ARI 10–30 mg	AOM 50 mg
PSMQ-Modified Score*, n (%)						
Treatment Satisfaction						
Baseline†	n=385	n=268	n=134	n=257	n=254	n=125
Extremely satisfied	91 (23.6)	91 (34.0)	55 (41.0)	68 (26.5)	73 (28.7)	38 (30.4)
Very satisfied	195 (50.6)	129 (48.1)	54 (40.3)	130 (50.6)	127 (50.0)	58 (46.4)
Somewhat satisfied	92 (23.9)	40 (14.9)	20 (14.9)	49 (19.1)	47 (18.5)	28 (22.4)
Somewhat unsatisfied	5 (1.3)	5 (1.9)	4 (3.0)	5 (1.9)	5 (2.0)	1 (0.8)
Very unsatisfied	1 (0.3)	3 (1.1)	1 (0.7)	5 (1.9)	1 (0.4)	0 (0)
Extremely unsatisfied	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)
Last visit‡	n=402	n=261	n=127	n=258	n=253	n=120
Extremely satisfied	146 (36.3)	89 (34.1)	32 (25.2)	97 (37.6)	88 (34.8)	40 (33.3)
Very satisfied	183 (45.5)	111 (42.5)	52 (40.9)	106 (41.1)	112 (44.3)	41 (34.2)
Somewhat satisfied	60 (14.9)	42 (16.1)	24 (18.9)	40 (15.5)	41 (16.2)	26 (21.7)
Somewhat unsatisfied	9 (2.2)	10 (3.8)	12 (9.4)	11 (4.3)	6 (2.4)	5 (4.2)
Very unsatisfied	4 (1.0)	3 (1.1)	4 (3.1)	1 (0.4)	3 (1.2)	5 (4.2)
Extremely unsatisfied	0 (0)	6 (2.3)	3 (2.4)	3 (1.2)	3 (1.2)	3 (2.5)
Treatment Side Effects						
Baseline†	n=385	n=268	n=134	n=256	n=254	n=125
No side effects	192 (49.9)	146 (54.5)	73 (54.5)	117 (45.7)	118 (46.5)	65 (52.0)
Much less side effects	77 (20.0)	59 (22.0)	26 (19.4)	60 (23.4)	62 (24.4)	30 (24.0)
Less side effects	73 (19.0)	37 (13.8)	25 (18.7)	41 (16.0)	49 (19.3)	22 (17.6)
The same as previous medication	28 (7.3)	19 (7.1)	9 (6.7)	25 (9.8)	14 (5.5)	4 (3.2)
A little more side effects	12 (3.1)	4 (1.5)	1 (0.7)	11 (4.3)	10 (3.9)	2 (1.6)
Much more side effects	3 (0.8)	3 (1.1)	0 (0)	2 (0.8)	1 (0.4)	2 (1.6)
Last visit‡	n=402	n=261	n=127	n=258	n=253	n=120
No side effects	219 (54.5)	144 (55.2)	67 (52.8)	124 (48.1)	129 (51.0)	73 (60.8)
Much less side effects	85 (21.1)	47 (18.0)	24 (18.9)	65 (25.2)	62 (24.5)	19 (15.8)
Less side effects	62 (15.4)	41 (15.7)	22 (17.3)	38 (14.7)	36 (14.2)	8 (6.7)
The same as previous medication	28 (7.0)	11 (4.2)	7 (5.5)	18 (7.0)	12 (4.7)	10 (8.3)
A little more side effects	5 (1.2)	12 (4.6)	7 (5.5)	7 (2.7)	9 (3.6)	4 (3.3)
Much more side effects	3 (0.7)	6 (2.3)	0 (0)	6 (2.3)	5 (2.0)	6 (5.0)
Patient Preference						
Baseline†	n=380	n=268	n=133	n=246	n=253	n=125
Current medication	357 (93.9)	254 (94.8)	130 (97.7)	226 (91.9)	235 (92.9)	116 (92.8)
Previous medication	23 (6.1)	14 (5.2)	3 (2.3)	20 (8.1)	18 (7.1)	9 (7.2)
Last visit‡	n=401	n=261	n=126	n=255	n=252	n=119
Current medication	384 (95.8)	225 (86.2)	108 (85.7)	232 (91.0)	231 (91.7)	98 (82.4)
Previous medication	17 (4.2)	36 (13.8)	18 (14.3)	23 (9.0)	21 (8.3)	21 (17.6)

AOM=aripiprazole once-monthly; ARI=aripiprazole; PSMQ-Modified=Patient Satisfaction with Medication Questionnaire-Modified.
*No comparative statistical analyses were conducted. †In the AOM stabilization phase (52-week study) and the double-blind phases (both studies), baseline data are the values at the end of the preceding respective study phase. ‡Last visit data represent the last postbaseline evaluation.

In the double-blind phase of the 52-week study, comparable proportions of patients in the AOM 400-mg and placebo groups preferred their current medication at baseline (data not shown) and last visit (see Table 2). In the double-blind phase of the 38-week study, the proportion of patients preferring current treatment was comparable across all 3 groups at baseline (data not shown); however, the proportion at last visit was numerically lower for the AOM 50-mg group (82.4%) compared with the AOM 400-mg (91.0%) or oral aripiprazole (91.7%) groups (see Table 2).

Resource Utilization and Hospitalization Form

As noted previously, data from the resource utilization and hospitalization form were analyzed using descriptive statistics. During the 52-week study, most patients in the double-blind, placebo-controlled sample did not have outpatient visits with healthcare professionals that were outside of the scheduled study visits during any of the study phases (oral stabilization, 86.4%; AOM stabilization, 81.1%; double-blind, placebo-controlled, 79.4%). Likewise, most patients in this sample were not hospitalized during any of the study phases (oral stabilization, 95.8%; AOM stabilization, 96.5%; double-blind, placebo-controlled phase, 93.5%). A numerically greater proportion of patients in the placebo group (9.0%) were hospitalized compared with the AOM 400-mg group (5.2%). Most patients were not employed at the baseline assessment of all study phases (oral stabilization phase, 83%; AOM stabilization phase, 80.9%; double-blind, placebo-controlled phase, 78.4% [AOM 400] and 80.6% [placebo]) or at the last study visit (81.1% [AOM 400] and 79.5% [placebo]). In the double-blind, placebo-controlled phase, 16.0% of patients in the AOM 400-mg group and 29.9% of patients in the placebo group had outpatient visits outside of study visits.

In the 38-week study, most patients in the double-blind, placebo-controlled sample did not have outpatient visits with healthcare professionals that were outside of the study visits during the oral stabilization (76.3%) or double-blind phase (71.6%). Similar to the 52-week study, most patients were not hospitalized during the oral stabilization phase (95.3%) or during the double-blind, active-controlled phase (91.3% [AOM 400], 92.9% [oral aripiprazole], and 91.6% [AOM 50 mg]). Most patients in the 38-week study were not employed at the baseline assessments of the oral stabilization phase (82.2%) and double-blind, active-controlled phase (81.1% [AOM 400], 75.9% [oral aripiprazole], and 81.5% [AOM 50 mg]) or at the last study visit (80.5% [AOM 400], 75.1% [oral aripiprazole], and 83.2% [AOM 50 mg]). In the double-blind, placebo-controlled phase, 30.9% of patients in the AOM 400-mg group, 28.9% of patients in the oral aripiprazole group, and 22.1% of patients in the AOM 50-mg group had outpatient visits outside of planned study visits.

Discussion

This is the first report of patient-centered outcomes from the AOM 400 pivotal studies in patients with schizophrenia. In both studies of AOM 400, mean DAI scores improved during stabilization on oral aripiprazole and then remained stable and positive across subsequent study phases, and change scores were comparable among treatment groups. Mean MAQ scores indicated that, on average, patients reported that they were adherent to their medication throughout the trial, and change scores were comparable among treatment groups in both studies. For both the DAI and MAQ, scores remained stable when patients transitioned from oral aripiprazole to AOM. Likewise, PSMQ-Modified scores indicated that most patients were extremely or very satisfied with AOM 400 in both studies. Furthermore, most patients indicated no side effects, much less side effects, or less side effects with AOM 400 after switching from oral aripiprazole or other oral antipsychotic treatments to AOM 400. In addition, treatment discontinuation rates among AOM 400 recipients were low throughout both studies (~25% for any reason in double-blind phases). Hospitalization rates and unscheduled outpatient visits were low and comparable among treatment groups as might be expected in controlled clinical trials in stabilized patients with intensive monitoring. However, in an open-label, naturalistic, mirror-image study, rates of psychiatric hospitalization were significantly lower during the 6-month period after switching to AOM 400 versus the 6-month retrospective period when patients were taking oral antipsychotics (8.8% vs 38.1%, $p<0.0001$) (14).

Taken together, these data indicate that patient-reported treatment satisfaction and positive perceptions of tolerability were maintained at high levels after long-term treatment with AOM 400. Results were consistent across all study phases, including the critical period when patients were switched from oral aripiprazole to AOM treatment. In both studies, the majority of patients (>92%) who initiated AOM 400 had no dose change. Similar tolerability of the 400-mg dose has been observed in other clinical studies (14, 15). Findings from our analyses are important because they demonstrate that switching from oral aripiprazole 10–30 mg to the 400-mg long-acting injectable formulation of aripiprazole did not negatively affect patients' perception of their pharmacotherapeutic treatment. Based on our findings, physicians may expect that, on average, treatment satisfaction and perceptions will remain stable after initiating AOM 400 for patients who have never taken oral aripiprazole and, thus, must establish tolerability (8). Similar findings

were noted in the aforementioned open-label, naturalistic, mirror-image study in which mean changes from baseline in DAI scores demonstrated significant improvement after switching from oral antipsychotics (including oral aripiprazole and other antipsychotics) to AOM 400 (16).

Findings from the current analyses are difficult to compare with results from other studies because of differing study designs and patient selection criteria among studies. Nonetheless, in a 26-week, open-label study that examined the impact of switching to oral aripiprazole from another oral new-generation antipsychotic (risperidone, olanzapine, or amisulpride) on cognitive and social functioning and attitudes toward medication, DAI scores significantly improved from baseline in patients with schizophrenia (17). However, the study did not require patients to achieve stability criteria with oral aripiprazole before baseline assessment (17). In a 50-week, multicenter, open-label study that examined the effectiveness, tolerability, and safety of switching to LAI risperidone in symptomatically stable patients with schizophrenia who had poor medication adherence to oral antipsychotics, patients demonstrated significant improvements from baseline throughout the study on DAI scores (18). Here too, patients were not required to achieve stability criteria with an oral antipsychotic before switching to open-label treatment with LAI risperidone. Also, in a 24-week, open-label study (N=291), DAI scores significantly improved from baseline to endpoint in patients with schizophrenia who switched from other antipsychotics to paliperidone extended release (19). Patients were required to be stabilized on an atypical antipsychotic for ≥2 weeks before study enrollment. In the current studies, changes in DAI were maintained after an oral stabilization period of 4 weeks and an aripiprazole once-monthly 400-mg stabilization period of 12 weeks in the 52-week study, and after an oral stabilization period of 8 weeks in the 38-week study, suggesting that improvements were sustained during double-blind treatment.

Several limitations of these studies are worthy of note. These were relapse-prevention studies that enrolled relatively stable patients and were designed to evaluate stability and not improvement. In addition, in these long-term trials, it might be difficult for patients to recall their experience with therapy before study entry. Patients enrolled in clinical trials are more likely to be adherent than patients in general. In addition, selection bias may limit extrapolation of these data to the general population of patients with schizophrenia. In both studies, patients were required to meet predefined stability criteria to enter the double-blind, randomized phase. Thus, the results from the double-blind phases represent patients who had responded to medication and may not be applicable to patients who are not yet stabilized. Likewise, in both studies, most patients had illness duration of approximately 14 years, and patients with psychiatric comorbidities (e.g., substance dependence) were excluded, which may limit the generalizability of these findings. Additionally, the patient-centered outcomes (i.e., the DAI, MAQ, PSMQ-Modified, and resource utilization and hospitalization form) were not primary study outcomes, and substantial changes in these measures would not be expected during long-term therapy. Furthermore, early termination of the 52-week study (because of positive efficacy results for AOM 400 versus placebo in the interim analysis) limited the number of patients treated with AOM 400, potentially reducing the ability to detect statistically significant differences between treatment arms on the DAI and MAQ.

In conclusion, patient-centered outcome measures from these 2 long-term clinical trials indicated that patients with schizophrenia who had previously responded to and tolerated oral aripiprazole maintained positive perceptions of their antipsychotic therapy after being switched to AOM 400, without experiencing increased serious and/or distressing side effects or increasing their resource utilization.

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