

The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine

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Received: 26 November 2005 / Accepted: 3 May 2006 / Published online: 30 June 2006
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Abstract

Rationale Cognitive deficits are a core feature of schizophrenia. As a target of intervention, improvements in cognition may lead to improvements in functional outcome.

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Objectives The present paper is the first report, to our knowledge, on the neurocognitive effects of aripiprazole. Unlike other second-generation antipsychotics, aripiprazole is a D₂ and D₃ receptor partial agonist. It is unknown what effects this unusual pharmacological profile may yield on neurocognition.

Materials and methods The present open-label study included data on 169 patients with schizophrenia or schizoaffective disorder who were randomly treated with aripiprazole or olanzapine. Subjects received a neurocognitive battery at baseline, week 8, and 26.

Results The aripiprazole group had a significantly greater dropout rate than the olanzapine group. Neurocognitive data were reduced through a principal components analysis that yielded a three-factor solution. The factors were general cognitive functioning, executive functioning, and verbal learning. For general cognitive functioning, both groups improved from baseline and the effects were relatively stable over the 26-week protocol. There were no differential treatment effects. For executive functioning, neither group improved significantly from baseline. For verbal learning, the aripiprazole group improved significantly from baseline to the 8th and 26th week of assessment, and there was a between-group effect favoring aripiprazole over olanzapine that was largely attributable to the differences in performance within the 8th week. Separate analyses were conducted for a measure of sustained attention (Continuous Performance Test–Identical Pairs). There were no differential treatment effects on this measure.

Conclusions The findings from this open-label study suggest that the neurocognitive effects of aripiprazole are at least as good as those of olanzapine.

Keywords Schizophrenia · Aripiprazole · Olanzapine · Neurocognition · Learning · Memory · Dopamine · Agonists

Table 1 Demographic characteristics

Demographic variables	Aripiprazole (<i>n</i> =76)	Olanzapine (<i>n</i> =93)
Age (years)	39.6 (9.8)	40.4 (10.6)
Gender (M:F)	48:28	61:32
Ethnicity (% Caucasian)	63.2	58.1
Neurocognitive measures		
WAIS-III Vocabulary (raw score)	33.4 (14.7)	29.7 (14.5)
WAIS-III Block Design (raw score)	31.6 (13.5)	29.8 (13.4)
WAIS-III Information (raw score)	13.6 (5.7)	12.3 (5.7)
NAART (errors)	35.2 (12.2)	35.5 (13.9)
Clinical measures		
PANSS, total	70.0 (17.3)	73.5 (18.5)
PANSS, positive	16.7 (5.8)	17.9 (6.5)
PANSS, negative	18.6 (5.6)	19.5 (5.3)

Introduction

Cognitive deficits are now widely recognized as a core feature of schizophrenia, largely independent of the psychotic symptoms of the illness (Gold 2004). The cognitive domains affected include, among others, impairments in attention, working memory, verbal and visual learning, speed of processing, language abilities, and reasoning and problem-solving (Aleman et al. 1999; Cornblatt et al. 1985; Goldberg et al. 1987; Heinrichs and Zakzanis 1998; Nuechterlein and Dawson 1984; Nuechterlein et al. 2004; Saykin et al. 1991). It is important to note that there is a growing awareness that these deficits are linked to impairments in community outcome and rehabilitation success (Green 1996; Green et al. 2000, 2004).

A number of reports have examined the effects of second-generation antipsychotic (SGA) medications on cognition in schizophrenia. Most report advantages when compared with conventional antipsychotic agents (Bilder et al. 2002; see Keefe et al. 1999; Meltzer and McGurk 1999 for reviews). However, there are relatively few replicated findings of specific treatment effects at the domain level (e.g., Green et al. 1997; Hagggar et al. 1993; Hoff et al. 1996; Kern et al. 1999; Lee et al. 1994; Rossi et al. 1997). In general, the effect sizes for SGAs compared with standard doses of conventional agents were small to medium (Woodward et al. 2005; Harvey and Keefe 2001).

This is the first report, to our knowledge, of the neurocognitive effects of aripiprazole. Aripiprazole was shown to be effective, safe, and well-tolerated for the treatment of positive and negative symptoms in persons with schizophrenia and schizoaffective disorder (Potkin et al. 2003), and to have a low liability for extrapyramidal side-effects and a low incidence of clinically significant weight gain (Marder et al. 2003; McQuade et al. 2004). It has a unique pharmacology among SGAs in that it is a partial agonist at D₂ and D₃

dopamine receptors, behaving as a functional antagonist in hyperdopaminergic states and as a functional agonist in hypodopaminergic states (Burriss et al. 2002; Kikuchi et al. 1995; Shapiro et al. 2003). Aripiprazole exhibits a high binding affinity for D₂ and D₃ receptors, a moderate affinity for D₄ receptors, and a low affinity for D₁ receptors. Preclinical studies have also indicated that aripiprazole has a relatively high affinity for serotonin 5HT_{2A} and 5HT_{1A} receptors. It displays partial agonist activity at the 5HT_{1A} receptor and antagonistic activity at the 5HT_{2A} receptor (Jordan et al. 2002; McQuade et al. 2002). It is not known what neurocognitive effects might be expected from an antipsychotic with this complex mechanism of action. This paper reports on the results of a multicenter study that assessed the neurocognitive effects of aripiprazole vs olanzapine using an open-label, randomized study design.

Materials and methods

Subjects The study included 19 sites and 255 randomly picked patients (aripiprazole=128 and olanzapine=127). All patients in the study were outpatients who met the Diagnostic and Statistical Manual of Mental Disorders–IV diagnostic criteria for schizophrenia or schizoaffective disorder, were between ages of 18 and 65, able to speak and understand English, were on a stable dose of an oral typical antipsychotic, risperidone, or quetiapine for at least 1 month, and had not been hospitalized for psychiatric treatment for at least 2 months before randomization. Exclusion criteria included current suicidality, neurological disorder (e.g., epilepsy), acute or unstable medical condition, a clinically significant laboratory test value, gastrointestinal resection or stapling that may interfere with study medication absorption, and alcohol- or substance-dependence within the past 3 months. Patients were also excluded if they had received aripiprazole in a prior clinical study, had taken a selective serotonin reuptake inhibitor within 2 weeks before screening, or if they had taken an investigational drug within 4 weeks before randomization. Patients were included in the analyses if they had a neurocognitive assessment at baseline and at least one follow-up assessment (aripiprazole=76 and olanzapine=93, total *n*=169). Table 1 presents the demographic and symptom ratings for the sample, divided according to treatment group. Of the 255 patients enrolled in the study, 109 (43%) completed the entire 26-week protocol [60 subjects (47%) from the olanzapine group and 49 subjects (38%) from the aripiprazole group]. Of the 146 patients who discontinued the study, 21 were lost to follow-up, 23 withdrew consent for personal reasons, 46 discontinued due to adverse events, 39 discontinued due to lack of clinical response or worsening of clinical symptoms

of schizophrenia, 13 were excluded for noncompliance, and 4 were excluded for violation of protocol. The overall difference in dropout between aripiprazole and olanzapine was attributable to differences in the number of subjects who discontinued the study due to personal reasons (14 vs 9), adverse events (25 vs 21), lack of clinical response (22 vs 17), and medication noncompliance (9 vs 4); not because of lost to follow-up (8 vs 13) or protocol violations (1 vs 3). After complete description of the study to the subjects, written informed consent was obtained.

The study was designed to assess short- and longer-term neurocognitive treatment effects and included a baseline and two postbaseline assessments scheduled at 8 and 26 weeks after randomization (1:1 ratio) to either 30 mg of oral aripiprazole or 15 mg of oral olanzapine (olanzapine-treated patients received 10 mg for the first 7 days and 15 mg from day 8 onwards). The selection of the olanzapine dosing regimen was based on published clinical efficacy data (Beasley et al. 1996) and clinical practice at the time of the initiation of the study. Randomization was stratified according to prior antipsychotic therapy (conventional vs atypical). Administration of nonstudy antipsychotic medications was prohibited during the course of the study. However, prior antipsychotic medications could be tapered during the first 2 weeks of the study protocol to prevent destabilization. Patients on mood stabilizing medications before the onset of the study were maintained on these medications during the study. Anxiolytic medications (e.g., lorazepam) were permitted for use during the study for treatment of anxiety or insomnia. Twenty-one percent of aripiprazole patients compared with 10% of olanzapine patients received anxiolytic medication as a concomitant treatment. Anticholinergics (e.g., benztropine) were tapered and discontinued by the end of the second week of study treatment. At baseline, 12% of olanzapine patients and 10% of aripiprazole patients were receiving anticholinergic medications for treatment of extrapyramidal symptoms (EPS). During the study, EPS were treated with medications other than anticholinergics (e.g., propranolol). Administration of antidepressant agents was prohibited after randomization. At baseline, 12% of both olanzapine and aripiprazole patients were receiving antidepressant medication. Patients who elected to discontinue the study before completion of the 26-week trial were administered the neurocognitive battery at the time of departure.

Procedure Neurocognitive and symptom assessments were conducted at baseline, week 8, and week 26. The neurocognitive battery assessed areas commonly impaired in schizophrenia and included measures of attention, memory, executive functioning, and manual dexterity. The battery required approximately 90 min of administration time and is described below.

At baseline, subjects were administered the North American Adult Reading Test (NAART; Blair and Spreen 1989), a widely used measure of premorbid intelligence. In addition, subjects were administered the Vocabulary, Block Design, and Information subtests from the Wechsler Adult Intelligence Scale (WAIS III; Wechsler 1997) to measure current intellectual functioning.

Neurocognitive battery

The neurocognitive tests used in the study are as follows:

1. California Verbal Learning Test (CVLT; Delis et al. 1987). The CVLT is a test of learning and memory. A 16-item list is presented over five learning trials with recall assessed after each trial. After the fifth trial, a new list of 16 items is presented and recall assessed. Tests of cued and free recall for the first list are administered after short and long (20 min) delays. After the long delay recall, a 44-item recognition test is administered. The same form was used across assessment points. The dependent measures selected for the current study were: (1) list A trials 1–5 total recall (a measure of learning), (2) semantic clustering ratio (a measure of learning strategy), and (3) the discriminability index (a measure of recognition).
2. Benton Visual Retention Test–Revised (BVRT-R; Benton 1974). The BVRT-R is a test of visual memory. The subject is shown ten cards that contain abstract geometrical designs. After presentation of each card, the subject is asked to draw it from memory. The test includes different administration conditions. For the current study, Administration A was used. This administration involves a 10-s exposure with no delay. The test includes three alternate forms that were counter-balanced across assessment points. The dependent measure was the number of errors.
3. Wisconsin Card Sorting test (WCST; Heaton et al. 1993). The WCST is a test of concept formation and the ability to maintain and shift cognitive set. The computerized version used in the present study measures the ability of subjects to match a deck of stimulus cards to one of four key cards. The cards can be matched according to color, shape, or number of figures. Subjects are provided little instruction about how to match the cards; only whether their attempt(s) were correct or not. Unbeknownst to the subject, the correct sorting rule changes after ten correct matches and the subject must adjust their sorting strategy to the new matching rule. The present protocol used an abbreviated 64-card version. The primary dependent measures were (1) number of categories, (2) percent conceptual level responses, and (3) percent perseverative errors.

4. Trail Making A and B (Army Individual Test Battery 1944). This test measures fine motor speed, visual search, and the ability to alternate cognitive set. In Part A, subjects are asked to connect as quickly as possible a series of circled numbers that are haphazardly located on a sheet of paper. The numbered circles are to be connected in ascending order. Part B is similar to A except that some circles contain numbers and others letters. The subject is instructed to connect the circles by alternating between numbers and letters (e.g., 1-A-2-B-3-C and so on). The dependent measures for Parts A and B were time of completion.
5. Verbal fluency (letter and category; Spreen and Benton 1977). Tests of verbal fluency assess verbal productivity under selected search conditions. For the current study, verbal fluency was assessed under two conditions. In the letter (phonological) fluency condition, subjects were asked to generate as many words as possible that begin with a certain letter of the alphabet (e.g., F, A, and S). In the category (semantic) fluency condition, subjects were asked to generate as many exemplars of a particular category (e.g., animals, fruits, and vegetables). All trials were 1 min in length. The dependent measure was the total number of correct words generated across the two conditions.
6. Letter–Number Sequencing subtest from the WAIS-III (Wechsler 1997). This test of auditory working memory includes two conditions. In the first condition (without reordering), subjects are presented strings of letters and numbers of increasing length and asked to repeat them back in the same order. The numbers/letters are presented at the rate of approximately 1 s^{-1} . In the second condition (with reordering), strings of numbers and letters are again presented, but this time subjects are asked to reorder them, first by saying aloud the numbers in their ascending order and then the letters in alphabetical order. The dependent measures were number of correct items/responses for each condition.
7. Grooved Pegboard test (Matthews and Klove 1964). This test measures manual dexterity. The subject is instructed to insert a series of grooved metal pegs into a metal template with corresponding grooved slots as quickly as possible. Administration includes trials for right and left hand performance. The dependent measure was time of completion for the dominant hand.
8. Continuous Performance Test–Identical Pairs version (CPT-IP; Cornblatt et al. 1988). The CPT-IP is a computerized measure of sustained attention. Subjects are asked to respond to target stimuli that are flashed briefly on a computer screen by lifting up their finger from a mouse pad whenever a number repeats itself. For the current study, the two- and four-digit conditions were used. Three hundred trials were administered for

each of the two conditions. The primary dependent measure for each condition was d-prime, which indicates the response sensitivity for discrimination of target from nontarget stimuli.

Symptom assessments

Severity of psychiatric symptoms was measured using the Positive and Negative Symptom Scale (PANSS; Kay et al. 1992). The PANSS includes three scales: positive scale, negative scale, and general psychopathology scale. The positive scale items include delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness, and hostility. The negative scale items include blunted affect, emotional withdrawal, poor rapport, passive pathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general psychopathology scale includes items for somatic concern, anxiety, guilt, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The dependent measure was change from baseline for the PANSS total score.

Statistical analyses

Statistical analyses were performed using Statistical Analysis System (SAS 1990). Data were initially examined for normality of distribution and where violations occurred transformations were performed. The neurocognitive data were reduced by means of a principal components analysis (PCA) with the resultant factor scores used as the primary outcome variables in the analyses. Data from the CPT-IP had a relatively large amount of invalid and missing data due to technical and administrative problems at a subset of the sites. Because PCA requires complete cases for meaningful results, these data for the CPT-IP were analyzed separately.

We conducted two initial analyses to address the cognitive effects of aripiprazole vs olanzapine, and then two specific follow-up analyses to consider the effects of clinical state and dropout on the study results. The primary analytic approach was the last observation carried forward (LOCF) procedure, which was the original analytic plan and the way the data were presented at conferences. The data were then reanalyzed using a mixed model procedure for repeated measures analysis of variance (Gueorguieva and Krystal 2004) to confirm the LOCF results. Baseline factor scores were entered as covariates. Efficacy was assessed by examining within- and between-group contrasts on the resultant factor scores at the weeks 8 and 26 assessments.

Table 2 Factor structure for neurocognitive battery

Neurocognitive variable	Factor 1 (general cognitive functioning)	Factor 2 (executive functioning)	Factor 3 (verbal learning)
BVRT, total no. of errors	-0.66	-0.27	-0.11
Letter–no. sequencing (without reordering), total correct	0.73	0.01	-0.18
Letter–no. sequencing (with reordering), total correct	0.78	0.17	-0.02
Grooved Pegboard, time for dominant hand	-0.46	-0.09	-0.37
WCST, no. of categories	0.19	0.91	0.05
WCST, % conceptual level responses	0.17	0.95	0.06
WCST, % perseverative errors	-0.20	-0.85	-0.11
CVLT, total recall trials 1–5	0.48	0.22	0.59
CVLT, semantic clustering ratio	-0.05	0.00	0.84
CVLT, discriminability index	0.50	0.32	0.27
Verbal Fluency (total score for phonologic+semantic conditions)	0.58	0.19	0.25
Trail Making A, time to completion	-0.57	-0.12	-0.40
Trail Making B, time to completion	-0.75	-0.20	-0.22

Highest factor loadings for each variable appear in bold face type.

Treatment group changes in psychiatric symptoms and differential rates of attrition are sources of variance that could confound interpretation of study results. To address the contribution of symptom changes, the LOCF analyses were reconducted with the PANSS total score entered as a time-varying covariate. To address the effects of attrition, we first examined group differences in dropout (i.e., subjects with baseline plus at least one postbaseline assessment) using chi-square analyses. In response to the differential dropout rates, the data were then reanalyzed using propensity score weighting (Hirano et al. 2003; Rosenbaum and Rubin 1983).

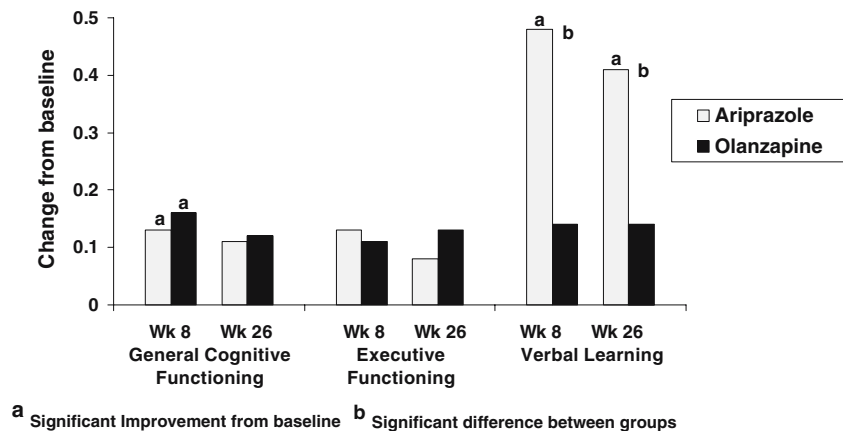
The propensity-weighting method is based on the assumption that subjects remaining in a study share, to differing degrees, characteristics with those who drop out, and these characteristics or predictor variables can be used to weigh scores to assess possible biasing effects of dropout. Propensity weighting involves a two-step process. First, logistic regression is used to identify variables that predict dropout and generate predicted probabilities for each case remaining in the study. Second, the analyses are done using the inverse of these probabilities as case weights. Cases who remained in the study, but whose propensity scores indicate they were “likely to drop out” are thus similar to those who actually did drop out. Such cases are therefore weighted more heavily in the analyses. In the current study, demographic and baseline neurocognitive factor scores were examined in the first step to determine their relationship to dropout. Variables yielding a *p* value <0.10 were retained in the logistic regression. The logistic regression model generated predicted probabilities for remaining cases (propensities). The inverse of those propensities, rescaled so that the sum of weights in each treatment group equaled one, were then used as case weights in the propensity-weighted data analyses.

Results

Examination of scores for normality of distribution showed the Trail Making A and B scores to be negatively skewed. These scores were subsequently transformed using a log transformation. The neurocognitive battery included 13 selected variables. To condense the data and reduce Type I error, we performed a PCA (Nunnally 1967). Factors yielding eigenvalues greater than 1.00 were retained (i.e., they extracted at least as much as the equivalent of one original variable; Gorsuch 1983; Kaiser 1960) for varimax (orthogonal) rotation. The results of the PCA yielded a three-factor solution. The resultant factors were labeled general cognitive functioning (factor 1), executive functioning (factor 2), and verbal learning (factor 3; see Table 2). A number of neurocognitive variables including measures of visual memory, manual dexterity, verbal recognition memory, working memory, verbal fluency, and psychomotor speed loaded on the general cognitive functioning factor. This factor accounted for approximately 40% of the overall variance. The remaining two factors loaded primarily on two measures, the WCST and CVLT, respectively. These factors best represent individual measures and the method variance tied to those measures. Consistent with the data reduction purpose of these analyses, the factor labels were used to facilitate presentation of results and not to identify constructs. Factors 2 and 3 accounted for an additional 13 and 9% of the overall variance, respectively.

Initially, the data from the two treatment groups were examined for baseline comparability on demographics, symptoms, measures of current and premorbid intellectual functioning, and baseline scores from the neurocognitive battery (Table 1). The two groups were comparable in their demographic characteristics, premorbid and current intellectual functioning, and symptom severity ratings.

Fig. 1 Mean change from baseline to weeks 8 and 26 for aripiprazole vs olanzapine on general cognitive functioning, executive functioning, and verbal learning factors (LOCF analyses)



The results from the LOCF analyses are illustrated in Fig. 1. An increase in factor score value indicated improvement in neurocognitive functioning. For factor 1 (general cognitive functioning), both aripiprazole and olanzapine showed significant improvement from baseline at week 8 ($p=0.023$ and 0.015 , respectively) that fell to a trend at week 26 ($p=0.055$ and 0.087 , respectively). There were no significant between-group differences at either week 8 or 26 comparisons. Results from the mixed model analyses were similar to the LOCF analyses. Both groups showed improvement from baseline to week 8 (aripiprazole: $t=2.29$, $df=166$, and $p=0.024$; olanzapine: $t=2.68$, $df=166$, and $p=0.008$), and there were no overall group differences ($F=0.00$, $df=1,166$, and $p=0.99$). The primary difference in the results for the mixed model analyses was that the group trends for improvement at week 26 seen in the LOCF analyses were no longer evident.

For factor 2 (executive functioning), the results from the LOCF analyses failed to show significant improvement from baseline to week 8 or 26 for either group (all $p>0.20$) and there were no between-group differences. The results from the mixed model analyses yielded the same findings.

For factor 3 (verbal learning), the results from the LOCF analyses revealed that aripiprazole showed a significant improvement from baseline at both week 8 ($p<0.0001$) and week 26 ($p<0.0001$); olanzapine did not. Examination of between-group differences at these assessment points revealed a significant difference in favor of the aripiprazole group compared to the olanzapine group at both week 8 ($p=0.020$) and week 26 ($p=0.040$). For the mixed model analyses, aripiprazole showed a significant improvement from baseline at both week 8 ($t=4.94$, $df=166$, and $p<0.0001$) and week 26 ($t=3.02$, $df=166$, and $p=0.003$); olanzapine showed a trend at week 8 ($t=1.96$, $df=166$, and $p=0.052$) but no significant improvement at week 26 ($p>0.25$). There was a significant overall effect of group favoring aripiprazole over olanzapine ($F=4.97$,

$df=1,166$, and $p=0.027$). Follow-up of between-group contrasts at the assessment points revealed the group difference to be due largely to a significant difference favoring aripiprazole at week 8 ($F=5.58$, $df=1,166$, and $p=0.019$) that was smaller and nonsignificant at week 26. In sum, both the LOCF and mixed model analyses showed within group improvement from baseline for aripiprazole at the weeks 8 and 26 assessment points and both analyses showed a significant group difference favoring aripiprazole. The LOCF analyses indicated a more stable pattern over the 26-week period, whereas the more conservative mixed model analyses indicated group differences only at week 8.

CPT-IP As mentioned in the “Statistical analyses” section, data from the two conditions of the CPT-IP were analyzed separately. For the two-digit condition, the results of the LOCF analyses on the smaller CPT-IP data set indicated a significant improvement from baseline for aripiprazole at week 8 ($p=0.034$) and week 26 ($p=0.027$); but no significant changes for olanzapine. There were no differential treatment effects at either week 8 or 26. For the four-digit condition, there were no significant within- or between-group effects for either aripiprazole or olanzapine (all $p>0.30$). For the mixed model analyses of the two-digit condition, aripiprazole showed a significant improvement at week 8 [$t(109)=2.74$ and $p=0.007$] that was weaker and nonsignificant at week 26 ($p=0.16$). There were no differential treatment effects.

Analyses with PANSS as time-varying covariate When the LOCF analyses of the factor scores and CPT data were conducted with the PANSS total score entered as a time-varying covariate for weeks 8 and 26 assessment points, the results remained essentially the same. That is, the significant results remained significant and nonsignificant results remained nonsignificant.

Propensity-weighted analyses A chi-square analyses of treatment group×dropout indicated a significant overall effect ($\chi^2=4.08$ and $p=.043$), indicating greater dropout for the aripiprazole group relative to the olanzapine group. Examination of predictor variables indicated that older age, male gender, and lower scores on the baseline neurocognitive executive functioning factor were the strongest predictors of dropout. To assess whether the differential treatment effect favoring aripiprazole on the verbal learning factor was influenced by dropout, propensity weighted scores were calculated for this factor and these scores were entered into a mixed model analyses. The overall group effect favoring aripiprazole vs olanzapine remained significant ($F=4.80$, $df=1,166$, and $p=0.030$). Like the mixed model analyses without the propensity weightings, the overall group effect was largely due to group differences at week 8 ($F=5.81$, $df=1,166$, and $p=0.017$) that were smaller and nonsignificant at week 26.

Discussion

The primary aim of this open-label study was to compare the neurocognitive effects of aripiprazole vs olanzapine in schizophrenia and schizoaffective disorder outpatients over a 26-week protocol. In general, the findings revealed aripiprazole and olanzapine to be comparable in their effects on neurocognition. On a factor that represented general cognitive functioning, and accounted for most of the variance in the overall battery, both the aripiprazole group and the olanzapine group showed small but significant improvements from baseline that were relatively stable over the 26-week period. The two other factors, executive functioning and verbal learning, that loaded primarily on the WCST and CVLT, respectively, accounted for much less of the variance in the neurocognitive battery. For the executive functioning factor, neither treatment group showed significant improvement from baseline or any differential treatment effects. For the verbal learning factor, aripiprazole showed a differential treatment effect compared to olanzapine that was primarily accounted for by differences at week 8. For the separate analyses conducted on the measure of sustained attention, no differential treatment effects were observed.

Regarding the differential treatment effect on verbal learning, the magnitude of the effect size for aripiprazole vs olanzapine was modest, falling in the small to medium range ($d=0.36$; Cohen 1988). The two CVLT variables that loaded highest on this factor included the ability to acquire new verbal information (total recall trials 1–5) and the use of efficient organizing strategies to facilitate recall (semantic clustering ratio). The CVLT total recall measure is a commonly used measure to assess verbal learning in

schizophrenia and is frequently used in studies of neurocognitive predictors of functional outcome (Green 1996; Green et al. 2000). Performance gains associated with olanzapine treatment on this list learning measure were more modest than that noted in other studies (Harvey et al. 2006; Purdon et al. 2000; Stip et al. 2003). The performance differences may be linked to differences in the measures, characteristics of the samples, dosing levels, or length of treatment, and may have contributed to the magnitude of the effect size favoring aripiprazole in the current study. It should also be noted that the group difference favoring aripiprazole over olanzapine in the mixed model analyses was largely due to differences at week 8 that were smaller and nonsignificant at week 26. The waning strength of effects may be due to declining sample size or changes in the composition of the sample. The difference between the LOCF and mixed model analyses may be due to larger performance differences being carried forward in the LOCF analyses compared with the parameter estimates used for missing cases in the mixed model procedure.

Higher levels of performance on list learning measures such as the CVLT are linked to better community outcome, better social problem-solving ability, and rehabilitation success (Green et al. 2000). There is optimism in the field that improvements in cognition such as verbal learning will lead to improvements in real world functioning. However, it is unknown whether changes in cognition will lead directly to improvements in functional outcome in patients with schizophrenia. It may be more likely that changes in cognition will enable patients to acquire component skills (e.g., coping strategies and communication skills) necessary to succeed in the workplace or social environments, and the incorporation of these skills in their daily lives will lead to improvements in work and social functioning.

The study yielded a differential dropout for the two drugs with more patients dropping from the aripiprazole than the olanzapine group. The differences in dropout may be due to differences in dose-related side effects (e.g., restlessness) or other random factors, but may be due to the open-label nature of the study and the possibility that clinicians had a lower threshold for removing subjects from the arm with an investigational drug (aripiprazole was not an FDA-approved antipsychotic medication at the time of the study). The 30-mg/day of aripiprazole dose may have led to some of the excess dropout in this group. Premarketing studies do not suggest any additional clinical benefit from doses above 15 mg/day, and the higher dose may have been associated with increased side effects. It is not possible to know for sure what the results would have yielded had dropout for the two drugs been comparable. However, when the effects of dropout were estimated in the statistical analyses, the primary findings on cognition remained the same.

The primary finding from this open label study is that aripiprazole is at least as good as olanzapine on general cognitive functioning, executive functioning, and attention, and may be better at improving verbal learning. Interpretation of the results on verbal learning requires consideration of a number of potential confounds. First, the open-label nature of the study should be considered. Findings from open-label studies deserve a more conservative interpretation than double-blind studies. However, it is not obvious how a potential bias or difference in expectation would lead to a differential treatment effect in one cognitive domain, but not the others. Second, the differential treatment effect could be related to differential effects of the two drugs on psychiatric symptoms. However, the results were unchanged when the PANSS total score was entered as a time-varying covariate in the analyses. Third, group differences at baseline could potentially bias the results in favor of one group over the other. Here, randomization procedures resulted in the two groups being comparable across demographic, clinical, and neurocognitive variables at baseline. In addition, the contribution of baseline neurocognitive functioning was addressed in the analyses by entering baseline neurocognitive factor scores as covariates. Fourth, the results cannot be due to differential coadministration of adjunctive anticholinergic medications that can produce adverse effects on memory functioning because the study protocol required discontinuation of anticholinergics 2 weeks after randomization to drug. Fifth, dosing is a general consideration in studies of this type. The level of olanzapine used in the present study falls within the therapeutic range, was comparable to that used in a multisite trial of the neurocognitive effects of olanzapine vs haloperidol and risperidone (Purdon et al. 2000), and was held stable over the course of the trial. Sixth, interpretation of the factors derived from the PCA is limited in that we had different indices but not different measures for the executive functioning and verbal learning factors. Hence, these factors may represent method differences between these and other measures in the battery and not necessarily independent cognitive constructs. Seventh, it is possible that sampling methods may have affected the study results. Subjects who had received aripiprazole in a previous clinical trial were not included, but subjects who had previously been maintained on olanzapine were. Therefore, it is possible that the study included a number of subjects who had a poor previous clinical response to olanzapine and were seeking an opportunity to try a novel drug. Eighth, given that the study did not use alternate forms for the CVLT, it is possible that the findings on verbal learning reflect enhanced practice effects and not direct benefits on learning per se. However, it should also be noted that schizophrenia patients generally show minimal practice effects on list learning measures such as the CVLT.

This study used an open-label study and it will be important to replicate these findings in a double-blind

design. Given the suggestion for a treatment-related difference in verbal learning, future studies may wish to target this neurocognitive domain using a more specialized battery aimed at assessing a wide range of memory-related processes. If replicated, these findings would suggest that the D₂ partial agonism of aripiprazole might have specific cognitive benefits compared with the full antagonism of other antipsychotic medications.

Acknowledgements The authors would like to thank the patients and staff of the participating hospitals and clinics who made this study possible. Dr. Kern, Dr. Green, and Dr. Cornblatt have served as consultants for Otsuka America Pharmaceutical and Dr. Green and Dr. Cornblatt have also served as consultants for Bristol-Myers Squibb Company. Dr. Kern, Dr. Green, and Dr. Cornblatt received no funds or other compensation for preparation of this manuscript. The data analyses were conducted by Jim Mintz, Ph.D., UCLA Department of Psychiatry and Biobehavioral Sciences and Department of Veterans Affairs VISN 22 MIRECC. Funding for this research study was provided by Otsuka America Pharmaceutical.

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