CNS Drugs (2012) 26:975–982
DOI 10.1007/s40263-012-0003-4

SHORT COMMUNICATION

Effect of Aripiprazole on Verbal Memory and Fluency in Schizophrenic Patients

Results from the ESCAPE Study

Chris Bervoets · Manuel Morrens · Kristof Vansteelandt · Frank Kok · Annick de Patoul · Veronique Halkin · Didier Pitsi · Eric Constant · Joseph Peuskens · Bernard Sabbe

Published online: 22 September 2012

Abstract
Background Second-generation antipsychotics have gradually replaced first-generation antipsychotics as first-line treatment for patients with schizophrenia. Some positive effects on verbal cognition have been shown for the second-generation antipsychotics, but most studies are based on relatively small numbers of patients.
Objective In the frame of the prospective, multi-centre, open-label study ESCAPE (A Prospective, Multicenter, Open-Label Study to Evaluate the Effectiveness and the Effect on Cognitive Function of a Treatment With Aripiprazole in a Broad Range of Schizophrenic Patients; clinicaltrials.gov identifier NCT00329810) evaluating the effectiveness and effect on cognitive functioning of aripiprazole in schizophrenic patients, we conducted a post hoc analysis to examine changes in verbal cognition and investigate the predictive value of a cognitive improvement on quality of life.
Study Design This was a prospective, multi-centre, non-comparative, open-label study of aripiprazole in schizophrenic patients. At study enrolment, these patients were being treated with various first- or second-generation antipsychotics or were without previous antipsychotic treatment. On entering the study, all patients were treated with aripiprazole (Abilify®; Otsuka, Tokyo, Japan) monotherapy; those patients who had received prior treatment with antipsychotics had their current drug(s) tapered off over a 2-week period. A post hoc analysis of the effect of aripiprazole on two verbal cognitive measures and their correlation with efficacy measures and quality of life was conducted.
Setting Patients with schizophrenia were recruited in 56 psychiatric hospitals.
Patients A total of 361 patients with schizophrenia, ranging from 18 to 65 years, entered the study.
Intervention Patients were treated with aripiprazole monotherapy at a dosage of 10–30 mg/day. Those who were receiving first- or second-generation antipsychotics at enrolment were switched to aripiprazole monotherapy by tapering off their current drug(s) over a 2-week period.
Main Outcome Measure Physician- and patient-rated parameters were measured to gain a complete view of the effectiveness of aripiprazole on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) at baseline and at weeks 4, 8 and 12 and on the Clinical Global Impression—Severity of Illness (CGI-S) scale at baseline and at weeks 1, 2, 4, 8 and 12. A secondary

C. Bervoets (✉)
Psychiatric Hospital Onze Lieve Vrouw,
Koning Albert 1 laan 8, 8200 Brugge, Belgium
e-mail: chris.bervoets@ua.ac.be

C. Bervoets · M. Morrens · B. Sabbe
Collaborative Antwerp Psychiatric Research Institute,
Antwerp, Belgium

M. Morrens
Psychiatric Centre Broeders Alexianen, Boechout, Belgium

K. Vansteelandt · J. Peuskens
University Psychiatric Centre KU Leuven, Kortenberg, Belgium

F. Kok
MSOURCE, Vianen, The Netherlands

A. de Patoul · V. Halkin · D. Pitsi
Bristol-Myers Squibb SA, Braine-l'Alleud, Belgium

E. Constant
Cliniques Universitaires Saint Luc, Brussels, Belgium

B. Sabbe
Psychiatric Hospital Sint Norbertus, Duffel, Belgium

endpoint of verbal cognitive function was measured by the California Verbal Learning Test (CVLT) and the Verbal Fluency (VF) test at baseline and at weeks 4 and 12. The hypothesis of an improvement in verbal cognition and its predictive value on the quality of life was formulated during data collection.

Results 238 patients completed the study. A significant improvement in verbal cognition was observed from week 4 with the long term free recall (LTFR) in the CVLT over the scheduled visits in the trial ($F(2,519) = 29.67$, $p < 0.0001$). For the phonemic (letter) subtest of the VF test, patients scored significantly better at week 12 in comparison with baseline ($F(2,519) = 3.57$, $p = 0.0289$). There was no significant effect on the semantic (categories) subtest of the VF test ($F(2,518) = 0.57$, $p = 0.5614$). Improvement in CGI-S scores at a particular moment in time predicted improvement in LTFR scores at that same moment ($F(1,519) = 38.38$, $p < 0.0001$) and in the phonemic ($F(1,519) = 42.77$, $p < 0.0001$) and semantic ($F(1,518) = 67.43$, $p < 0.0001$) subtests of the VF test. Similarly, CGI-S score improvement globally predicted quality-of-life improvement over visits. The Q-LES-Q scales leisure ($F(1,144) = 14.03$, $p < 0.0001$) and social relations ($F(1,469) = 5.28$, $p = 0.0220$) also directly correlated with verbal cognition.

Conclusion The findings suggest that switching to, or initiating aripiprazole in schizophrenic patients results in improvement in verbal cognitive functioning. The observed improvement on quality of life is explained by the effect of aripiprazole on the CGI-S score, though the leisure and social relations scales of the Q-LES-Q also independently correlated with verbal fluency. Randomized, controlled, clinical trials of this effect of aripiprazole for selected patients are needed.

1 Introduction

Second-generation antipsychotics (SGAs) are becoming the first-line treatment for patients with schizophrenia. They are at least as effective as first-generation antipsychotics (FGAs) in the treatment of positive and negative symptoms [1] and also appear to have a positive effect on the cognitive symptoms [2] of the illness. The enhancement of different aspects of cognition is correlated with a better outcome in schizophrenia, thus reducing the impact on the cost and disability associated with the disease. This is particularly true for verbal memory, and to a lesser extent verbal fluency [2]. Specific treatment of the verbal cognitive deficit seems to be largely independent of the psychotic symptoms of the illness [3] and verbal cognitive deficits are more enduring than psychotic symptoms. These cognitive deficits are strongly linked to impairments in community outcome, subjective quality of life and rehabilitation success [4].

In a recent meta-analysis, Leucht et al. [1] reported that only amisulpride, clozapine, olanzapine and risperidone were better than FGAs in terms of overall efficacy but with small to medium effect sizes. In the same study, other SGAs were not more efficacious than the FGAs, even for negative symptoms, and differences were highlighted between SGAs regarding their sedating properties, their propensity for inducing extrapyramidal symptoms (EPS) and for inducing weight gain. Cognitive functioning was not assessed in this meta-analysis. Woodward et al. [5] showed that in prospective, double-blind, randomized trials comparing an SGA with haloperidol, overall cognitive performance in patients with schizophrenia taking haloperidol also improved. Only doses of haloperidol >24 mg showed a negative effect on cognition compared with an SGA. For two out of the six tests (digit symbol substitution and verbal fluency) the magnitude of change observed in the haloperidol arm was significantly less than practice effects, indicating not only a deleterious effect of high doses of haloperidol, but also a negative effect of haloperidol in specific cognitive domains, these effects probably not being the sole explanation to the broader cognitive improvements observed with SGAs.

Aripiprazole is a partial agonist at dopamine D_2, D_3 and serotonin 5-HT_{1A} [6–8] receptors and is an antagonist at 5-HT_{2A} receptors. Aripiprazole is effective in short-term (4–6 weeks) [9] and long-term (26–52 weeks) alleviation of the positive symptoms of schizophrenia [10] and is well tolerated [11].

Riedel et al. [12] evaluated the cognitive effect of aripiprazole in the treatment of schizophrenic patients in an open-label 8-week trial that demonstrated significant improvement in verbal memory. Kim et al. [13] also reported on the improvement in verbal cognitive function in 40 schizophrenic patients after switching to aripiprazole in a 26-week, open-label, multi-centre study.

The present study was a planned post hoc evaluation of the data from an effectiveness study of aripiprazole, the ESCAPE study (A Prospective, Multicenter, Open-Label Study to Evaluate the Effectiveness and the Effect on Cognitive Function of Treatment With Aripiprazole in a Board Range of Schizophrenic Patients; clinicaltrials.gov identifier NCT00329810) [14], and specifically examined the verbal cognitive function of the patients after a switch from other antipsychotics to, or an initiation of, a treatment with aripiprazole in relation to two clinical outcome measures, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Clinical Global Impression—Severity of Illness (CGI-S) scale.

We hypothesize that treatment with aripiprazole leads to an improvement in verbal cognition in male and female

schizophrenic patients. In addition, we hypothesize that the improvement in verbal cognition and/or in the severity of the illness will lead to an improvement in the patient's self-reported quality of life.

2 Patients and Methods

2.1 Study Design

The ESCAPE study was a prospective, multi-centre, uncontrolled, open-label study that was designed to assess the effectiveness and verbal cognitive function of a 12-week treatment with aripiprazole in patients with schizophrenia. Patients were recruited between March 2005 and March 2006 from 55 centres in Belgium and one centre in Luxembourg. The decision to prescribe aripiprazole or to switch from another antipsychotic to aripiprazole, as well as the final dose, was based on the physician's judgement and was clearly separated from the decision to include any patient in the study. All baseline assessments were done at the time of inclusion in the study. Clinical and verbal cognitive assessments were repeated at weeks 4 and 12 (end of study). This study was conducted in accordance with Good Clinical Practice (defined by the International Conference on Harmonization), the ethical principles underlying the EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study was also in line with all regulatory requirements of participating countries and the ethical guidelines of the Declaration of Helsinki. Patients were required to give written informed consent.

2.2 Patients

The study population included male or female patients aged 18–65 years, who had been diagnosed with schizophrenia as defined by the DSM-IV-TR criteria and for whom an antipsychotic switch was deemed clinically necessary or an initiation of aripiprazole was required. A baseline CGI-S score between the range of 2–6 (inclusive) was required. Exclusion criteria were a schizoaffective or bipolar disorder, depression or organic brain syndromes; treatment with a long-acting antipsychotic with the last dose within 3 weeks of treatment; initiation or being enrolled in a clinical trial with any investigational agent (including aripiprazole) within the last month; a history of seizures, stroke, neuroleptic malignant syndrome or epilepsy; active suicidal ideation; meeting DSM-IV-TR criteria for any significant psychoactive substance use disorder within 3 months prior to screening; and pregnancy, breastfeeding or refusal to use contraception. A total of 361 patients entered the study of which 238 patients completed the study.

2.3 Study and Concomitant Medications

Aripiprazole was administered once daily with a starting dose of 15 mg/day. The investigator decided the dose adjustments but within a total daily dose range of aripiprazole of a minimum of 10 mg/day and a maximum of 30 mg/day. Concomitant antipsychotics were forbidden except during the first 2 weeks of the study when pre-study medication needed tapering off. Mood stabilizers and antidepressants were allowed if they had been administered prior to study commencement. Use of benzodiazepines and anticholinergics during the study were permitted.

2.4 Clinical Outcome Measures

The results of the primary effectiveness analysis are reported in another article [14]. Secondary effectiveness measures were evaluated on two levels as follows: (1) by physicians, using the CGI-S scale; and (2) by patients, using the Q-LES-Q.

The CGI-S scale was assessed at baseline and at weeks 1, 2, 4, 8 and 12 and the Q-LES-Q was assessed at baseline and at weeks 4, 8 and 12. Quality of life was measured with the Q-LES-Q, a questionnaire that assesses for the dimensions of physical functioning, household duties, work, leisure, social support and relationships and subjective feelings. The Q-LES-Q has been frequently used in recent investigations into the subjective quality of life of schizophrenic patients [3].

2.5 Verbal Cognitive Measures

Verbal cognitive function was monitored using two tests, the California Verbal Learning Test (CVLT) and the Verbal Fluency (VF) test. With the CVLT, examinees are read a list of words and are asked to recall them across a series of trials. This test has been shown to accurately assess learning potential in patients with schizophrenia [15]. The VF test consists of two subtests in which participants have to say as many words as possible from a category in a given time. This category can be semantic (category) or phonemic (letter). These tests were undertaken at baseline and at weeks 4 and 12.

2.6 Statistical Analysis

To examine the evolution of verbal cognitive measurements over time, repeated measures analyses were performed with mixed models. This statistical methodology uses all available data, can properly account for correlation

between repeated measurements on the same subject, has greater flexibility to model time effect and can handle missing data more appropriately [16]. These analyses are performed with cognitive variables as criteria and visits and gender as categorical predictor variables. In addition, to examine the co-evolution of cognitive measures and CGI-S, models were estimated with measurements of CGI-S at the different visits as time-varying covariates. For quality of life, similar mixed models were estimated with the quality-of-life scales as criteria and visits as categorical predictor variables and CGI-S and cognitive measurements as time-varying covariates. For all analyses, statistical significance was set at the level of the 95 % confidence interval (CI). For these models, different alternative specifications of the error covariance structure were considered including the 'compound symmetry' (CS), 'Huynt-Feldt' (HF) and the 'Unstructured' (UN) form as suggested by Wolfinger and Chang [17]. For each model, an optimal error-covariance structure was selected on the basis of likelihood ratio tests, Akaike's information criterion and the Bayesian information criterion (AIC, BIC) [18, 19]; these criteria allow one to choose an optimal choice between model fit and model complexity. All analyses were done with the Statistical Analysis Software (SAS) version 9.2.

Table 1 Patient baseline and demographic characteristics

Characteristics	Patients receiving aripiprazole, n = 361
Age, years, mean (±SD)	36.1 (11.8)
Gender, n (%)	
Male	204 (56.5)
Female	157 (43.5)
Race, n (%)	
White	342 (94.7)
Black	5 (1.4)
Asian	6 (1.7)
Other	8 (2.2)
Duration of illness, n (%)	
<5 years	173 (50.1)
5–10 years	83 (24.1)
>10 years	89 (25.8)
CGI-S score, mean (±SD)	4.3 (1.0)
Normal, n (%)	0 (0)
Borderline ill, n (%)	16 (4.5)
Mildly ill, n (%)	65 (18.1)
Moderately ill, n (%)	125 (34.8)
Markedly ill, n (%)	110 (30.6)
Severely ill, n (%)	43 (12.0)
Extremely ill, n (%)	0 (0)

CGI-S Clinical Global Impression—Severity, *SD* standard deviation

3 Results

3.1 Patient Disposition and Demographics

In total, 363 patients were enrolled; two patients were baseline failures so 361 patients took study medication. Just above one in four (26.4 %) patients took more than one antipsychotic including an FGA. Of all the participants, 238 patients (65.9 %) remained on the study medication for the entire 12-week treatment period. The most common reasons cited for study discontinuation were adverse events (9.7 %), lack of efficacy (8.3 %), withdrawal of consent (6.9 %) and loss to follow-up (6.6 %). The baseline demographic characteristics of the study participants are summarized in Table 1. At baseline, 87.3 % of patients were currently taking antipsychotic medications. Among the medications taken by the participants prior to the study, risperidone (20.7 %) and olanzapine (16.3 %) were the most frequently prescribed. A group of patients (3.1 %) were drug-naïve. The most commonly cited primary reasons for study participation are shown in Table 2.

3.2 Dosing and Concomitant Medication

Aripiprazole was started at a dose of 15 mg while the mean daily dose at endpoint was 17.8 mg/day. The majority of patients were receiving a dose of aripiprazole 15 mg/day at study end, although 40 patients (17.0 %) received 10 mg/day and 53 patients (22.5 %) received 30 mg/day. In total, 80.6 % of patients were taking one or more concomitant medications, as can be expected in this population.

3.3 Effectiveness of Aripiprazole on Verbal Cognitive Function and Relationship Over Time with Clinical Global Impression—Severity of Illness (CGI-S)

The four different verbal cognitive measures of the CVLT, short term free recall (STFR), long term free recall (LTFR), short term cued recall (STCR) and long term cued recall (LTCR), were very highly correlated at baseline (Pearson's r ranging from 0.84543 to 0.91432, $p < 0.0001$). The phonemic (letter) and semantic (categories) measures of the VF test were highly correlated as well (r = 0.69091, $p < 0.0001$). Given these high correlations and in order to keep Type I errors under control, only one measurement from the CVLT (LTFR) was retained. The VF test showed different results for both letter and category subtests and was retained.

Results of a mixed model with LTFR of the CVLT as the criterion and subject-specific intercepts and slopes for visits, and fixed effects for gender, and CGI-S (time-varying

Table 2 Primary reason for initiating or switching to aripiprazole

Category	n (%)
No antipsychotic in past	11 (3.1)
Antipsychotic in past but not currently	35 (9.7)
Currently taking antipsychotic	315 (87.3)
Lack of efficacy	
Positive symptoms	78 (24.7)
Negative symptoms	70 (22.2)
Other	
Intolerability	9 (2.9)
Somnolence	23 (7.3)
Weight gain	57 (18.0)
Prolactin elevation	8 (2.5)
Akathisia	3 (1.0)
Other EPS	8 (2.5)
Lipid abnormality	3 (1.0)
Glucose abnormality	4 (1.3)
Other	9 (2.9)
Other	
Cognition	11 (3.5)
Energy	25 (7.9)
Mood	5 (1.6)
Other	3 (1.0)
No reason reported	34 (10.5)

EPS extrapyramidal symptoms

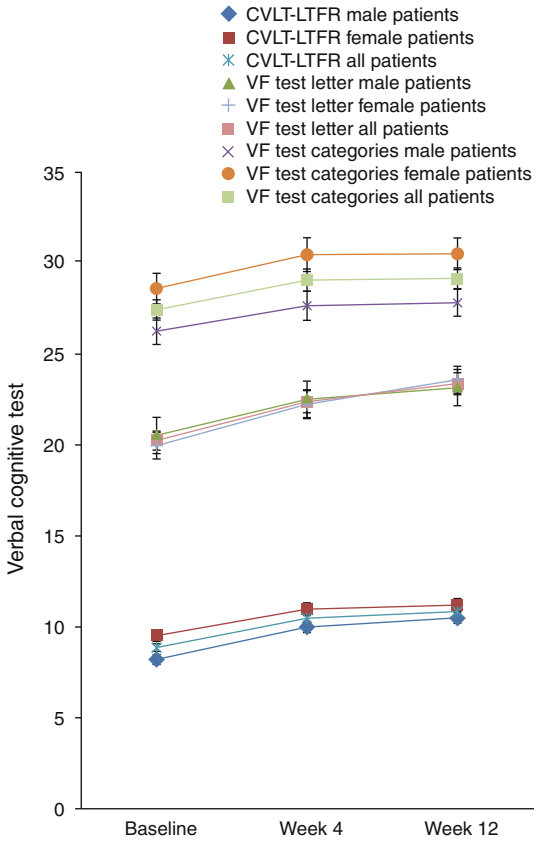

Fig. 1 Effectiveness of aripiprazole on verbal cognitive function over visits. *CVLT* California Verbal Learning Test, *LTFR* long term free recall, *VF* verbal fluency; *$p < 0.0001$, **$p = 0.0289$

covariate) as predictors showed a significant improvement in LTFR over the scheduled visits in the trial, $F(2,519) = 29.67$, $p < 0.0001$. As depicted in Fig. 1, patient improvement was already significant at week 4 and remained so until endpoint (week 12). Furthermore, at all visits, women scored significantly higher than men on LTFR, $F(1,347) = 6.01$, $p = 0.0147$ (no significant visit × gender interaction, $F(2,519) = 1.55$, $p < 0.2128$). Finally, improvement in CGI-S scores at a particular moment in time predicted improvement in LTFR scores at that same moment, $F(1,519) = 38.38$, $p < 0.0001$. The effect sizes for all verbal cognitive measures of the CVLT from baseline to endpoint are shown in Table 3.

For the VF test, a different pattern was observed. In the phonemic (letter) subtest, there is a main effect of visits, $F(2,519) = 3.57$, $p = 0.0289$, with patients scoring significantly better at week 12 in comparison with baseline, as depicted in Fig. 1. For this subtest, gender differences or an interaction between gender and visit were not observed (main effect, $F(1,348) = 0.09$, $p = 0.7707$, visit × gender interaction, $F(2,519) = 0.73$, $p = 0.4813$). The semantic part (categories) yielded no significant changes over visits, and male patients perform consistently at a significantly lower level than female patients (main effect visit, $F(2,518) = 0.57$, $p = 0.5614$, main effect gender, $F(1,348) = 6.33$, $p = 0.00123$, visit × gender interaction, $F(2,518) = 0.12$, $p = 0.8840$). Finally, for both the phonemic and semantic subtests, improvement in CGI-S score at a particular visit predicted improvement in VF test scores at that visit ($F(1,519) = 42.77$, $p < 0.0001$, and, $F(1,518) = 67.43$, $p < 0.0001$). The effect sizes for all verbal cognitive measures of both subtests of the VF test from baseline to endpoint are shown in Table 3.

3.4 Quality of Life in Relation to Verbal Cognitive Function and CGI-S

To analyse quality of life, we estimated mixed models in two steps. First, to examine the evolution of quality of life over visits, we estimated models with subject-specific intercepts and slopes with visits as predictor. The results of these first analyses are depicted in Table 4. In this table, it can be seen that quality of life improved over visits on all scales of the Q-LES-Q with the exception of work and school. Just like in the analyses for cognition, it can be seen that there is a strong improvement of quality of life from baseline to week 4, which then remains stable until study

Table 3 Effect sizes for the cognitive measures of the California Verbal Learning Test and the Verbal Fluency test

Cognitive measure	Baseline			Endpoint			Effect size (Cohen's d)
	N	Mean	Standard deviation	N	Mean	Standard deviation	
CVLT-LTCR	347	9.74063	3.80548	243	12.07819	3.54401	0.63
CVLT-STCR	346	9.40173	3.70317	245	11.79592	3.58492	0.66
CVLT-LTFR	346	8.78324	3.90122	244	10.99590	4.03737	0.56
CVLT-STFR	347	8.36023	3.89826	245	10.61633	3.97839	0.57
VF test-letter	346	20.23121	9.70096	243	23.42798	10.20887	0.32
VF test category	346	27.26590	10.33434	243	29.04527	9.46732	0.18

CVLT California Verbal Learning Test, *LTCR* long term cued recall, *LTFR* long term free recall, *STCR* short term cued recall, *STFR* short term free recall, *VF* verbal fluency

Table 4 Mixed models analysis on Quality of Life Enjoyment and Satisfaction Questionnaire scores with visits as only predictor

Scale	Baseline	Week 4	Week 12	*F*-test	*P*-value
Health	37.8330	43.9515	43.1374	$F(2,344) = 46.61$	<0.0001
Feeling	42.0175	47.9047	47.1948	$F(2,342) = 43.27$	<0.0001
Work	42.5000	44.8331	44.7537	$F(2,105) = 2.40$	0.096
Household	31.4698	34.3179	33.8062	$F(2,270) = 8.93$	0.0002
School	32.3951	31.9386	34.7700	$F(2,75) = 2.58$	0.0825
Leisure	17.8714	20.5344	19.9954	$F(2,453) = 27.16$	<0.0001
Social relations	33.3818	37.5717	36.0352	$F(2,346) = 31.45$	<0.0001
General activities	44.5347	51.6050	49.5291	$F(2,316) = 33.55$	<0.0001

end. Further, it may be noted that the two non-significant scales are domains (work and school) that are only applicable to a smaller subset of patients.

Secondly, we estimated these models again with the CGI-S scale and cognitive measures as time-varying covariates. Since the observed correlations between the six different verbal cognitive measures (at baseline) were very high, in order to avoid multicollinearity problems, only the effects of the LTFR of the CVLT and the VF letter subtest were considered. The results of these analyses are depicted in Table 5. In this table, it can be seen that for all analyses with the exception of health and feeling, there is no longer a main effect of visit after adjusting for the time-varying covariates mentioned above. In addition, for all scales, with the exception of school, the CGI-S scale is a significant time-varying covariate. These analyses imply that the improvement in quality of life over visits, which were significant in the models without covariates, may be explained by the improvement in the CGI-S score over visits. Interestingly, improvements in the leisure and social relations sub-scales of the quality-of-life scale are also predicted by improvements in LTFR. On the other hand, there is still a significant main effect of visit regarding the health and feelings scales, implying that the improvement over visits on these scales can only be partially explained by improvements in the CGI-S score.

4 Discussion

In this naturalistic study, we addressed the change in verbal cognitive functioning in schizophrenic patients during a 12-week treatment with aripiprazole.

A significant improvement in verbal cognition from baseline to endpoint was observed. On the CVLT, this improvement was significant as early as week 4, with patients remaining significantly improved at the endpoint. On the VF test, the phonemic part (letter) showed statistical improvement at week 12, while no improvement was observed in the semantic (categories) part. Interestingly, the corresponding effect sizes (Cohen's d) were of medium size for all cognitive measures obtained from the CVLT and of small size for the VF test cognitive measures, the effect sizes for the CVLT scores being consistently larger than those reported by Harvey and Keefe [2] in their meta-analysis of 20 studies reporting on cognitive changes in patients with schizophrenia treated with recent antipsychotics.

The observation of an isolated improvement in the phonemic part but not in the semantic part of the VF test is surprising. This finding might be related to the fact that the semantic part of the test involves a cognitive process of forming clusters of related words within a certain category and the switching to another cluster if the cluster is exhausted. There is a high demand of retrieval of semantically

Table 5 Mixed models analysis on Quality of Life Enjoyment and Satisfaction Questionnaire scores with visits as only predictor and Clinical Global Impression—Severity of Illness/cognitive measures as time-varying covariates

Scale	Baseline	Week 4	Week 12	Visit	CGI-S	LTFR	Letter fluency
Health	39.9342	42.0637	42.4588	F(2,478) = 7.96***	F(1,478) = 88.53***	F(1,478) = 3.55	F(1,478) = 0.43
Feeling	44.0489	45.9881	46.4335	F(2,479) = 6.44**	F(1,479) = 77.39***	F(1,479) = 2,87	F(1,479) = 0.30
Work	44.0543	43.3646	43.5691	F(2,100) = 0.14	F(1,100) = 22.86***	F(1,100) = 0.31	F(1,100) = 0.52
Household	32.9731	33.1405	33.3603	F(2,268) = 0.20	F(1,268) = 34.75***	F(1,268) = 2.70	F(1,268) = 0.00
School	33.5651	32.2524	34.0839	F(2,32) = 0.37	F(1,32) = 2.19	F(1,32) = 3.29	F(1,32) = 3.29
Leisure	18.7854	19.6521	19.5779	F(2,444) = 2.46	F(1,444) = 23.50***	F(1,444) = 14.03***	F(1,444) = 3.57
Social relations	34.9366	36.1530	35.4902	F(2,469) = 2.24	F(1,469) = 64.21***	F(1,469) = 5.28*	F(1,469) = 2
General activities	47.3005	49.4751	48.6430	F(2,368) = 2.86	F(1,368) = 87.29***	F(1,368) = 2.39	F(1,368) = 1.21

CGI-S Clinical Global Impression—Severity of Illness, *LTFR* long term free recall

* $p = 0.0220$, ** $p = 0.0017$, *** $p < 0.0001$

related words (requiring an intact semantic network and memory) in this part of the test and stable schizophrenic patients are known to have great difficulties with this [20]. It could be argued that this group of patients (half of the patients had durations of illness of more than 5 years) was in a condition of low performance on the semantic part of the test and had a lack of response when compared to the (easier) phonemic part, which only relies on associative processes in finding words. However, in this study design it was not possible to find evidence for this hypothesis. Furthermore, although the observed statistical difference between the onset of improvement in the CVLT (at week 4) and in the VF test (at endpoint) may reflect the possibility that the CVLT is a more sensitive test for detecting changes in verbal cognition in patients or having a higher impact of learning effects, again this study design could not produce evidence for this hypothesis.

Women performed better than men at baseline, although men and women displayed the same kind of improvement evolution. Gender differences in verbal learning and memory found here among schizophrenic patients, are also found in the healthy population [21], and hence do not account for a specific effect of the disease or of the treatment response of schizophrenic patients. In the phonemic part of verbal fluency, gender differences were not found, again possibly due to better-preserved associative processes in finding words.

We found a relationship over time and within a subject between improvement in illness severity and improvement in verbal cognition. It is known that a lower CGI-S score is correlated with a lower score on key schizophrenia symptoms such as positive symptoms [22]. Importantly, though somehow contra-intuitively, cross-sectional analyses have reported that these positive symptoms seem to evolve independent of cognitive function [23]. Here, using a statistical method that accounts for within-subject effects, we were able to demonstrate that when illness severity improves, verbal cognitive function improves as well. This seems much more logical in that a clinically more severe degree of illness could be expected to deeper impair verbal cognitive performance and in that more pronounced psychotic experiences could deviate more one's attentional processes from performing the task at hand, as could be adverse events such as sedation [24] or EPS. It remains, however, that a causal relationship between the improvement in the CGI-S score and the improvement in verbal cognitive function is unclear, and it seems altogether more likely that aripiprazole improves the illness, which in turn results in the observed improvement in cognition.

The observed improvement in quality of life over time is dependent on the degree of illness severity and is not related to the study duration. This means that a lower illness severity contributes the most to the prediction of a better quality of life. Although quite logically sounding, this finding is in contrast with Mohamed et al. [25], who reported no relationship between illness severity and quality of life.

Our study has several limitations that limit the interpretation of the results. It is an open trial without a control group and within a relatively short period for observing changes in verbal cognitive functioning and quality of life. Since a control group is lacking, we cannot strictly attribute the observed improvement in cognition to aripiprazole, as opposed, for example, to the tapering of previous treatments. Also, the role of practice effects on the cognitive improvement in our patient sample is not to be disregarded. Moreover, we did not control for possible confounders such as, for example, previously taken antipsychotics and duration of illness. Lastly, reduced EPS or improvements in psychopathology could account for improved scores on cognitive function tests.

As a naturalistic study, which includes a fairly large number of patients in need of medication change for different reasons and which relies on the both clinician and

patient global impressions, the results presented in this paper are of value to everyday psychiatric practice. However, further research in a design with a control group and over a longer period of time remains clearly necessary to unequivocally identify the effects of aripiprazole on the studied cognitive processes.

5 Conclusions

In this report we showed that a 12-week treatment with aripiprazole was associated with an improved disease state and verbal cognitive functioning. We found empirical evidence for a relationship between illness severity and verbal cognition. Moreover, while all aspects of quality of life were predicted by the severity of the illness, leisure and social relations were also predicted by verbal cognitive performance.

Acknowledgments This study was funded by Bristol-Myers Squibb Belgium. Data were obtained from the ESCAPE study (clinicaltrials.gov identifier NCT00329810), funded by Bristol-Myers Squibb Belgium and supported by Bristol-Myers Squibb Pharmaceuticals (Princeton, NJ, USA) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). The funding organization did not contribute to the analysis and interpretation of the data. The funding organization did not contribute to the preparation of the paper but did contribute to the review process and the approval of the manuscript. Frank Kok, senior statistician at MSOURCE, was responsible for the data analysis in the ESCAPE study. Annick de Patoul, Veronique Halkin and Didier Pitsi are, or were employees at the time, of BMS Belgium. For all the other authors in this paper, there are no conflicts of interest to report.

References

1. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31–41.
2. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry. 2001;158:176–84.
3. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007;64:633–47.
4. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004;72:41–51.
5. Woodward ND, Purdon SE, Meltzer HY, et al. A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: dose effects and comparison to practice effects. Schizophr Res. 2007;89(1–3):211–24.
6. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002;302:381–9.
7. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT(1A) receptor. Eur J Pharmacol. 2002;441:137–40.
8. Jordan S, Koprivica V, Dunn R, et al. In vivo effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function. Eur J Pharmacol. 2004;483:45–53.
9. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2002;63:763–71.
10. Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol. 2003;6:325–37.
11. Croxtall JD. Aripiprazole: a review of its use in the management of schizophrenia in adults. CNS Drugs. 2012;26(2):155–83.
12. Riedel M, Spellmann I, Schennach-Wolff R, et al. Effect of aripiprazole on cognition in the treatment of patients with schizophrenia. Pharmacopsychiatry. 2010;43(2):50–7.
13. Kim CY, Chung S, Lee JN. A 12-week, naturalistic switch study of the efficacy and tolerability of aripiprazole in stable outpatients with schizophrenia or schizoaffective disorder. Int Clin Psychopharmacol. 2009;24(4):181–8.
14. Peuskens J, Bervoets C, Kok F, et al. A prospective, multicentre, open-label study to evaluate the effectiveness of aripiprazole in the treatment of a broad range of patients with schizophrenia. Eur Psychiatry. Epub 2011 Sept 13.
15. Vaskinn A, Sundet K, Friis S. Can learning potential in schizophrenia be assessed with the standard CVLT-II? An exploratory study. Scand J Psychol. 2008;49(2):179–86.
16. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry. 2004;16:310–7.
17. Wolfinger R, Chang M. Comparing the SAS GLM and MIXED procedures for repeated measures. Cary: SAS Institute Inc.; 1998.
18. Russell D, Wolfinger R. Fitting nonlinear mixed models with the new NLMIXED procedure: repeated measures. Cary: SAS Institute Inc.; 1997.
19. Keselman HJ, Algina J, Rhonda K, et al. A comparison of two approaches for selecting covariance structures in the analysis of repeated measurements. Commun Stat Simul Comput. 1998;27:591–604.
20. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia. Am J Psychiatry. 1996;153:321–30.
21. Bozikas VP, Kosmidis MH, Peltekis A, et al. Sex differences in neuropsychological functioning among schizophrenia patients. Aust N Z J Psychiatry. 2010;44(4):333–41.
22. Wobrock T, Köhler J, Klein P, et al. Achieving symptomatic remission in out-patients with schizophrenia: a naturalistic study with quetiapine. Acta Psychiatr Scand. 2009;120(2):120–8.
23. Popolo R, Vinci G, Balbi A. Cognitive function, social functioning and quality of life in first-episode psychosis: a 1-year longitudinal study. Int J Psychiatry Clin Pract. 2010;14:33–40.
24. Harvey PD, Hassman H, Mao L, et al. Cognitive functioning and acute sedative effects of risperidone and quetiapine in patients with stable bipolar I disorder: a randomized, double-blind, crossover study. J Clin Psychiatry. 2007;68(8):1186–94.
25. Mohamed S, Rosenheck R, Swartz M, et al. Relationship of cognition and psychopathology to functional impairment in schizophrenia. Am J Psychiatry. 2008;165:978–87.