Schizophrenia Research 134 (2012) 59–64

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Assessment of the effects of AZD3480 on cognitive function in patients with schizophrenia

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ARTICLE INFO

Article history:
Received 12 June 2011
Received in revised form 5 October 2011
Accepted 11 October 2011
Available online 15 November 2011

Keywords:
Schizophrenia
Cognitive dysfunction
AZD3480
Neuronal nicotinic acetylcholine receptor

ABSTRACT

AZD3480 is a selective agonist of α4β2 central neuronal nicotinic receptors (NNRs). This study investigated its effects on cognition, relative to placebo, in 440 patients with stable schizophrenia who were taking a single atypical antipsychotic medication and who were active cigarette smokers. Mean age was 41 (range 19 to 55) years and the majority of patients (88%) had a diagnosis of paranoid schizophrenia. Patients were randomized to one of 3 doses of AZD3480: 5 mg, 20 mg, and 35/100 mg (depending on CYP2D6 metabolic status), or to placebo. Treatment was given once daily for 12 weeks. The primary outcome measure was change in cognitive function from baseline to Week 12, as measured by IntegNeuro computerized test battery of cognitive function scores. Secondary outcome measures included assessment of functional capacity (University of California at San Diego Performance Based Skills Assessment [UPSA2]) and adaptive function (Social Functioning Scale [SFS]). AZD3480 failed to improve cognition relative to placebo in this population of patients or in subpopulations defined by disposition, metabolic status, antipsychotic treatment, age, age of illness onset, and sex. Likewise, no improvement relative to placebo was observed in either the SFS measure of adaptive functioning or the UPSA2 measure of functional capacity. AZD3480 was generally well tolerated in the population studied.

1. Introduction

Schizophrenia is a severe and persistent psychiatric disorder with an onset typically in the late teenage or early adult years (Mueser and Jeste, 2008). The disorder is associated with a large economic burden in terms of both direct and indirect costs (Kendler et al., 1996; Wu et al., 2005) and is characterized by both positive symptoms such as delusions, hallucinations, and disorganized speech and behavior, and negative symptoms such as diminished social interest, volition, and affect. In addition, schizophrenia is often marked by a characteristic pattern of stable cognitive dysfunction that can be identified at, or even before, the time of a patient's initial psychotic episode (Cornblatt et al., 1992; Bilder et al., 2000). This cognitive dysfunction is distinct from the positive and negative symptoms of the condition, and is strongly associated with functional impairment (Green, 1996; Velligan et al., 1997; Green et al., 2000; Bryson and Bell, 2003; Green et al., 2004). Since schizophrenia patients with normal intelligence quotient (IQ) scores also exhibit dysfunction in memory and visual processing (Wilk et al., 2005), cognitive dysfunction in schizophrenia (CDS) is now recognized as a core feature of the disease (Gray and Roth, 2007).

To date, no pharmacologic agents have been approved specifically to treat CDS (Marder and Fenton, 2004; Bowie and Harvey, 2006) and, to this end, a collaborative program, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), proposed a series of guidelines to promote their development (Kern et al., 2004; Marder and Fenton, 2004). The US Food and Drug Administration (FDA) has since endorsed the MATRICS guidelines and has established the indication of CDS under its Critical Path program as one of high priority for drug development.

Although the causes of CDS are not well understood, post-mortem binding studies in individuals with schizophrenia have implicated deficiencies in nicotinic receptor expression, particularly of the α4β2 and α7 subtypes (Freedman et al., 1995; Court et al., 1999; Breese et al.,

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doi:10.1016/j.schres.2011.10.004

2000). Clinical and animal studies have also demonstrated the primordial role played by nicotine in cognitive processes involving memory, attention and learning either by direct stimulation of neuronal nicotinic receptors (NNRs) with subsequent acetylcholine (ACh) release, or by activation of other presynaptic receptors effecting the release of other neurotransmitters (Rezvani and Levin, 2001). Furthermore, the incidence of cigarette smoking in schizophrenic patients is extremely high relative to the general population (incidences of up to 80–90% have been reported versus 25 to 30% in the general population), raising the question of a possible attempt at self-medication, using nicotine to correct pathophysiological abnormalities of the disease (Goff et al., 1992; Dalack et al., 1998; Kumari and Postma, 2005). Indeed, nicotinic agonists have been shown to interact with NNRs to enhance cognition in animal models of cognitive function (Levin et al., 1992; Arendash et al., 1995). A nicotinic agonist that is selective for central nervous system (CNS) NNRs may therefore have the potential to enhance cognitive function in patients with schizophrenia while limiting peripheral side effects.

AZD3480 is a selective agonist of $\alpha4\beta2$ NNRs concentrated in the CNS but has negligible activity at peripheral nicotinic ACh receptors. The compound has shown cognition-enhancing properties in preclinical studies (Gatto et al., 2004) and, in healthy male volunteers, has also been shown to improve cognitive domains pertinent to those seen in CDS (Dunbar et al., 2007). Dunbar et al. (2007) examined the effects of AZD3480 in two samples of healthy controls. Participants were non-smoking, healthy males who were admitted to an inpatient unit for the 10-day duration of the study. Individuals on doses of 100 or 200 mg AZD3480 performed better on cognitive tests assessing attention and episodic memory after 10 days compared with those randomized to placebo. The effect was due both to a decline in the placebo group and improvement in the AZD3480 groups indicating perhaps that prolonged time at an inpatient unit could lead to a decrease in cognitive performance which was then reversed by the medication. The authors pointed out, however, that it is difficult to show improvements in cognition in healthy subjects who typically perform near ceiling on many cognitive tests.

The rationale for this study was based on available clinical evidence that central cholinergic neurotransmitters play an important role in cognitive function. Designed to conform to MATRICS recommendations, the aim of the study was to assess the hypothesis that 12 weeks of treatment with AZD3480 would improve cognition, compared with placebo, in patients with stable schizophrenia who were taking a single atypical antipsychotic medication and who were active cigarette smokers.

2. Methods

2.1. Study design

This Phase IIb study (Study NCT00528905) was of a multicenter, double-blind, randomized, placebo-controlled, parallel-group design conducted in adult patients with stable schizophrenia. Active cigarette smokers were selected to minimize variation due to the confounding effect of nicotine use, and because the majority of individuals with schizophrenia in western countries are active smokers. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, which are consistent with the International Conference on Harmonization/Good Clinical Practice guidelines. Approval from the Institutional Review Board or Independent Ethics Committee of each participating center was required, and written informed consent was obtained from all patients.

2.2. Drug treatment

AZD3480 is metabolized predominantly by cytochrome P450 2D6 (CYP2D6). Patients were prospectively genotyped with respect to their metabolism of CYP2D6 substrates and then stratified as either rapid or slow metabolizers (RMs or SMs). RMs were defined as patients with $\geq$1.5 functional CYP2D6 alleles who were not taking any medications known to be strong or moderate inhibitors of CYP2D6. SMs were defined as patients with <1.5 functional CYP2D6 alleles and/or were being treated with drugs known to be strong or moderate inhibitors of CYP2D6. This categorization was intended to achieve similar plasma concentrations of AZD3480 in RMs and SMs following administration of the highest-exposure dose.

The study consisted of an 8-week stability period, a 12-week treatment period with 1 of 4 treatment regimens (AZD3480 5 mg, 20 mg or 35/100 mg [SMs/RMs, respectively] or placebo) and a 2-week follow-up period (Fig. 1). Treatment was administered once daily for 12 weeks.

Patients were randomized to treatment if they had fulfilled all inclusion and exclusion criteria at enrolment and then again 2–4 weeks later, at the end of the prospective stability period. Efficacy and safety assessments were conducted 2, 6 and 12 weeks after the start of treatment. In addition, patients were contacted by telephone 9 weeks after the start of treatment for collection of adverse events (AEs) and to monitor study retention. A final follow-up assessment was conducted 2 weeks after the end of treatment.

2.3. Patient eligibility

Patients, aged 18 to 55 years, with a diagnosis of schizophrenia according to the Structured Clinical Interview for DSM-IV (SCID), including disorganized, catatonic, residual, or undifferentiated subtypes were eligible for study participation. Other key inclusion criteria were: receiving a single atypical antipsychotic medication (quetiapine, olanzapine or risperidone) for a minimum of 8 weeks and at a stable dose throughout the 4-week period before enrolment; stable psychotic symptoms without a hospitalization for psychosis over 8 weeks of

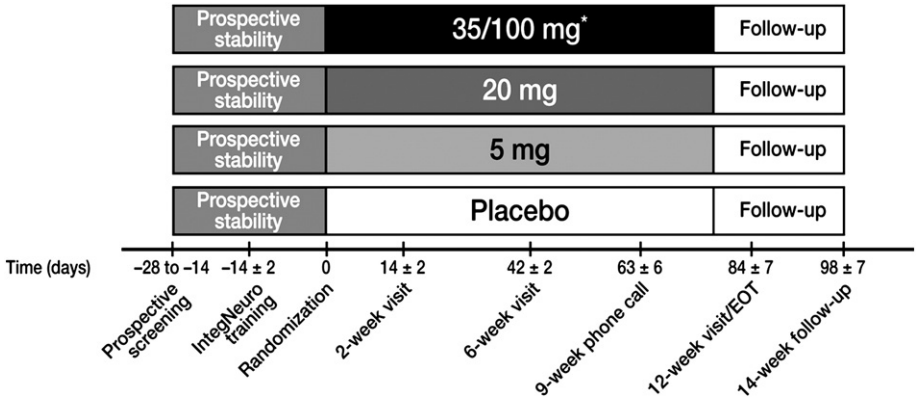

Fig. 1. Study design. *35 mg for slow metabolizers (SMs), 100 mg for rapid metabolizers (RMs). Categorization was based on the number of functional CYP2D6 alleles and concomitant CYP2D6 inhibitor medication. EOT, end of therapy.

clinical stability; no more than a "moderate" severity rating (score ≤4) measured on the Positive And Negative Syndrome Symptom Scale (PANSS) for any negative symptom item or for any item related to delusions, hallucinations, conceptual disorganization and unusual thought content; no more than a minimum level of depressive symptoms as assessed by the Calgary Depressive Scale for Schizophrenia (CDSS; total score <10); a Simpson-Angus Scale (SAS) total score of ≤6; outpatient at the time of screening and randomization, with stable housing in the community; active cigarette smoking (≥10 per day).

Key exclusion criteria included a diagnosis of schizoaffective or schizophreniform disorder; a known IQ<70 established prior to the onset of symptoms or signs of schizophrenia; use of acetylcholinesterase inhibitors, memantine, or other drugs affecting cognitive function within 8 weeks of the enrolment visit; use of smoking cessation therapy within 4 weeks of enrolment: initiation of such therapy was not permitted during the study.

2.4. Assessment of study endpoints

The primary endpoint of the study was the assessment of cognition following AZD3480 treatment, relative to placebo. This was measured by the change from baseline (time of randomization) to Week 12 (last observation carried forward [LOCF], during randomized treatment) using the IntegNeuro (Brain Resource Company Ltd, Ultimo, Australia) computerized test battery of cognitive function. Domains assessed were Attention/Vigilance, Working Memory, Verbal Learning, Speed of Processing, and Reasoning and Problem Solving. In addition, the composite score determined by the unweighted average of the 5 primary domain scores was computed. IntegNeuro is psychometrically comparable to the MATRICS Cognitive Consensus battery (Silverstein et al., 2010).

Secondary endpoints of the study included additional non-computerized cognitive tests and assessment of functional capacity. Non-computerized tests of cognition included the Wechsler Memory Scale III (WMSIII) Spatial Span, Brief Visuospatial Memory Test—Revised, and Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding score. Functional Capacity was measured by the change from baseline to Week 12 on the University of California at San Diego Performance Based Skills Assessment (UPSA2) and adaptive functioning as assessed by the Social Functioning Scale (SFS). These secondary endpoints were included to determine whether the impact of improved cognitive test performance would generalize to more face valid indices of everyday life functioning.

2.5. Statistical analyses

The efficacy analysis population included all treated patients who had at least 1 efficacy observation from the randomized treatment period. For patients who discontinued before the final visit of the randomized treatment period, the last observation from the randomized treatment period was used as the final observation. Efficacy variables were analyzed using a fixed-effect analysis of covariance (ANCOVA) model with treatment and metabolic capacity as fixed effects and baseline score as a covariate. Dunnett's multiple-comparison method was used to control for multiplicity in the comparisons of AZD3480 dose versus placebo.

Hypothesis tests were one-sided for most analyses, including the primary analysis, with p-values for the differences between the least-squares (LS) mean scores. Two-sided 95% confidence intervals (CIs) were calculated for both estimated values and estimated differences. The 95% CIs were adjusted for multiple-dose versus placebo comparisons using Dunnett's two-sided method. For the 5 cognitive function domains in the primary analysis, a globally adjusted 95% CI was calculated in the same way, as a further multiplicity adjustment across the cognitive domains using a Bonferroni adjustment.

All calculated IntegNeuro domain scores are z-scores relative to baseline, i.e., the baseline mean of the domain over all patients was subtracted from each score and divided by the baseline standard deviation. In this way, the change from baseline expresses the improvement as standard deviations of the baseline scores.

The SFS and UPSA2 scores are raw scores (i.e., with no transformations); changes from baseline represent changes in the raw points.

3. Results

3.1. Patient demographics

A total of 675 patients were enrolled into the study. Of these, 445 were randomized to treatment, 440 received treatment, and 308 completed the study. Of the 440 patients treated, 410 had at least one valid efficacy measure and were included in the efficacy analysis; the baseline demographic variables and disease characteristics for these patients are summarized in Table 1. The patients were predominantly male (70%), and had a mean age of 41 years; 43% were RMs and 57% were SMs. The majority of patients (88%) had a diagnosis of paranoid schizophrenia. The remainder met the criteria for chronic undifferentiated (8%),

Table 1
Baseline demographic and disease characteristics.

		AZD3480			Placebo	Total
		5 mg (N=116)	20 mg (N=92)	35/100 mg (N=97)	(N=105)	(N=410)
Mean age, years (SD)		41.7 (7.78)	40.9 (8.37)	40.6 (9.21)	40.6 (9.28)	41.0 (8.64)
Median		42.0	42.5	42.0	43.0	42.5
(range)		(24 to 55)	(19 to 54)	(20 to 55)	(20 to 55)	(19 to 55)
Gender, n (%)	Male	80 (69.0)	64 (69.6)	69 (71.1)	72 (68.8)	285 (69.5)
DSM-IV Schizophrenia Diagnosis n (%)	Disorganized	3 (2.6)	3 (3.3)	0	3 (2.9)	9 (2.2)
	Paranoid	101 (87.1)	81 (88.0)	85 (87.6)	94 (89.5)	361 (88.0)
	Residual	3 (2.6)	5 (5.4)	0	2 (1.9)	10 (2.4)
	Undifferentiated	9 (7.8)	3 (3.3)	12 (12.4)	6 (5.7)	30 (7.3)
Age at time of schizophrenia diagnosis (years)	Mean (SD)	27.5 (9.25)	27.9 (9.55)	27.8 (8.46)	26.9 (8.26)	27.5 (8.87)
Years since schizophrenia diagnosis	Mean (SD)	16.8 (9.07)	15.6 (9.58)	15.4 (9.29)	16.3 (9.54)	16.1 (9.34)
CDSS total score	n[a]	109	84	84	97	374
	Mean (SD)	2.5 (2.60)	2.3 (2.21)	1.9 (2.10)	2.4 (2.25)	2.3 (2.32)
CGI severity of illness score	Mean (SD)	3.3 (0.56)	3.4 (0.58)	3.2 (0.69)	3.1 (0.57)	3.3 (0.61)
PANSS total score	Mean (SD)	60.7 (12.72)	61.5 (11.82)	59.1 (12.83)	59.0 (14.04)	60.1 (12.90)
PANSS general subscale score	Mean (SD)	29.6 (7.00)	30.1 (6.79)	28.8 (7.15)	29.5 (7.47)	29.5 (7.10)
PANSS negative subscale score	Mean (SD)	16.1 (4.22)	16.0 (4.27)	15.2 (4.41)	15.0 (4.48)	15.6 (4.36)
PANSS positive subscale score	Mean (SD)	15.0 (3.77)	15.3 (3.58)	15.1 (4.45)	14.5 (4.35)	15.0 (4.05)

CDSS Calgary Depression Scale for Schizophrenia. CGI Clinical Global Impression. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. N Number of patients in treatment group. n number of patients. PANSS Positive and Negative Syndrome Scale.

[a] For all other categories, n numbers are as indicated in the table header.

disorganized (2%) and residual (2%) schizophrenia. Overall, the 4 treatment groups were balanced with respect to demographic variables, baseline characteristics, and concomitant medications.

Baseline cognitive deficits were typical of patients with chronic schizophrenia when compared with a group of 75 healthy controls taken from a separate study using the same cognitive battery (Malinovsky et al., 2009; Fig. 2).

3.2. Efficacy assessment

The results of the primary analysis indicated that AZD3480 failed to improve cognition in patients with stable schizophrenia who were being treated with an atypical antipsychotic medication and who were active smokers (Fig. 3). Similar results were seen in all subgroups defined by disposition (i.e., reason for premature discontinuation from the study), metabolic stratum, antipsychotic treatment, age, age of illness onset, and sex.

Additional non-computerized cognitive tests also showed that AZD3480 treatment had no beneficial effect on cognition relative to placebo (Table 3). Following 12 weeks of treatment with AZD3480, no improvement relative to placebo was observed in either the SFS patient-reported measure of adaptive or real-world functioning or on the UPSA2 measure of functional capacity (Fig. 4).

3.3. Safety assessment

AZD3480 was generally well tolerated. The overall incidence of AEs was similar across all treatment groups (37.9%, 38.5% and 49.0% for AZD3480 5 mg, 20 mg and 35/100 mg groups, respectively; and 47.3% for the placebo group). The most frequently reported AEs across all AZD3480-treated patients were headache (3.6%), nasopharyngitis (3.6%), and nausea (3.3%), while the most frequently reported AEs among placebo-treated patients were nasopharyngitis (5.5%), headache (4.5%), dyspepsia (4.5%), and wheezing (4.5%).

There was a slightly higher incidence of SAEs and discontinuations due to AEs in the AZD3480-treated patients, predominantly of a psychiatric nature (Table 2).

The results for clinical laboratory tests, vital signs, and ECGs were similar across treatments.

There were no changes in mean PANSS and CGI scores in comparison with baseline scores and relative to placebo, indicating that the patients' underlying disease remained stable during the study treatment period in all treatment groups.

There were no changes in mean CDSS, SAS, and BARS scores, in any of the treatment groups indicating no onset of, or increase in, depressive or extrapyramidal symptoms.

4. Discussion

AZD3480 failed to improve cognition relative to placebo as measured by the IntegNeuro computerized test battery of cognitive function

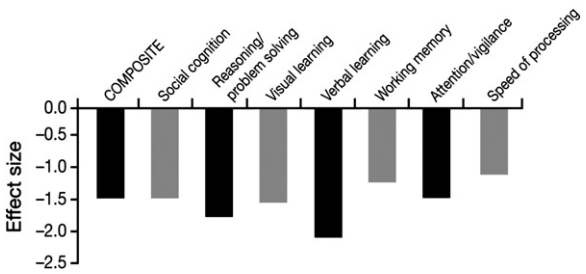

Fig. 2. Baseline cognitive domain scores relative to healthy controls. Age and gender adjusted z-scores relative to healthy controls were calculated using an algorithm provided by Brain Resource Company Ltd (Australia) based upon a regression analysis of IntegNeuro scores of healthy, normal control patients.

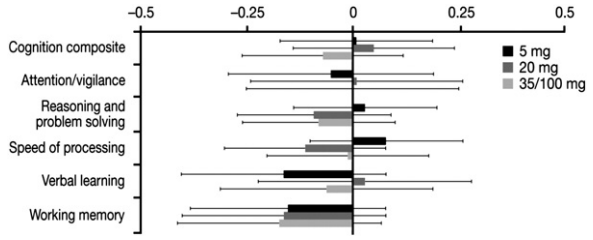

Fig. 3. Differences vs placebo in change from baseline to Week 12 (LOCF) in cognitive domains; relative effect sizes ± 95% CI. A positive difference corresponds to an advantage of AZD3480. LOCF, last observation carried forward.

scores. Likewise, no improvement relative to placebo was observed in either the SFS measure of adaptive functioning or the UPSA2 measure of functional capacity. Consistent results were observed for each endpoint in subgroups of patients defined by disposition, metabolic status, antipsychotic treatment, age, age of illness onset, and sex.

The population studied conformed to MATRICS guidelines for a phase II study in terms of stability and severity of psychiatric symptoms, level of depression, and extrapyramidal symptoms. The proportion of patients with paranoid subtype was larger than in most studies of schizophrenia. This may have been related to the MATRICS criteria for study entry, which eliminate patients experiencing more than moderate positive symptoms, conceptual disorganization and negative symptoms. Nevertheless the population studied did have cognitive deficits typical of those reported in the literature. The entry criteria employed also ensured a population that was reasonably stable in terms of psychiatric status; hence, any effect on cognition would most likely have been considered specific rather than 'pseudospecific' (i.e., explained by confounds rather than efficacy per se).

Serious adverse events (SAEs) occurred during treatment in 2.4% of patients taking AZD3480 compared with 0.9% of those on placebo. SAEs during treatment with AZD3480 tended to be psychiatric in nature although there was no clear consistency in the type of events observed. Given the relatively small number of events, the significance of this result is not clear and, in summary, AZD3480 was well tolerated with no overall difference in the incidence of AEs in comparison to placebo, including those of a psychiatric nature.

In view of preliminary data suggesting that AZD3480 improved cognitive domains pertinent to the cognitive dysfunction seen in schizophrenia (Dunbar et al., 2007), it is surprising that the compound showed no effect on cognition in this trial. Apart from the properties of AZD3480, several factors could potentially contribute to the lack of effect. It is possible that the cognitive deficits observed in schizophrenia are limited by other factors not subject to influence by perturbation of the $\alpha4\beta2$ NNR. Also, interaction with nicotine use may have diminished the chances for an NNR agonist to exert its effect: the plasma level of nicotine in smoking schizophrenics is approximately 500 nM, whereas the Ki of nicotine is around 2 nM, thus it is likely that the $\alpha4\beta2$ receptors were fully occupied by nicotine and possibly inaccessible to AZD3480. Studies in healthy volunteers excluded smokers. Furthermore, as a consequence of applying MATRICS inclusion criteria (which require stability at a mild-to-moderate level for positive as well as negative symptoms), an overwhelming number of patients in this trial were classified as paranoid subtype according to DSM-IV criteria. It is possible that this group of individuals is not the ideal target group to study pharmacological effects on CDS, and that greater allowance of stable negative symptoms (some of which co-vary with cognitive deficits) would have resulted in a different outcome. Finally, the MATRICS battery is a cognitive battery developed through the process of consensus. Tests were not selected for sensitivity to change in schizophrenia from cognitive-enhancing therapies. This approach has been criticized on both theoretical and empirical grounds (Sweeney et al., 2007; Barch and Carter, 2008; Adcock et al., 2009; Carter et al., 2011). Perhaps

Table 2
Serious adverse events and adverse events leading to discontinuation of treatment[a].

	AZD3480				Placebo (N = 110)
	5 mg (N = 124)	20 mg (N = 104)	35/100 mg (N = 102)	Total (N = 330)	
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any SAE[a,b]	3 (2.4)	1 (1.0)	4 (3.9)	8 (2.4)	1 (0.9)
Depression	2 (1.6)	0	0	2 (0.6)	0
Psychotic disorder	1 (0.8)	0	1 (1.0)	2 (0.6)	0
Atrial fibrillation	0	0	1 (1.0)	1 (0.3)	0
Dehydration	0	0	1 (1.0)	1 (0.3)	0
Schizophrenia	0	0	1 (1.0)	1 (0.3)	0
Suicidal ideation	0	1 (1.0)	0	1 (0.3)	0
Endometriosis	0	0	0	0	1 (0.9)
Patients with any AE leading to discontinuation[c]	7 (5.6)	4 (3.8)	10 (9.8)	21 (6.4)	3 (2.7)
Irritability	1 (0.8)	1 (1.0)	1 (1.0)	3 (0.9)	0
Agitation	1 (0.8)	1 (1.0)	0	2 (0.6)	0
Anxiety	0	1 (1.0)	1 (1.0)	2 (0.6)	0
Nausea	1 (0.8)	0	1 (1.0)	2 (0.6)	1 (0.9)
Paranoia	1 (0.8)	1 (1.0)	0	2 (0.6)	0
Psychotic disorder	1 (0.8)	0	1 (1.0)	2 (0.6)	0
Schizophrenia	0	0	2 (2.0)	2 (0.6)	0
Suicidal ideation	1 (0.8)	1 (1.0)	0	2 (0.6)	0
Vomiting	1 (0.8)	0	1 (1.0)	2 (0.6)	1 (0.9)

N, number of patients in treatment group; n, number of patients with event; SAE, serious adverse event.
[a] All events were recorded, irrespective of relationship to study medication or the underlying illness.
[b] Number (%) of patients with ≥1 SAE.
[c] Events listed are those that occurred more than once across all treatment groups.

measurement limitations restrict our ability to find changes in cognitive functioning.

In conclusion, AZD3480 treatment did not improve cognitive function in patients with stable schizophrenia who were taking an atypical antipsychotic medication and who were active cigarette smokers. The drug was generally well tolerated in this population.

Role of funding source

This study was funded by AstraZeneca Pharmaceuticals. The sponsor was also responsible, with input and support from the investigators, for the design and implementation of the study, the analysis and interpretation of the data, the preparation of the study report, and the decision to publish. AstraZeneca also provided funding for editorial support.

Contributors

All authors contributed to the design, the implementation, the interpretation of data and/or the reporting of the study. As Principal Investigators, Drs Velligan, Brenner, Sicuro, Walling, Riesenberg, Sfera and Merideth played significant roles in both the running of the study and the collection of data. Dr Sweitzer performed the statistical analysis. Dr Velligan prepared the initial draft of the manuscript and worked with her co-authors on its final preparation. All authors critically reviewed drafts of the manuscript and approved the final manuscript before submission.

Conflicts of interest

Within the last 3 years, Dr. Velligan has received honoraria and grant support from AstraZeneca Pharmaceuticals, Merck Pharmaceuticals, Roche Pharmaceuticals, OrthoMcNeil Janssen Pharmaceuticals, Teva Pharmaceuticals, Lilly Pharmaceuticals, Genentech, and Takeda Pharmaceuticals. Dr Brenner has received research grants from Eli Lilly and Co., Sunovion Pharmaceuticals, Takeda Pharmaceuticals, Abbott Laboratories, Pfizer Inc., Novartis, Forest Laboratories, Sanofi-Aventis, Hoffman La Roche, Bristol Myers Squibb, Johnson and Johnson, and Otsuka Pharmaceutical Co. He is also on the speaker Bureau of Novartis. Dr Walling reports that he has received funding from Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol Myers Squibb, Cephalon, Eisai, Eli Lilly, Forest Laboratories, Glaxo SmithKline, Janssen Pharmaceuticals, Johnson and Johnson, Novartis, Otsuka Pharmaceutical Co., Pfizer Inc., Sanofi, Shire Pharmaceuticals, and Solvay. He also works as a consultant for Janssen and Otsuka Pharmaceutical Co. Drs Jaeger and Sweitzer report that they are employees of the sponsor company, and that they own AstraZeneca stock. Drs Sicuro, Sfera, Riesenberg and Merideth report no competing interests.

Acknowledgments

We thank the patients, their families and all of the investigators who participated in the Halo study. Their contributions were crucial to the smooth running of the study. The Principal Investigators at each center that recruited patients are listed by country as follows: *USA*: Dawn Velligan, Padmini Atri, John Gilliam, Lawrence Adler, Gustavo Alva, Kelly Askins, Sarah Atkinson, Rakesh Bansil, Jason Baron, Prakash Bhatia, Ronald Brenner, David Brown, Miranda Chakos, Mark Dibuono, Anil Malhotra, Deepak D'Souza, Edward

Table 3
Differences vs placebo in change from baseline to EOT (Week 12): ANCOVA on non-computerized cognitive test scores.

			Change from baseline		Difference from placebo		
Test	AZD3480 dose	N	LS mean (SE)	95% CI	LS mean (SE)	Adjusted 95% CI[a]	One-sided p-value[a]
Brief visuospatial memory test—revised	5 mg	88	0.95 (0.97)	(−0.97, 2.86)	−1.48 (1.39)	(−4.76, 1.80)	0.974
	20 mg	74	2.36 (1.07)	(0.25, 4.47)	−0.07 (1.46)	(−3.51, 3.38)	0.775
	35/100 mg	65	1.12 (1.14)	(−1.12, 3.36)	−1.30 (1.51)	(−4.88, 2.27)	0.956
	0 (placebo)	86	2.43 (0.99)	(0.48, 4.38)	na	na	na
Symbol coding score	5 mg	88	1.68 (0.87)	(−0.04, 3.40)	−1.78 (1.24)	(−4.71, 1.16)	0.991
	20 mg	74	1.10 (0.96)	(−0.79, 2.99)	−2.36 (1.29)	(−5.42, 0.70)	0.998
	35/100 mg	65	0.83 (1.02)	(−1.18, 2.83)	−2.63 (1.34)	(−5.81, 0.55)	0.999
	0 (placebo)	86	3.46 (0.88)	(1.72, 5.19)	na	na	na
WMSIII spatial span score	5 mg	88	1.52 (0.90)	(−0.24, 3.28)	−0.93 (1.28)	(−3.96, 2.09)	0.940
	20 mg	74	1.62 (0.98)	(−0.32, 3.55)	−0.84 (1.34)	(−4.00, 2.32)	0.924
	35/100 mg	65	0.60 (1.05)	(−1.46, 2.65)	−1.86 (1.38)	(−5.12, 1.41)	0.988
	0 (placebo)	86	2.45 (0.91)	(0.66, 4.25)	na	na	na

ANCOVA, Analysis of covariance; CI, Confidence interval; EOT, End of treatment; LS, Least squares; N, Number of patients in treatment group; na, Not applicable; SE, Standard error; WMSIII, Wechsler Memory Scale III.
[a] Adjusted for multiple dose comparisons vs placebo by Dunnett's method.

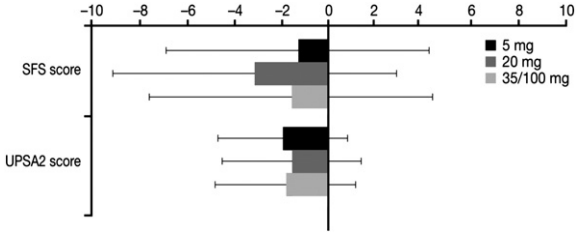

Fig. 4. Differences vs placebo in change from baseline to Week 12 (LOCF) in life functioning measures; relative effect sizes ± 95% CI. A positive difference corresponds to an advantage of AZD3480. All comparisons vs placebo were not significant. LOCF, last observation carried forward; UPSA2, University of California at San Diego Performance Based Skills Assessment; SFS, Social Functioning Scale.

Perry, Carlos Figueroa, David Flaherty, Daniel Gruener, Hisham Hafez, Mark Hamner, Naveed Iqbal, Javed Iqbal, Richard Josiassen, Gregory Kaczenski, Brian Keefe, Mary Knesevich, Alex Kopelowicz, David Krefetz, Sherry Soefje, John Downes, Jean-Pierre Lindenmayer, James Lohr, Cosme Lozano, Raymond Manning, Morteza Marandi, Charles Meredith, Stephen Olson, Georgios Petrides, Jorge Porras, Robert Riesenberg, David Rissmiller, Linda Harper, Richard Saini, Bruce Saltz, Adonis Sfera, Anantha Shekhar, Rajinder Shiwach, Franco Sicuro, Nicholas Vatakis, David Walling, Blaise Wolfrum, John Zajecka, Leon Rosenberg, Daniel Chueh, Carlos Danger, Paul Gross, William Lawson, Michael Banov, Azfar Malik; *Canada*: Leonardo Cortese, Sunny Johnson, Peter Turner, Norman Costigan, Alexander McIntyre, Theodore Kolivakis, Michael Teehan, Henry Chuang, Autar Munshi, Ramamohan Veluri, Richard Williams, Serge Lessard, Nabil Philips.

We also thank Dr Lawrence Rodichock, formerly of AstraZeneca, for his significant contribution to this study.

Medical writing/editorial assistance was provided by Dr Colette O'Sullivan of Scriva Medical Communications, funded by AstraZeneca.

References

Adcock, R.A., Dale, C., Fisher, M., et al., 2009. When top–down meets bottom–up: auditory training enhances verbal memory in schizophrenia. Schizophr. Bull. 35, 1132–1141.

Arendash, G.W., Sanberg, P.R., Sengstock, G.J., 1995. Nicotine enhances the learning and memory of aged rats. Pharmacol. Biochem. Behav. 52, 517–523.

Barch, D.M., Carter, C.S., 2008. CNTRICS Executive Committee. Measurement issues in the use of cognitive neuroscience tasks in drug development for impaired cognition in schizophrenia: a report of the second consensus building conference of the CNTRICS initiative. Schizophr. Bull. 34, 613–618.

Bilder, R.M., Goldman, R.S., Robinson, D., et al., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 157, 549–559.

Bowie, C.R., Harvey, P.D., 2006. Treatment of cognitive deficits in schizophrenia. Curr. Opin. Invest. Drugs 7, 608–613.

Breese, C.R., Lee, M.J., Adams, C.E., et al., 2000. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 23, 351–364.

Bryson, G., Bell, M.D., 2003. Initial and final work performance in schizophrenia: cognitive and symptom predictors. J. Nerv. Ment. Dis. 191, 87–92.

Carter, C.S., Barch, D.M., Bullmore, E., et al., 2011. Cognitive neuroscience treatment research to improve cognition in schizophrenia II: developing imaging biomarkers to enhance treatment development for schizophrenia and related disorders. Biol. Psychiatry 70 (1), 7–12 1.

Cornblatt, B., Lenzenweger, M.F., Dworkin, R., et al., 1992. Childhood attentional dysfunction predicts social deficits in unaffected adults at risk for schizophrenia. Br. J. Psychiatry 161 (Suppl. 18), 59–64.

Court, J., Spurden, D., Lloyd, S., et al., 1999. Neuronal nicotinic receptors in dementia with Lewy bodies and schizophrenia: alphabungarotoxin and nicotine binding in the thalamus. J. Neurochem. 73, 1590–1597.

Dalack, G.W., Healy, D.J., Meador-Woodruff, J.H., 1998. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am. J. Psychiatry 155, 1490–1501.

Dunbar, G., Boeijinga, P.H., Demazieres, A., et al., 2007. Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology 191, 919–929.

Freedman, R., Hall, M., Adler, L.E., et al., 1995. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol. Psychiatry 38, 22–33.

Gatto, G.J., Bohme, G.A., Caldwell, W.S., et al., 2004. TC-1734: an orally active neuronal nicotinic acetylcholine receptor modulator with antidepressant, neuroprotective and long-lasting cognitive effects. CNS Drug Rev. 10, 147–166.

Goff, D.C., Henderson, D.C., Amico, E., 1992. Cigarette smoking in schizophrenia: relationship psychopathology and medication side effects. Am. J. Psychiatry 149, 1189–1194.

Gray, J.A., Roth, B.L., 2007. Molecular targets for treating cognitive dysfunction in schizophrenia. Schizophr. Bull. 33 (5), 1100–1119.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.

Green, M.F., Kern, R.S., Braff, et al., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26, 119–136.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72, 41–51.

Kendler, K.S., Gallagher, T.J., Abelson, J.M., et al., 1996. Life prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis in a US community sample: the National Comorbidity Survey. Arch. Gen. Psychiatry 53, 1022–1031.

Kern, R.S., Green, M.F., Nuechterlein, K.H., et al., 2004. NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. Schizophr. Res. 72, 11–19.

Kumari, V., Postma, P., 2005. Nicotine use in schizophrenia: the self medication hypotheses. Neurosci. Biobehav. Rev. 29, 1021–1034.

Levin, E.D., Briggs, S.J., Christopher, N.C., Rose, J.E., 1992. Persistence of chronic nicotine-induced cognitive facilitation. Behav. Neural. Biol. 58, 152–158.

Malinovsky, I., Jaeger, J., Donovan-Lepores, A.M., et al., 2009. Relationships between test and factor scores, and psychometric properties: the matrics consensus cognitive battery (MCCB) and the IntegNeuro computerized battery in schizophrenia. Schizophr. Bull. 35 (Suppl. 1), 258.

Marder, S.R., Fenton, W., 2004. Measurement and treatment research to improve cognition in schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. Schizophr. Res. 72, 5–9.

Mueser, K.T., Jeste, D.V., 2008. Clinical Handbook of Schizophrenia. Guilford Press, New York.

Rezvani, A.H., Levin, E.D., 2001. Cognitive effects of nicotine. Biol. Psychiatry 49, 258–267.

Silverstein, S., Jaeger, J., Donovan-Lepore, A.-M., et al., 2010. A comparative study of the MATRICS and IntegNeuro cognitive assessment batteries. J. Clin. Exp. Neuropsychol. 32, 937–952.

Sweeney, J.A., Luna, B., Keedy, S.K., et al., 2007. fMRI studies of eye movement control: investigating the interaction of cognitive and sensorimotor brain systems. NeuroImage 36 (Suppl. 2), T54–T60 7.

Velligan, D.I., Mahurin, R.K., Diamond, P.L., et al., 1997. The functional significance of symptomatology and cognitive function in schizophrenia. Schizophr. Res. 25, 21–31.

Wilk, C.M., Gold, J.M., McMahon, R.P., et al., 2005. No, it is not possible to be schizophrenic yet neuropsychologically normal. Neuropsychology 19, 778–786.

Wu, E.Q., Birnbaum, H.G., Shi, L., et al., 2005. The economic burden of schizophrenia in the United States in 2002. J. Clin. Psychiatry 66, 1122–1129.