

# Neuropsychological course in the prodrome and first episode of psychosis: Findings from the PRIME North America Double Blind Treatment Study <sup>☆</sup>

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## Abstract

**Objective:** There is uncertainty regarding the onset timing of the cognitive deficiencies of schizophrenia. We investigated whether conversion to psychosis and/or olanzapine altered the neuropsychological course of subjects within the first-ever double blind medication study of the putative schizophrenia first episode prodrome.

**Method:** Sixty participants in a double blind trial of olanzapine as a treatment for putative prodromal states were assessed at entry (pre-randomization), and again at 6 and 12 months (if they remained non-psychotic), or at any of these points prior to psychosis followed by post-psychosis and 6 months post-psychosis assessments.

**Results:** Participants who converted to psychosis did not differ from placebo non-converters in pre-randomization global neuropsychological status. Early converters did not differ from later converters in entry neuropsychological status. Subjects who converted after 6 months did not show neuropsychological declines during the initial, pre-psychosis, 6 months. Neuropsychological course did not differ between converters to psychosis and non-converters, or between olanzapine and placebo-assigned subjects.

**Conclusions:** Neither the onset of frank psychosis nor olanzapine treatment of the prodrome significantly alters neuropsychological course in persons considered to be at high risk at their initial (pre-psychosis) assessment. These findings suggest that the neuropsychological deficiencies associated with psychotic conditions largely pre-exist the first frank psychotic episode.

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## 1. Introduction

Schizophrenia is typically accompanied by neuropsychological deficiencies that contribute to the difficulties patients experience in managing their daily lives (Green, 1996; Hawkins et al., 1999). These deficits are present at the first episode and show little or no progression thereafter (Kurtz, 2005; Heaton et al., 2001). These deficits are not wholly dependent on the emergence of frank illness, since neuropsychological weaknesses are detectable in first-degree relatives and in children at familial risk (Cornblatt et al., 1989; Faraone et al., 1999). In addition, intellectual and scholastic declines that precede the first episode – sometimes by many years – have been reported (Kremen et al., 1998; Fuller et al., 2002; Caspi et al., 2003; Bilder et al., 2006).

Though there are indications that further declines occur during the prodrome of the first episode, or the first episode itself (Caspi et al., 2003), the magnitude, timing, and nature of these declines remains unclear. First episode samples typically include patients who were psychotic for lengthy periods before receiving treatment, or before being tested, and so shed only limited light on the neuropsychological status of patients immediately following psychosis onset (and no light on their status during the preceding prodrome). More generally, there is a dearth of detailed pre- to post-first episode neuropsychological data beyond IQ sub-test or scholastic attainment scores.

The burgeoning of interest in the first episode prodrome makes a correction for these shortfalls possible. Samples considered prodromal for a first episode of psychosis typically display neuropsychological impairments (Hawkins et al., 2004; Keefe et al., 2006; Eastvold et al., 2007; Simon et al., 2007), sometimes despite normal intelligence (Hawkins et al., 2004; Niendam et al., 2006). Among the putatively prodromal, larger deficiencies in subjects who subsequently become psychotic (e.g. in memory, or olfactory sensitivity) have been reported (Brewer et al., 2003; Brewer et al., 2005; Lencz et al., 2006).

We have reported that though subjects identified as being at high risk for psychosis are not fully normal from a neuropsychological standpoint, they exhibit superior neuropsychological status to that seen in first episode and established schizophrenia samples (Hawkins et al., 2004; Keefe et al., 2006). More than one explanation for this is possible. False positive subjects may elevate sample means on neuropsychological measures; consequently, the neuropsychological functioning of true positives may approximate that of first episode patients. An alternative explanation is that a decline in neuropsychological functioning occurs late in the prodrome and/or during the period of overt psychosis. In support of this

possibility, one study has reported that closer proximity to psychosis is associated with inferior neuropsychological status (Hafner et al., 2004).

To address the issue of the course of neuropsychological deficits pre and during the first psychotic episode, we included neuropsychological assessments within an investigation of the efficacy of olanzapine as a treatment for prodromal presentations (McGlashan et al., 2006). To the best of our knowledge, this is the first report of a double blind medication treatment trial for the putative schizophrenia prodrome. This study allowed us to address several questions regarding neuropsychological course during the prodrome and first episode, specifically: (a) whether neuropsychological status predicts conversion to psychosis among subjects with similar “prodromal” clinical presentations, (b) whether subjects closer to conversion display worse neuropsychological status, (c) whether conversion to psychosis is accompanied by neuropsychological decline, and whether this persists despite early identification and treatment, and (d) whether the treatment of putatively prodromal subjects with olanzapine has any effect on neuropsychological course.

## 2. Method

### 2.1. Subjects

Subjects were 39 male and 21 female ( $M$  age=17.8,  $SD=4.8$ ) who were diagnosed as exhibiting states prodromal to a first episode of psychosis per criteria detailed in an earlier report (McGlashan et al., 2003). Sixty-seven percent were Caucasian, 65% male, and 92% single. The sample exhibited little evidence of affective disturbance, but rather displayed symptoms similar to those seen in psychosis, but less severe and restrained by intact insight (McGlashan et al., 2006). Exclusion criteria included a past or current psychotic disorder, a treatable psychiatric disorder that could account for the prodromal symptoms, suicidal or homicidal ideation, or drug or alcohol use that could be responsible for their symptoms. Data for 14 of these 60 subjects were included in baseline analyses, and six of the 60 in course analyses, reported in a prior publication (Keefe et al., 2006). After a complete description of the study to subjects, written informed consent was obtained.

### 2.2. Overall design

Subjects entered a double blind study of the efficacy of olanzapine as a treatment for prodromal states (McGlashan et al., 2006). Baseline (study entry)

assessments were conducted pre-randomization to one of two conditions, olanzapine (5–15 mg/day) or placebo for one year, or psychosis onset (which ever came first). After 12 months the medication/placebo was discontinued and the patients followed for a further year. Patients meeting study psychosis criteria at any time were treated with open label olanzapine for 6 months (5–20 mg/day).

### 2.3. Clinical measures

Symptom and clinical efficacy assessments included the Scale of Prodromal Symptoms (SOPS; (McGlashan et al., 2003), PANSS (Kay et al., 1987), Clinical Global Impression-Severity of Illness Scale, Montgomery Asberg Depression Rating Scale (Montgomery and Asberg 1979), and the Young Mania Rating Scale (Young et al., 1978). Since DSM-IV does not specify an onset threshold for psychosis, the Presence of Psychosis Scale (POPS) was developed to operationally define psychosis onset (McGlashan et al., 2003). All measures and baseline status are detailed in earlier reports (McGlashan et al., 2003; Miller et al., 2003).

### 2.4. Medications during the double blind phase

Olanzapine (5 mg pills) and placebo treatments were administered in a double blind, fixed-flexible dose fashion. The starting dose of olanzapine or placebo of one pill daily could be raised to two pills at the second visit after randomization and to three pills (maximum dose) at the third visit. After the third visit, prescribers could adjust the dose between the minimum and the maximum. Pills were dispensed in prepackaged bubble packs for compliance monitoring. No other psychoactive medications were permitted.

### 2.5. Neuropsychological design

Subjects were assessed pre-randomization, and again at 6 and 12 months (if they remained non-psychotic), or at any of these points prior to psychosis followed by assessments within three weeks of conversion to psychosis, and again 6 months post-conversion. All subjects were treated with open label olanzapine at post-conversion assessment points.

### 2.6. Neuropsychological measures

Numerous tests encompassing a large number of variables were administered. To minimize chance findings without unduly sacrificing sensitivity, analyses

were restricted to 19 variables displaying a test–retest correlation coefficient between the entry and 6 month assessments of .60+ in subjects exhibiting reasonable clinical stability (those who did not convert within that period). The variables meeting this requirement represent diverse cognitive functions, and are of known sensitivity to schizophrenia (Table 1).

### 2.7. Derived neuropsychological variables

Raw scores were transformed to *z* scores based on the mean and standard deviation of the entire sample at entry. This ensured equal weighting of variables within composite scores, and facilitated a direct comparison of course against entry data.

Twelve functional domain scores were formed on the basis of inter-variable relationships among the 19 variables at entry. Initial *a priori* groupings of variables were subjected to internal consistency analyses employing Cronbach's alpha (Bryman et al., 2001). Variables shown to weaken internal consistency were dropped from the relevant composite and were analyzed as stand alone variables. This process generated four high test–retest reliability multi-variable domain scores with reasonable internal consistency, and eight single variables (Table 1).

The mean of the 19 reliable variables was utilized as a global neuropsychological status score. Though exhibiting high reliability in the non-converting subjects, this variable incorporated a large number of variables known to be sensitive to change (e.g., attention, processing speed, new learning/memory, and executive measures; Table 1).

### 2.8. Data analysis

#### 2.8.1. Sample character

The effect of subject attrition on the sample was assessed via two-tailed *t* test and chi-square comparisons of early withdrawal cases against all others on demographic, clinical, and neuropsychological data.

#### 2.8.2. Characteristics of converters

To determine whether subsequent converters differed from non-converters at entry, single tailed *t* testing was employed in the comparison of placebo-assigned non-converters with converters on pre-randomization neuropsychological performance. Single tailed probabilities are reported because we hypothesized that true positives (converters) would display inferior neuropsychological functioning. To determine whether neuropsychological functioning was related to

Table 1  
Neuropsychological variables

Functional domain	Neuropsychological test	Variable	Test–retest reliability	Coefficient alpha for domain	Composite test–retest reliability
Manual motor speed	Finger tapping	Left and right hands mean	.70	Single variable	
Sustained attention	CPT IP 450	D'	.74	Single variable	
Response discrimination	Variable Interval Delayed Alternation (VIDA)	PR	.66	Single variable	
Working memory: visual	VIDA	Trials to acquisition	.71	Single variable	
Working memory: verbal	Letter–number sequencing	Total correct	.71	Single variable	
Perseveration	Ruff Figural Fluency Test	Non-unique responses	.86	Single variable	
Spatial orientation	Benton line orientation	Total correct	.85	Single variable	
Verbal memory	CVLT total score	Total recall trials 1–5	.69	Single variable	
Visual memory	Visual reproductions	Immediate recall	.84	.90	.85
	Visual reproductions	Delayed recall	.64		
Processing speed	Digit symbol	Total correct	.84	.87	.87
	Stroop word trial	Total correct	.68		
	Stroop color trial	Total correct	.83		
	Trail making part A	Time	.66		
Fluency	Controlled oral word association (FAS)	Total Correct	.78	.78	.86
	Semantic (category) fluency	Total correct	.61		
	Ruff Figural Fluency Test	Unique responses	.79		
Executive	Trails B	Time	.82	.73	.84
	WCST	Categories achieved	.79		
Global neuropsychological status		Mean of the above 19 variables			.94

proximity to conversion, subjects converting within 5 weeks were compared against all later converters on global neuropsychological entry status (two-tailed *t* test).

### 2.8.3. Treatment–outcome interactions

A univariate analysis of variance with treatment (olanzapine/placebo) and outcome (conversion/non-conversion) as factors, and change in global neuropsychological status as the dependent variable, was conducted to determine whether treatment and conversion status interacted in the determination of neuropsychological course.

### 2.8.4. Effect of olanzapine

Two tailed *t* test comparisons of neuropsychological change scores between olanzapine and placebo subjects (regardless of conversion status) were conducted to determine whether olanzapine *per se* had any effect on neuropsychological course.

### 2.8.5. Effect of psychosis on neuropsychological course

Two tailed *t* test comparisons of neuropsychological change scores between converting and non-converting subjects (regardless of initial treatment status) were conducted to determine whether the frank psychotic

episode *per se* had an impact on global neuropsychological course.

### 2.8.6. Effect of conversion on preceding neuropsychological course

To determine whether conversion was preceded by neuropsychological declines, change in global neuropsychological status from entry to 6 months in subjects who converted after 6 months was compared with change during the same time period in non-converters, and change between entry and post-psychosis testing in subjects who converted within the first 6 months.

### 2.8.7. Clinical and neuropsychological associations

The relationship between clinical and neuropsychological change was assessed via Pearson correlation using global neuropsychological scores and SOPS total scores.

### 2.8.8. Effect of psychosis on neuropsychological domains

*T* test comparisons of neuropsychological change scores between converting and non-converting subjects (regardless of initial treatment status) were conducted to determine whether the frank psychotic episode *per se* had an impact on specific domains of neuropsychological functioning.

### 3. Results

#### 3.1. Early withdrawals

Twenty subjects (33% of the entry sample) withdrew before providing follow-up neuropsychological data. These subjects did not differ from the remaining subjects in age (dropout data first),  $M=18.6$  ( $SD=4.9$ ) vs  $M=17.4$  ( $SD=4.7$ ), two-tailed  $t(58)=.91$ , *ns*; clinical presentation, SOPS total score  $M=36.2$  ( $SD=12.9$ ) vs.  $M=41.3$  ( $SD=16.9$ ), two-tailed  $t(58)=-1.12$ , *ns*, MADRS total score,  $M=15.00$  ( $SD=8.1$ ) vs.  $M=12.45$  ( $SD=9.0$ ), two-tailed  $t(58)=1.07$ , *ns*, IQ proxy (the mean of standardized raw scores on Wechsler Adult Intelligence Scale—Revised Information, Vocabulary, and Block Design subtests),  $M=.07$  ( $SD=.85$ ) vs.  $M=-.03$  ( $SD=.93$ ), two-tailed  $t(58)=.40$ , *ns*, or global neuropsychological status,  $M=.02$  ( $SD=.60$ ) vs  $M=.01$  ( $SD=.68$ ), two-tailed  $t(57)=.09$ , *ns*. Thirty-five percent of olanzapine assigned subjects withdrew prior to providing follow-up neuropsychological data versus 31% of placebo subjects,  $c^2(1, N=60)=.13$ , *ns*.

#### 3.2. Entry status of subsequent converters

Since olanzapine may have conferred some protection against conversion (McGlashan Zipursky et al., 2006), pre-randomization comparisons of subsequent converters and non-converters included only placebo-assigned subjects in the non-converter group ( $n=16$ ). Converters to psychosis ( $n=21$ ) did not differ from non-converters on age, the IQ proxy, or global neuropsychological status. Among the reliable variables/domains (Table 1), trends were noted for two. Subsequent converters perseverated more on the Ruff Figural Fluency test, single tailed  $t(35)=1.54$ ,  $p=.07$  (Cohen's  $d=.52$ ), and were inferior on visual memory, single tailed  $t(35)=1.3$ ,  $p=.10$  (Cohen's  $d=-.44$ ).

#### 3.3. Entry status and proximity to conversion

Early converters ( $n=9$ ) rated as psychotic within 5 weeks of study entry ( $M=21$  days) did not differ in entry global neuropsychological status from later converters ( $n=11$ ; psychosis onset  $M=244$  days),  $M=-.02$  ( $SD=.70$ ) vs.  $M=.04$  ( $SD=.71$ ), 2 tailed  $t(18)=-.19$ ,  $p=.85$  (Cohen's  $d=.09$ ).

#### 3.4. Treatment–outcome interactions

Analyses of interactions between treatment (olanzapine/placebo) and outcome (conversion/non-conver-

sion) were constrained by the small number of olanzapine converters (four with post-conversion neuropsychological data). A univariate analysis of variance with treatment and outcome as factors revealed no significant interaction for change in global neuropsychological status,  $F(1, 31)=.34$ , *ns*. Fig. 1 illustrates that though the gain is statistically significant only for the placebo non-converters, all treatment–outcome groups attained higher global scores at the later testing (whether at 6 months or post-conversion). The magnitude of change did not differ significantly across the groups, with three groups displaying essentially identical courses (placebo converters, olanzapine converters, and olanzapine non-converters).

#### 3.5. Effect of olanzapine on neuropsychological functioning

To further explore the effects of olanzapine on neuropsychological functioning, comparisons between the olanzapine and placebo groups were undertaken with neuropsychological change scores derived from entry and 6 month data. No subject included in these analyses had converted prior to the 6 month assessment.

There was no significant effect of olanzapine on global neuropsychological status,  $t(26)=-.84$ , 2 tailed  $p=.41$  (Cohen's  $d=-.33$ ). Among the 12 individual or composite variables, a significant difference was found only for change in visual memory,  $t(26)=-2.1$ , 2 tailed  $p=.045$  (Cohen's  $d=.82$ ). Whereas placebo-assigned subjects performed at slightly higher levels at 6 months,

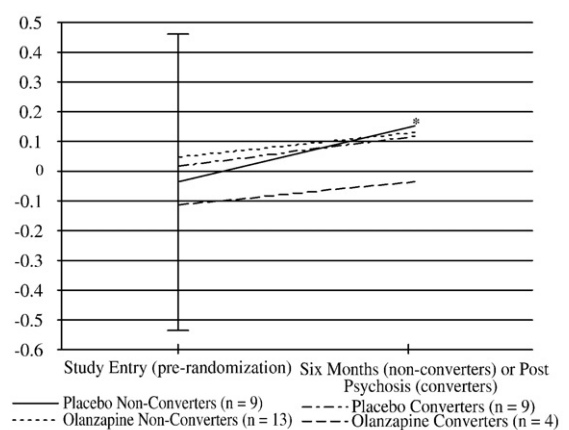


Fig. 1. Entry and 6 month (non-converters) or post-psychosis (converters) neuropsychological global scores. \*Entry and 6 month scores differ significantly for this group ( $p<.02$ ). Amount of change from entry to the later assessment point does not differ between groups. Entry standard deviation for placebo non-converter group displayed for perspective.

the olanzapine group declined slightly. In neither case was the change statistically significant.

Repeating these analyses after removal of the cases who converted later (four placebo and three olanzapine subjects) altered only one result: the difference in visual memory change scores declined to trend status,  $t(20) = -2.0$ , 2 tailed  $p = .055$ , reflecting a decline in power due to subject attrition (Cohen's  $d = .89$ ).

Longer term treatment effects were assessed via a comparison of subjects who did not convert within the one-year double blind period, with the comparison restricted to change scores on the global status variable. The olanzapine ( $n = 9$ ) and placebo ( $n = 7$ ) groups did not differ, change  $M = .33$  ( $SD = .40$ ) and  $M = .28$  ( $SD = .18$ ),  $t(14) = .28$ , *ns*. Fig. 2 reveals a virtually identical course.

### 3.6. Effect of conversion on neuropsychological functioning

Post-psychosis testing was undertaken within three weeks of conversion during the open label rescue arm of the study. To assess the effect of conversion, change from entry neuropsychological status to post-psychosis (converters) was compared against change from entry to six months post-entry (non-converters). Contrasting entry – post-psychosis change against entry – 6 month change ensured a modal two testings for each group, and provides the maximum power afforded in this study since additional subjects dropped out between these and later assessment points. There was no significant effect of conversion on global neuropsychological status,  $t(33) = -.47$ , 2 tailed  $p = .64$  (Cohen's  $d = -.16$ ).

Complete year one data (entry–6 months–12 months) provided by twelve non-converters displayed a highly

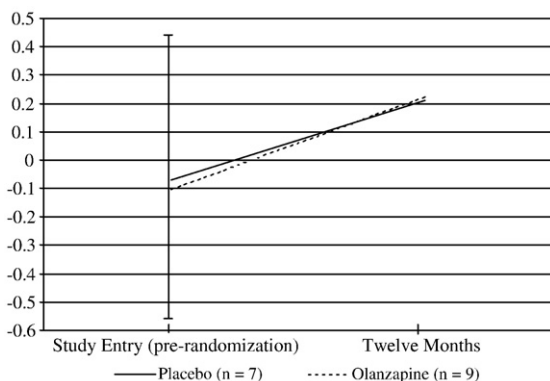


Fig. 2. Olanzapine versus placebo: entry and 12 month neuropsychological global scores in non-converters to that point. Entry standard deviation for placebo group displayed for perspective.

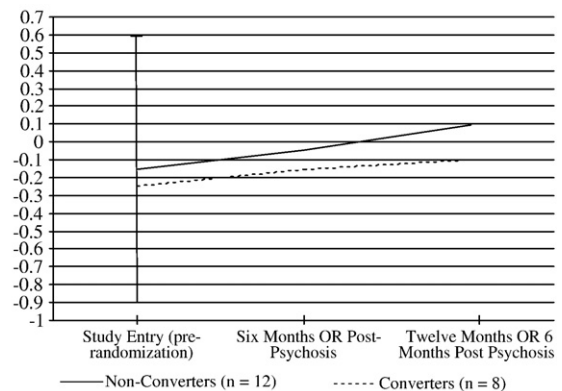


Fig. 3. Effect of psychosis: entry, 6 month, and 12 month (non-converters) or entry, post-psychosis onset, and 6 months post-psychosis (converters) neuropsychological global scores. Entry standard deviation for non-converter group displayed for perspective.

similar course to the entry–conversion–6 months post-conversion data provided by eight converters (Fig. 3). Non-converters and converters did not differ in mean global change from entry to 12 months (or 6 months post-conversion),  $M = .25$  ( $SD = .22$ ) and  $M = .16$  ( $SD = .35$ ),  $t(19) = .74$ , *ns*.

### 3.7. Neuropsychological course of later converters

To determine if subjects who converted later in the study (after 6 months) declined prior to converting, their entry to 6 month course was compared against (a) the entry to 6 month course of non-converters, and (b) the entry to post-conversion data of subjects who converted

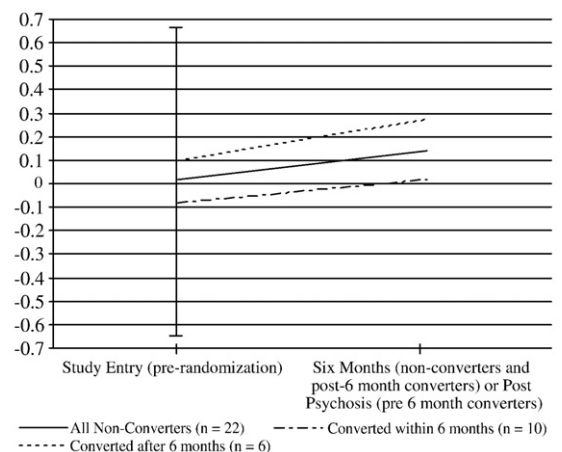


Fig. 4. Entry and 6 month (non-converters to that point) or post-conversion neuropsychological global scores. Entry standard deviation for non-converter group displayed for perspective.

prior to 6 months. As illustrated by Fig. 4, the three groups show virtually identical courses.

### 3.8. Relationship of changes in clinical status to neuropsychological gains

Within the overall sample, change in global neuropsychological score from entry to six months (non-converters) or entry to post-conversion did not correlate significantly with global clinical improvement, represented by SOPS total score change:  $r(35) = .26, p = .14$ .

### 3.9. Effect of conversion on specific domains

Change from entry to post-psychosis (converters) was compared against change from entry to six months post-entry (non-converters) for each of the 12 variables listed in Table 1. A significant difference was found for manual motor speed,  $t(33) = -3.26$ , 2 tailed  $p = .003$  (Cohen's  $d = 1.13$ ), reflecting a significant decline in the converter group,  $t(12) = -3.12$ , 2 tailed  $p = .008$ . This motor decline did not reflect regression to the mean, since the converting and non-converting groups did not differ significantly at entry.

At entry, all subjects were olanzapine free. At the post-psychosis testing all converters were administered olanzapine, raising the possibility of either a medication or conversion effects on motor functioning. This was explored by comparing 3 groups on motor change: all converters, placebo non-converters, and olanzapine non-converters. An analysis of variance revealed a significant difference between the groups,  $F(2, 32) = 5.86, p = .007$ . Placebo non-converters differed significantly from the all-converter group ( $p = .008$ ). The difference between the olanzapine non-converters and the all-converter group approached significance ( $p = .052$ ). However, though their gains in score were higher in absolute terms, the placebo non-converters did not show significantly greater gains than the olanzapine non-converters.

To shed further light on the role of treatment versus conversion on motor functioning, the number of subjects showing score declines was determined for each group. In absolute terms, 12 of 13 converters declined, yet only 6 of 13 olanzapine assigned non-converters declined. This suggests an effect of conversion. On the other hand, 7 of 9 placebo non-converters improved their motor scores, suggesting a practice effect in the non-medicated. Since 6 of 13 olanzapine non-converters declined despite this possible practice effect, the possibility that both olanzapine and conversion contributed to the manual motor speed declines observed in converting subjects remains open.

### 3.10. Course of potential predictor variables

To determine the stability of the entry weaknesses of subsequent converters in visual memory and in design fluency, the performances of these subjects post-conversion were compared against the 6 month performances of all non-converters. The visual memory performances of the converters improved to the point of becoming indistinguishable from non-converters. Though the converters continued to perseverate during design fluency, the difference in performance between the non-converting and converting groups did not differ significantly at the latter testings,  $M = -.46$  ( $SD = 1.77$ ) and  $M = .11$  ( $SD = .81$ ), single tailed  $t(33) = 1.1, p = .15$  (Cohen's  $d = .38$ ).

## 4. Conclusions

This first-ever double blind medication treatment study of the putative first psychotic episode prodrome provided a unique opportunity to simultaneously examine whether a decline in neuropsychological functioning occurs shortly before, or during, the first episode, and whether anti-psychotic treatment – in this case olanzapine – exerts an effect on neuropsychological course during this period. The main finding is that neither treatment with olanzapine nor conversion to psychosis had a significant impact on neuropsychological functioning. Three of the four treatment–outcome groups displayed near identical global neuropsychological courses, and the four groups did not differ in magnitude of change between entry and later assessments. Separate analyses of the main effects for treatment and psychiatric outcome (psychosis) showed no effect of either on global neuropsychological course.

Analyses at the level of individual domains (represented by 12 variables) were largely consistent with this finding. Converters exhibited a decline in manual motor speed, but the treatment of all converters post-conversion with olanzapine complicates the interpretation of this finding. Though olanzapine assigned non-converters did not display declines of the same magnitude, they also did not show the gains in motor speed exhibited by non-converting placebo subjects. Additionally, we cannot be certain that treatment compliance was the same across the olanzapine groups: whereas converters were tested shortly after the initiation of open label olanzapine, the non-converting subjects were retested substantially after randomization (i.e., six months after study entry) and could have been less medication compliant.

The inclusion of a placebo condition allowed us to assess whether true positives (subsequent converters)

displayed inferior neuropsychological status to false positives (subjects who did not convert). At study entry, subjects who subsequently converted tended to persevere more on a design fluency task, and were inferior on visual memory (with both results at trend level). Whereas the post-conversion performances of the converters in visual memory improved to the point where they became virtually identical to the follow-up performances of the non-converters, the converters continued to persevere on design fluency at greater, though statistically non-significant, levels compared to the non-converters. Given the number of comparisons made, these trends would not survive correction for multiple comparisons. These data nonetheless suggest that design fluency, perseverative tendencies, and visual memory warrant exploration in future prodromal and early psychosis research.

To further explore the predictive potential of neuropsychological data, we examined neuropsychological status in relation to proximity to conversion. The entry status of subjects who converted within 35 days of study entry did not differ from the status of later converters, and placebo non-converters. Additionally, our examination of the entry to 6 month course of subjects who converted *after* their 6 month assessments revealed no evidence of a global decline during that initial 6 month (pre-conversion) period.

In summary, our findings suggest that neuropsychological data possess at best a limited potential to differentiate true from false positives among persons exhibiting similar “prodromal” presentations via the diagnostic methodology employed within this study, and within the time frame of this study. Additionally, we found no evidence of a decline in neuropsychological functioning in the prodromal period prior to psychosis, or as a consequence of psychosis. This finding is consistent with the view that the neuropsychological deficiencies of schizophrenia are neurodevelopmental in nature, and largely in place prior to the first episode.

Though these conclusions are subject to the caveat of limited power, the non-significant findings reported also reflect the fact that any differences between groups of interest were typically small. On the other hand, our overall sample displays superior neuropsychological status to that typically reported for schizophrenia (Hawkins et al., 2004), consistent with findings reported for other prodromal samples followed through conversion (Keefe et al., 2006). Our subjects were relatively young, with many still within the timeframe of adolescent neurodevelopment, and there is evidence that structural brain changes occur in the years following the first schizophrenia psychotic episode (Ho et al., 2003). An

arrested development of neurocognitive functioning (if not an overt decline) beyond the first episode remains a possibility that awaits the serial testing of subjects from as early as possible in the prodrome through to several years beyond the onset of psychosis. Any such study should include a parallel assessment of healthy controls, the absence of which constitutes a weakness in our research. Though all groups in our study exhibited neurocognitive gains, we do not know how these would have compared with a normal course, since neither developmental gains nor practice effects were controlled for.

We found no evidence for a positive effect of olanzapine on neuropsychological functioning in the putative prodrome. Though early identification and treatment are supported on psychosocial grounds (Addington et al., 2003), and possibly for clinical reasons (McGlashan et al., 2006), our data do not support a neurocognitive rationale for the anti-psychotic treatment of the prodrome.

Caveats with regard to these results are in order. Though dropouts did not differ in entry status from subjects who supplied follow-up data, the high attrition rate led to small samples in some of the outcome groups of interest. Additionally, we cannot be certain of the fate of non-compliant subjects, or, for that matter, of the longer-term fate of subjects who were compliant for varying durations within the two-year period of study.

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#### **Conflict of interest**

Dr.'s Hawkins and Christensen report no biomedical financial interests or potential conflicts of interest. Dr. McGlashan reports receiving consulting fees for Solvay-Wyeth. Dr. Keefe has received grant/research support from AstraZeneca, Eli Lilly, Johnson & Johnson, Pfizer, as well as providing educational services to AstraZeneca, Eli Lilly, Forest Labs, GlaxoSmithKline, Johnson & Johnson, Pfizer, and Repligen. He has also served as a consultant and on advisory boards for Abbott Pharmaceuticals (advisory board), Acadia (consultant), AstraZeneca (advisory board, consultant), Bristol Myers Squibb (advisory board), Cephalon (consultant), Dainippon Sumitomo Pharma. (consultant), Eli Lilly (advisory board, consultant), Forest Labs (consultant), Glaxo SmithKline (consultant), Johnson & Johnson (advisory board, consultant), Lundbeck/Solvay/Wyeth (advisory board), Memory Pharmaceuticals (advisory board), Merck (advisory board, consultant), Orexigen (advisory board, consultant), Otsuka (consultant), Pfizer (advisory board, consultant), Repligen (consultant), Saegis (advisory board, consultant), Sanofi/Aventis (advisory board, consultant), and Xenoport (consultant). Dr. Keefe also receives royalties from the Brief Assessment of Cognition in Schizophrenia (BACS) testing battery and the MATRICS Battery (BACS Symbol Coding). Dr. Woods reports research funding from Bristol Myers Squibb, Eli Lilly, Janssen, and UCB Pharma, scientific advisory board service with Otsuka, and receipt of a patent for direct and indirect glycine

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