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Lack of an inverse relationship between duration of untreated psychosis and cognitive function in first episode schizophrenia

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ABSTRACT

This study assessed the relationship between duration of untreated psychosis (DUP) and cognitive measures in order to assess if longer DUP was associated with worse performance. One hundred two patients with first episode schizophrenia or schizoaffective disorder were assessed on cognitive measures of speed of processing, episodic memory, executive function, and visual spatial processing at baseline (when patients were drug naive and after 16 weeks of olanzapine or risperidone treatment), so that a change score could be derived. DUP was defined by the emergence of psychiatric symptoms and the emergence of psychotic symptoms. Data were analyzed correlationally, parametrically (after the group was divided into long and short DUP by median split), and by regression. We found that DUP for psychotic symptoms in this group of patients was long, with a median of 46 weeks. Neither correlational, parametric analyses in which DUP served as a class variable, nor multiple regression indicated that longer DUP was associated with worse cognition at baseline or smaller magnitude of improvement in cognition. Our results suggest that while early intervention may be critical for symptom amelioration by shortening DUP, early intervention for treatment of psychiatric symptoms may have little or no impact on cognitive function. Furthermore, assuming that cognition is a core symptom of schizophrenia, the notion that ongoing psychosis is somehow toxic for a variety of information processing domains appears questionable.

1. Introduction

Duration of untreated psychosis (DUP) is a potentially important construct for understanding schizophrenia. Interest in DUP increased when Wyatt (1999; Norman and Malla, 2001) proposed that it is neurotoxic by reducing neuronal connectivity. If there is a strong inverse relationship between DUP and illness course, outcome, symptom improvement, or cognitive level, this would support the idea that psychosis has a cumulative impact on plasticity-related phenomena. On the other hand, the absence of such a relationship would suggest that psychosis, while obviously reflecting aberrant neural circuitry, is not deleterious to such circuitry. The implications of this account are important because they suggest that early intervention is not only humane, but has neuroprotective effects.

Much research since has addressed DUP and symptom severity and short term outcome. The field was comprehensively reviewed by McGlashan (1999) and more recently subjected to a meta-analysis of 26 studies that found a significant, albeit modest, relationship between DUP and treatment response for such variables as symptom severity, positive symptoms, overall function, and remission, especially at six months post-initial

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treatment (Marshall et al., 2005). Strikingly, the relationship between baseline symptoms and DUP was found to be quite small. Our own previous work in a demographically similar sample to the one studied herein (Robinson et al., 1999, 2004) suggests that DUP had a small but measurable association with functional recovery dimensions five years after the first episode of psychosis.

Several large scale studies have examined the relationship between DUP and cognition at study entry. In one of the initial studies, Hoff et al. (2000) found no relationship between these classes of measures. Ho et al. (2003) examined the relationships between DUP and cognition in a large group of first episode (FE) patients. Of nine cognitive domains, verbal memory was the only one to demonstrate a significant relationship with DUP. Similarly, in a Scandinavian sample, Rund et al. (2004, 2007) also observed negligible associations in a large sample of FE patients with schizophrenia or schizophrenic spectrum disorders using multiple cognitive indices. An important study utilizing carefully measured DUP indices and a comprehensive selection of cognitive tests that included current IQ, premorbid IQ, fluency, problem solving, updating, and attention, reported a single, albeit counterintuitive, correlation between DUP and intellectual deterioration (Norman et al., 2001). In an interesting approach to the issue Addington et al. (2004) examined DUP and cognition after two years of treatment, but found no relationship. In a large sample of psychotic patients recruited in Brazil, Ayres et al. (2007) found no relationship between DUP and a variety of cognitive measures. Positive studies have been less frequent (Amminger et al., 2002; Joyce et al., 2002; Lappin et al., 2007); however, the inconsistency across studies, with regard to both methods and results, have made these data difficult to interpret.

Specifically, interpretation of these studies has been hampered by several methodological issues. First, a key implication of DUP suggests a reduction in plasticity-related phenomena, presumably including those related to learning and memory. Moreover, DUP has been associated with treatment response, i.e., a change in, but not the baseline severity of symptoms. Thus, assessment not only of baseline cognitive scores might be necessary, but also assessment of changes in cognition over time and with treatment. The literature has also examined different definitions of DUP. These have generally centered around the emergence of any psychiatric symptoms (e.g., anergia, dysthymia, isolation, oddities in speech, belief, or perception), or frank and ratable positive symptoms. Furthermore, the length of DUP varied across studies, with some studies (Rund et al., 2004; Norman et al., 2001) reporting a relatively short median DUP, perhaps minimizing the likelihood of observing relationships among key clinical variables. In this study we were able to address these issues by utilizing an FE sample with a very high proportion of drug naive patients assessed at baseline, who had relatively long median DUPs, and for whom we were able to generate cognitive change scores over a 4 month period. In addition, through careful clinical tracking and structured assessment, we were able to assess two distinct measures of DUP (one based on emergence of any psychiatric symptom, the other based on emergence of psychotic symptoms).

Table 1
Demographic Information

Age	23.9±4.9
Sex	71 M/31 F
WRAT-R	89.1+14.7
DUP psychosis	
Mean:	113.3±161.5
Median:	46
DUP psychiatric	
Mean:	222.1±255.8
Median:	256
Severity of Illness	
Baseline	5.6±.6
16 Weeks	3.9+1.0

2. Methods

2.1. Subjects

One hundred and two patients in their first episode of schizophrenia or psychosis participated in the study. By study's end 74 were diagnosed with schizophrenia, 10 with schizoaffective disorder, and 18 with schizophreniform disorder. Of these patients 80% were antipsychotic medication naive while assessed at baseline. Patients were then randomized to treatment with the SGA olanzapine or to the SGA risperidone. For the purposes of this study the treatment groups were collapsed, because in earlier studies no differences in treatment response to the two SGAs were found (Goldberg et al., 2007). Demographic information is in Table 1.

2.2. Design

The trial design has been presented in detail elsewhere. Briefly, subjects with FE schizophrenia, schizoaffective disorder, or schizophreniform disorder were assessed at baseline and randomly assigned to treatment with olanzapine ($N=51$) or risperidone ($N=51$) for 16 weeks. Psychopathology and cognitive assessments were performed by masked ("blinded") assessors. FE patients received cognitive assessments at baseline (when most FE patients were drug free), and after 6 and 16 weeks.

2.3. Cognitive tests

The cognitive tests listed in Table 2 were administered to all subjects. They are described more completely in Goldberg et al. (2007) and included measures of processing speed, episodic memory, working memory, executive function, and motor speed/dexterity. Ns for each test at baseline and at 16 weeks are listed in Table 2. We restricted our examination to a subset of those measures as based on presence of data at baseline and the choice of a single measure per test for the sake of clarity of presentation.

Cognitive change scores were based on the differences between baseline performance and performance after 16 weeks of SGA treatment.

2.4. Psychopathology ratings

Severity of illness was rated on the CGI.

2.5. DUP

DUP was measured in two ways after an interview with the FE patient and his/her parents. The first (called DUP psychosis

herein) measured the time in weeks from the emergence of psychotic symptoms to initiation of pharmacologic treatment. The second (called DUP psychiatric) measured DUP from the emergence of any psychiatric symptoms to pharmacologic treatment. DUP was based on information obtained from both the patient and family members during SCID interviews and SADS interviews in longitudinal follow-up and was based on the reconciliation of information from all sources. DUP means and medians are in Table 1.

2.6. Statistics

We analyzed the data in three different ways: first in zero order correlations between DUP and cognition using rank orders to minimize impact of outliers; second in ANOVAs in which DUP was treated as a categorical variable (i.e., long duration vs. short duration after a median split of the DUP data) and cognitive test performances as the dependent measures; and third in a series of regressions in which DUP, sex, and DUP × sex interaction served as independent predictors of cognitive measures. (We included sex under the assumption that it might modify response to antipsychotic medications or DUP.)

3. Results

The results of the zero order correlational analyses examining the relationship between DUP and cognition are listed in Table 2. We used Spearman's rho for rank order to minimize the impact of outliers. Two zero order correlations between DUP (psychosis) and cognition at baseline were significant: a measure of verbal story recall (WMS-R Logical Memory) and a test of visual-perceptual skill (Judgment of Line Orientation — JLO). Longer DUP was associated with better performance on both of these measures at baseline and greater improvement over the 16 weeks on JLO was associated with longer DUP.

Similarly, the ANOVA analyses based upon dichotomized long and short DUPs revealed only two significant findings: baseline WMS-R Logical Memory and Benton Judgment of JLO. Patients with longer DUPs outperformed patients with shorter DUPs on these variables (results available upon request). DUP had no significant impact on change scores in this class of analyses.

Furthermore, analyses from the stepwise linear regression, as shown in Table 3, and inspection of cell means demonstrated that for the two variables found to be significant above (namely, Logical Memory and JLO), females with the longest DUP had the highest scores while males with the shortest DUP had the lowest scores at baseline. For change scores, DUP entered significantly as a predictor of JLO, but not for other measures.

The relationship between DUPpsychiatric and cognition closely mirrored these results, as can be observed from Tables 2 and 3. When findings were positive, longer DUPpsychiatric was associated with better performance.

We found that baseline severity of illness did not differ between the short and long DUPpsychosis groups. However, degree of improvement in severity differed between the long and short DUP groups by ANOVA (mean long DUP improvement = 1.42, mean short DUP improvement = 1.94; $F1,77 = 4.15$, $p = .04$), such that patients with long DUP demonstrated smaller improvements.

Table 2
Correlations between DUP and cognitive measures

Cognitive		DUP (psychotic)		DUP (psychiatric)	
Baseline	N	Rho	P	Rho	P
Trails	95	−.11		−.24*	.02
Fluency	97	.06		.20*	.05
Dig Sym	79	.09		.17	
Log. Mem	101	.25*	.01	.23*	.02
CVLT	20	.07		.26	
Vis. Reproduc.	101	.12		.04	
J Line Orient	87	.28*	.01	.20*	.07
Wcst %pc	74	.10		−.04	
Change	N	R	P	R	P
Trails	72	−.12		−.16	
Fluency	73	.08		.22	
Dig Sym.	77	.15		.14	
Log Mem.	79	.02		−.02	
CVLT	18	.03		.21	
Vis. Reproduc.	79	.05		−.08	
JLO	87	.34*	.001	.23*	.06
WCST % pe	56	.20		−.05	

Table 3
Stepwise regression results for DUP as a predictor of cognition (significant findings only)

	DUP Psychotic		Sex * DUP		Sex	
	Step	R^2 (increment.)	Step	R^2	Step	R^2
Dig. Sym.	2	.13	1	.08		
Log. Mem.			1	.09		
JLO			2	.17	1	.10
JLO change	1	.12				
	DUP psychiatric		Sex* DUP		Sex	
	Step	R^2 (increm.)	Step	R^2	Step	R^2
Dig. Sym.	2	.14	1	.08		
Log. Mem.			1	.07		
JLO			2	.14	1	.10
JLO change	1	.05				

4. Discussion

We did not discern a relationship between longer DUP and worse cognition, irrespective of whether DUP was treated as a continuous variable or as a categorical variable or whether DUP was measured from the emergence of psychotic symptoms or any psychiatric symptom. Thus, our findings are not consistent with the hypothesis that psychosis per se is "toxic." These results came in the context of neurocognitive measures that involved both baseline and change scores and DUPs that were sometimes quite long. Furthermore, because we found no inverse relationship between DUP and the ability of patients to demonstrate improvements in cognition over time, the results were not analogous to those found when the relationship between DUP and treatment response was examined, but they are broadly consistent with several well-conducted studies that examined cognition and DUP (Hoff et al., 2000; Ho et al., 2003; Rund et al., 2004, 2007). Indeed, one of these (Norman et al., 2001), like ours, found that longer DUPs were associated with better cognitive performance.

There are several alternative interpretations of our results. The first is that symptoms and cognition are independent, as numerous correlational studies and factor analytic studies have demonstrated. Moreover, this lack of a relationship appears to antedate the onset of psychosis (Bilder et al., 2006; Lencz et al., 2006). A second and complementary way to conceptualize these results may be to consider that psychotic experiences are learned and become consolidated over time, and they thus become more difficult to treat (or in a sense, unlearn or extinguish associations) (Kapur, 2003). This view is also consistent with the aforementioned finding that DUP does not correlate with baseline symptoms, but rather with outcome and treatment response. In contrast, compromised moment-to-moment information processing may occur within the same circuitry, but is not learned and hence is not subject to a relationship with DUP. In this view, the lack of a significant relationship between DUP and information processing is an expected outcome. Our equivocal finding of sporadic positive correlations may be spurious (they would not survive correction for multiple comparisons) or may simply reflect a process in which there is increasing adaptation (e.g., reallocation of cognitive resources or changes in levels of saliency or novelty signals) to the presence of positive symptoms with time.

As noted, there are inconsistencies in the literature on DUP and cognition. Speculatively we think they might be related to differences in health care systems (in the US, UK, and Scandinavia) and different family tolerance to the mentally ill that might result in allowing individuals with high disease severity to remain untreated. This is similar to the point raised by Lappin et al. (2007), who noted that DUP could be a consequence, not a cause, of lower cognitive performance. Of course, the range of findings might simply reflect noise around a null mean.

We think that the high percentage of our patients who were not receiving antipsychotic medication at baseline would serve to promote a relationship; the fact that we did not find the predicted relationship in this context serves to strengthen our interpretations. Similarly we think that our finding that our sample demonstrated a relationship between treatment response and DUP serves to emphasize the representativeness of our sample (i.e., it is consistent with meta-analytic results) and hence the generalizability of our findings.

We do not have measures of the reliability of our measure of DUP and note this as a limitation of our study. Similarly, it is possible that if we had followed patients longer we might have discerned a relationship. We think this is unlikely, because we were able to discern a relationship sporadically, but it was in the non-predicted direction (i.e., shorter DUP/worse performance).

Our results imply that while early intervention may be critical for symptom amelioration by shortening DUP, early intervention for treatment of psychiatric symptoms may have less of an impact on cognitive function. We certainly appreciate that actively psychotic individuals may act impulsively, perform damaging acts, and may be self destructive; this set of behaviors requires early and sustained treatment (McGlashan, 1999). In contrast and assuming that cognition is a core symptom of schizophrenia, the notion that ongoing psychosis is somehow toxic for a variety of information processing domains appears questionable.

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Contributors

Drs. Goldberg, Goldman, Kane, Lencz, Malhotra, and Robinson were involved in the design of the study. Drs. Kane, Malhotra, and Robinson were involved in the execution and implementation of the study. Drs. Burdick, Goldman, Lencz, Patel, Sevy, and Robinson and Ms. McCormack participated in the collection of data. Dr. Goldberg, Ms. Napolitano, Dr. Lencz, and Dr. Robinson were involved in data analysis. Drs. Goldberg, Burdick, Malhotra, and Robinson were involved in the writing of the study. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Goldberg has consulted for Merck, Organon, Pfizer, and Wyeth. Dr. Kane is a consultant for Abbott, BMS, Pfizer, Janssen, and Lilly and lectures for BMS and Janssen. Dr. Robinson has received honoraria from Astra Zeneca Canada and grant support from Janssen and BMS. Dr. Goldman is now an employee of Pfizer, but at the time this study was designed and implemented, he was an employee at Zucker Hillside Hospital. All other authors have declared that they have no conflicts of interest.

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