Prolonged Untreated Illness Duration From Prodromal Onset Predicts Outcome in First Episode Psychoses

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Abstract

Several, although not all, studies suggest that prolonged duration of untreated illness (DUI) predicts poor outcome in psychotic disorders such as schizophrenia. It is unclear whether this association can be explained by factors such as baseline deficits or poor premorbid adjustment. First episode psychotic patients were evaluated at 1 and 2 years following baseline evaluations. Predictive measures showing significant correlations with outcome were entered in multiple regression analyses with Strauss-Carpenter scale (SC) and Global Assessment of Functioning scale (GAF) outcome scores as dependent variables. Illness duration computed from the onset of the prodrome (DUI-pro), used both as a dichotomous and as a continuous measure, highly significantly predicted both GAF and SC scores at 2 years. On the other hand, baseline functioning significantly predicted the 1-year but not the 2-year outcome. When Premorbid Adjustment Scale (PAS) scores were additionally entered into the analyses in a smaller subset, the relation between DUI-pro and the 2-year outcome scores remained significant. Significant associations were also seen between outcome and baseline neuropsychological deficits involving attention and memory. Further research is needed to examine whether prolonged untreated illness is simply associated with poor outcome or plays a causal role in relation to outcome. The latter, if true, would strongly support therapeutic intervention efforts in the prodromal and early psychotic phases of schizophrenia.

Keywords: Prodrome, psychosis, illness duration, outcome, schizophrenia.

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The outcome of schizophrenia is variable, and despite a great amount of existing research, we know relatively little about the predictors of outcome. Several studies have suggested that prolonged duration of untreated illness (DUI) may predict poor outcome (Wyatt 1991; Haas et al. 1998; Wyatt et al. 1998; McGlashan 1999), longer time to and level of remission (Loebel et al. 1992), and more negative symptoms (Scully et al. 1997; Haas et al. 1998). Given such findings, it has been suggested that decreasing DUI, perhaps by early identification and intervention, might lead to a more favorable outcome. It has also been argued that prolonged untreated illness might be causally related to poor outcomes, perhaps as a result of a neurotoxic process (Wyatt 1991). However, much controversy has shrouded this literature. DUI in various studies varies widely, ranging between 22 and 166.4 weeks (Norman and Malla 2001); some studies have not found an association between DUI and outcome (Craig et al. 2000; de Haan et al. 2000; Ho et al. 2000; Hoff et al. 2000).

Several methodological caveats are worth considering in order to understand the lack of consistency in the literature on the relation between DUI and outcome (Norman and Malla 2001). First, various approaches have been used to assess DUI, but they have used different definitions. In the majority of studies, DUI has been defined as duration of illness from onset of psychotic symptoms (Haas et al. 1998); another definition has been the onset of treatment (Larsen et al. 1996, 1998; Edwards et al. 1998; Craig et al. 2000). Very few studies have separately examined DUI from prodromal versus psychosis onset in the same patients. There has been increasing interest in recent years in the possibility that early therapeutic intervention during the prodromal phase of schizophrenia may favorably influence the overall course of schizophrenia (McGlashan 1999; McGorry et al. 2002). This suggests that including the prodromal phase in the definition of the illness duration is critically important.

Second, DUI measures, however defined, are usually not normally distributed; relatively few studies have addressed such skewed data by appropriate data transformations. Some studies have treated DUI as a continuous variable, while others have dichotomized DUI based on

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one or another cutoff point, such as 1 year (Haas et al. 1998; Robinson et al. 1999; Hoff et al. 2000), 6 months (Craig et al. 2000), or a median split (Ho et al. 2003). However, one disadvantage of using such cutoffs would be the risk of confounding the association between DUI and outcome by diagnosis (there could be less reliable diagnoses, and those patients that would more accurately meet criteria for nonschizophrenia psychoses would be likely to be among cases of shorter duration DUI). Examination of DUI as both a continuous variable and a categorical variable, if justified, has merit.

Third, it is still unclear as to whether prolonged DUI has an effect on outcome independent of other putative predictors of outcome. These include age, gender (Loebel et al. 1992), age of onset (Haas et al. 1998), baseline functioning (Scottish Schizophrenia Research Group 1987; Robinson et al. 1999), poor premorbid functioning (Verdoux et al. 1998; Larsen et al. 2000), level of negative symptoms and social disability (Johnstone et al. 1990; Addington and Addington 1993; Beiser et al. 1993, 1994; McGlashan and Johannessen 1996), and presence or absence of neurocognitive dysfunction (Malla et al. 2002). Addressing such potential confounding factors will be critical for examining their independent influence, if any, on outcome parameters.

Finally, outcome has been variously measured by individual measures such as social disability (Wiersma et al. 2000), change in symptoms (Szymanski et al. 1996), and time to remission (Loebel et al. 1992) or relapse (Linszen et al. 1998), rather than composite measures that encompass diverse outcome dimensions.

In this study, we examined the utility of DUI (measured by both prodromal and psychosis onset) and the potential confounding effects of predictive factors such as diagnosis, premorbid adjustment, age, gender, baseline functioning, and neurological and neurocognitive performance for predicting outcome in a series of previously untreated first episode psychotic patients who were followed up to 2 years. We hypothesized that increasing DUI prior to initial treatment, including the prodromal phase, would be correlated with unfavorable outcome as measured by two measures of outcome, the GAF and the SC outcome scales.

Subjects and Methods

A consecutive series of patients who were experiencing a first episode of psychosis (n = 104) and who met screening criteria were recruited into our study from the inpatient or outpatient services at the Western Psychiatric Institute and Clinic. The protocol had been approved by the University of Pittsburgh School of Medicine Institutional Review Board. All patients provided written informed consent. The patients were diagnosed by *DSM–IV* criteria (American Psychiatric Association 1994) at consensus conference meetings of senior diagnostician/clinical researchers (M.S.K., G.L.H., N.R.S.) approximately 1 month after entry into the study. All available clinical information was used, and data were gathered using the Structured Clinical Interview for DSM Disorders (SCID) (Spitzer 1990). Exclusion criteria were age greater than 50 or less than 12 (to avoid the likelihood of including organic psychoses or developmental disorders that might mimic schizophrenia), significant medical illness affecting the central nervous system function, IQ lower than 75 (to rule out mental retardation), and current diagnosis of substance use disorder (to rule out substance-induced psychotic disorders). To avoid the confounding effects of sustained medication treatment, we excluded subjects who had received more than 2 weeks (in their lifetimes) of antipsychotic treatment. These patients continue to participate in a longitudinal, prospective study that includes a careful diagnostic rereview to evaluate diagnostic stability (Keshavan and Schooler 1992). Patients are followed up and treated with standard antipsychotic medications and supportive individual and group psychotherapy.

Psychopathological ratings were carried out by trained raters (D.M., N.M., or E.D.R.) who also participated in the diagnostic meetings described above. Illness severity was assessed using the GAF. GAF scores at 4 weeks, following stabilization of acute psychotic symptoms, were taken to reflect baseline level of functioning. Positive and negative symptoms were measured, respectively, using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1990). We used averages of symptom items (0–4) rather than total scores to minimize the effect of missing or unassessable items on the data.

DUI was assessed in each case by the same raters (D.M., N.M., or E.D.R.) using all clinical information, including medical records, reports by family members or significant others, and SCID interviews. The most likely date of illness onset was then determined in consensus diagnostic conferences. The onset of the prodrome was defined as first appearance of prodromal symptoms of the illness contiguous (i.e., without clearly discernible periods of wellness intervening) with the subsequent onset of psychosis. In defining prodromal symptoms, we included both attenuated positive symptoms and attenuated negative symptoms (as defined in the SCID). The term *attenuated* was used to refer to symptoms that were severe enough to be considered by the patient or significant others to need treatment. Nonspecific symptoms such as depression or ADHD were not included. DUI–pro was defined as the time interval (in weeks) between onset of prodromal symptoms and index

admission (enrollment) into this study (there was no significant interval between index admission and treatment initiation, which was typically 2–5 days after admission), while DUI–psy was defined as the time interval (in weeks) between onset of psychotic symptoms (hallucinations, delusions, or disorganization of thinking; bizarre or catatonic behavior) and index admission into this study.

Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al. 1982). The PAS determines premorbid functioning during four periods: childhood, early adolescence, late adolescence, and adulthood. To compute the total PAS score, we combined the childhood and early adolescence scores in order to avoid any overlap with the prodromal period. Thus, premorbid functioning was evaluated for only a premorbid (preprodromal) phase of development.

Neurological evaluations were carried out by trained and reliable raters blind to clinical data using a modified version of the Buchanan and Heinrichs Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989; Keshavan et al. 2003) administered prior to initiation of antipsychotic medication. The modified NES is a 13-item scale in which most items are rated 0, 1, or 2 (strictly dichotomous measures are scored 0 or 2). Principal components analysis using Varimax normalized rotation yielded two factors (motor and cognitive neurological signs that explain most of the variance in these data [Sanders et al. 2000]); these subscale items were therefore used to compute NES scores. As with SAPS and SANS data, we used averages of NES items (0–2) rather than total scores in order to minimize the effect of missing or unassessable items on the data.

Within 72 hours of clinical ratings, neurocognitive assessment was conducted by trained raters who were blind to the clinical diagnosis. Verbal learning and memory were assessed with the California Verbal Learning Test (Delis et al. 1987) using the total recall over all five learning trials. Attention was assessed using the Digit Span tests from the Wechsler Adult Intelligence Scale–Revised (Wechsler 1981) and the Trail Making Forms A and B (Reitan and Wolfson 1985). Visual learning and memory were assessed with the immediate and delayed visual memory design reproduction of the Wechsler Memory Scale–Revised (Wechsler 1987). Problem solving and conceptual flexibility were assessed using the Wisconsin Card Sorting Test (WCST, 1981). In our prospective data, we have found neuropsychological parameters to be generally stable during followup (Schuepbach et al. 2002). For this reason, and because we had a larger number of subjects with baseline data, we chose to use the initial (pretreatment) neuropsychological data for our analyses.

Outcome was assessed using the GAF and the SC scales (Strauss and Carpenter 1974; Handel et al. 1996). The GAF provides a valid summary of symptoms and social functioning in schizophrenia, especially when assessed following stabilization from the initial psychotic episode (Startup et al. 2002). The SC scale provides a composite index of outcome based on four items: social functioning, hospitalization, symptomatology, and occupational functioning. This scale has been widely used in studies of prediction of outcome in schizophrenia (Handel et al. 1996). Because hospitalization rates are changing as a function of health care system changes, this item may not necessarily reflect the individual patient's outcome; for this reason, we also used the social subscale from the SC scale for analyses.

Statistical analyses were performed using Statistica (Statsoft Corp). First, normality of the study variables was examined using Lillifiore tests of normality. Where appropriate, data were normalized by square root transformations, as in the case of DUI-pro and DUI-psy. Because the data continued to show a nonnormal distribution for DUI-pro (Lillifiore test $p < 0.01$) and DUI-psy (Lillifiore test $p < 0.01$), we chose to categorize the data for our primary analytic approach. Second, the relationships between the hypothesized predictor variables (age, age of onset, positive and negative symptoms [average of item scores from the SANS and SAPS], baseline functioning as measured by GAF scores after initial stabilization at 4 weeks, DUI-pro, DUI-psy, PAS scores [average of the childhood, and early and late adolescence subscale items], NES total scores, neuropsychological measures, and dependent variables [SC and GAF scales at 1 and 2 years] were examined by using Pearson correlations. GAF assessment near the time of discharge and following clinical stabilization was chosen as an appropriate measure of baseline functioning because this was less likely to be confounded by acute psychosis or agitation. The relationships between categorical predictor variables (sex, diagnosis-schizophrenia vs. other psychoses) and outcome were examined using independent t tests. Third, predictive measures that were significantly correlated with the primary measures of outcome at a conservative p value of 0.01 or less were examined using a forward stepwise regression analysis. Finally, we performed a hierarchical multiple regression analysis using an approach similar to that used by Harrigan et al. (2003). The predictive variables were entered into the regression equation as guided by their temporal relationship to outcome (e.g., premorbid adjustment before DUI-pro, followed by neuropsychological function, baseline GAF, and diagnosis in that order).

Results

Clinical and Demographic Characteristics. The study sample (n = 104) consisted of 64 males and 40 females with age 25.64 ± 8.2 years for patients for the 1-year

analyses, and 44 males and 24 females for the 2-year analyses (total $n = 68$). Table 1 contains the demographic, clinical, and neuropsychological data. The diagnostic breakdown was as follows: schizophrenia ($n = 63$), schizoaffective disorder ($n = 10$), delusional disorder ($n = 7$), psychotic depression ($n = 9$), bipolar disorder with psychotic features ($n = 7$), brief psychotic disorder ($n = 2$), and atypical psychosis ($n = 6$). The mean DUI-pro was 184.85 ± 235.44 weeks (median 97 weeks) and DUI-psy was 95.71 ± 163.37 weeks (median 34 weeks). There were no significant differences between male and female patients with regard to GAF (1 year, $t = -0.99$, $p = 0.32$; 2 years, $t = -1.23$, $p = 0.22$) or SC scores (1 year, $t = -0.91$, $p = 0.36$; 2 years, $t = -1.77$, $p = 0.08$). Patients with schizophrenia or schizoaffective disorders ($n = 73$) had worse outcomes than patients with nonschizophrenia psychotic disorders ($n = 31$) as measured by GAF (1 year, $t = -2.67$, $p = 0.009$; 2 years, $t = -3.71$, $p = 0.0004$) or SC scores (1 year, $t = -2.29$, $p = 0.02$; 2 years, $t = -2.04$, $p = 0.048$).

We compared patients with both 1- and 2-year outcome data available ($n = 68$) to those in whom the 2-year data were not available ($n = 36$) in order to examine the possible effect of sample attrition on the clinical and demographic characteristics. The former group members were older (26.86 ± 8.58 vs. 23.34 ± 6.96 years; $t = 2.19$; $df = 102$; $p = .04$) and had a later age of onset (26.60 ± 8.4 vs. 23.07 ± 6.94 years; $df = 102$; $t = 2.14$; $p = .03$). None of the other measures listed in table 1 differed significantly between the two groups.

Correlations Between Predictor and Outcome Variables. The psychopathological and demographic variables that significantly correlated ($p = 0.01$ or less) with outcome included DUI-pro, GAF scores at 4 weeks, and total PAS scores (table 2). DUI-pro was correlated most strongly at 2 years for both measures of outcome (GAF and SC). Among the neurological/neuropsychological measures, the significant variables were NES (item

Table 1. Clinical and demographic characteristics of the study sample: Predictive measures and outcome measures

	All Subjects						Subjects With PAS Data					
	n	Mean	SD	Median	Min	Max	*n*	Mean	SD	Median	Min	Max
Predictive measures												
Age	104	25.64	8.198	23.6	13.17	49.82	48	27.24	8.94	24.44	13.17	49.82
Race (W/B/O)	73/23/8						35/10/3					
Sex (M/F)	64/40						27/21					
Age of onset	104	25.38	8.121	23.37	12.06	49.8	48	27.02	8.96	24.38	12.06	49.8
SES	92	41.05	14.31	39.25	13	66	46	41.15	15	39.25	13	66
PAS							48	17.77	7.33	17.5	4	33
GAF baseline	100	45.18	12.72	42.5	15	72	47	44.91	12.7	43	15	72
DUI-pro (wks)	103	184.85	235.44	97.14	2.857	1,307	48	188.3	253	91	2.857	1,307
DUI-psy (wks)	104	95.71	163.37	34.14	0.286	1,171	48	79.68	132	30.36	1.857	770.6
SANS	104	2.126	0.657	2	1	4.316	48	2.09	0.71	1.895	1	4.316
SAPS	104	0.888	0.73	0.625	0	2.967	48	0.95	0.6	0.948	0.033	2.967
WCST PE	83	21.34	15.5	19	4	76	39	22.03	15.1	19	4	65
Trails A (mins)	93	32.97	19.03	28	13	135	43	37.98	23.5	30	13	135
Trails B (mins)	92	76.01	37.16	65	20	216	43	77.37	38.1	63	20	207
WMS immediate	92	32.74	6.014	34	16	41	43	31.7	5.86	33	16	41
WMS delayed	93	28.71	8.998	31	2	41	43	28.16	8.18	30	7	41
Digit span	93	14.94	4.278	14	7	27	43	13.84	4.02	13	7	22
NES average	88	0.647	0.452	0.583	0	2	42	0.715	0.49	0.688	0	2
Outcome measures												
GAF 1 yr	104	53.34	14.33	53	22	80	48	53.52	13.9	53	22	80
GAF 2 yrs	68	57.53	13.94	58	25	89	44	57.25	13.9	58	25	89
SC 1 yr	95	11.63	3.14	12	5	16	48	11.56	3.13	12	5	16
SC 2 yrs	55	12.11	3.201	13	4	16	36	11.89	3.18	12.5	4	16

Note.—DUI-pro = duration of untreated illness—prodrome (wks); DUI-psy = duration of untreated illness—psychosis (wks); GAF = Global Assessment of Functioning scale; max = maximum; min = minimum; NES = Neurological Evaluation Scale (average of the cognitive and motor subscale items); PAS = Premorbid Adjustment Scale (child and early adolescence subscales combined); PE = perseverative errors; SANS = Scale for the Assessment of Negative Symptoms (average of items); SAPS = Scale for the Assessment of Positive Symptoms (average of items); SC = Strauss-Carpenter scale; SD = standard deviation; SES = socioeconomic scale; W/B/O = white/black/other; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.

Table 2. Results of correlation analyses (Pearson correlations) showing the relations between hypothesized predictor variables and outcome scores[1]

Baseline	GAF (1 yr)	GAF (2 yrs)	SC (1 yr)	SC (2 yrs)
Age	–0.062 (n = 104)	–0.071 (n = 68)	–0.141 (n = 95)	–0.275 (n = 55)
Age of onset	–0.06 (n = 104)	–0.06 (n = 68)	–0.14 (n = 95)	–0.27* (n = 55)
PAS	–0.38** (n = 48)	–0.29 (n = 44)	–0.33** (n = 48)	–0.45** (n = 36)
SES	0.14 (n = 92)	0.22 (n = 65)	0.09 (n = 86)	0.03 (n = 53)
DUI-pro[2]	–0.15 (n = 103)	–0.31** (n = 67)	–0.12 (n = 94)	–0.33** (n = 54)
DUI-psy[2]	–0.13 (n = 104)	–0.28* (n = 68)	–0.13 (n = 95)	–0.19 (n = 55)
SANS	–0.23* (n = 104)	–0.28* (n = 68)	–0.20 (n = 95)	–0.14 (n = 55)
SAPS	–0.15 (n = 104)	–0.23 (n = 68)	–0.09 (n = 95)	–0.17 (n = 55)
GAF (4 wks)	**0.48**** (n = 100)	**0.33**** (n = 67)	**0.49**** (n = 92)	**0.20** (n = 54)

Note.—DUI-pro = duration of untreated illness—prodrome (wks); DUI-psy = duration of untreated illness—psychosis (wks); GAF = Global Assessment of Functioning scale; PAS = Premorbid Adjustment Scale (child and early adolescence subscales combined); SANS = Scale for the Assessment of Negative Symptoms (average of items); SAPS = Scale for the Assessment of Positive Symptoms (average of items); SC = Strauss-Carpenter scale; SES = socioeconomic scale.

[1] Values represent r values with p values in parentheses.

[2] Square root transformed.

*$p \leq 0.05$; **$p \leq 0.01$

average) scores; WCST (perseverative errors), Trails A and B (time, in minutes), Wechsler Memory Scale (immediate and delayed recall), and Digit Span (table 3).

Attrition of the sample from year 1 to year 2 could potentially account for the observed increase in correlations from year 1 to year 2 (by a possible retention of more extreme scorers). For this reason, we repeated the correlation analyses using 1-year outcome measures for only the subset of subjects who had both 1- and 2-year GAF and SC data (n = 54). The results were similar to those presented in tables 2 and 3, with more robust correlations for DUI-pro being observed in year 2.

To examine whether the observed predictors of outcome were interrelated, we examined correlations between these variables. DUI-pro did not correlate significantly with GAF at 4 weeks or with any of the neuropsychological or NES measures that were significantly associated with outcome. However, DUI-pro showed a trend for a correlation with PAS scores (r = 0.27; p = 0.08) such that a longer time since onset of prodrome was associated with poorer premorbid functioning.

Multiple Regression Analyses. To examine the independent value, if any, of these measures in prediction of outcome, we conducted one forward stepwise regression analysis with each of the outcome parameters, choosing predictors that were significant correlates of outcome (table 4). This analysis included subjects who had data on all the above-listed predictor variables and at least one measure of outcome (n = 68). DUI-pro (dichotomized as above vs. below the median, 97 weeks) predicted both GAF (R^2 = 0·41; $p < 0.00001$) and SC scores (R^2 = 0.23; p = 0.002) at 2 years, while GAF at 4 weeks predicted both GAF (R^2 = 0.20; $p < 0.0001$) and SC scores (R^2 = 0.13; p = 0.004) at 1 year. Independent effects were seen for neuropsychological variables; WCST (perseverative errors) predicted GAF scores at 1 year (R^2 = 0.28; p = 0.007) and SC scores at 2 years (R^2 = 0.51; p = 0.03). Wechsler Memory Scale (delayed) predicted GAF at 2 years (R^2 = 0.49; p = 0.012). Trails A predicted SC scores at both 1 year (R^2 = 0.21; p = 0.012) and 2 years (R^2 = 0.44; p = 0.001).

We also conducted a separate stepwise multiple regression analysis using all the variables including PAS

Table 3. Results of correlation analyses (Pearson correlations) showing the relations between neurological/neuropsychological variables and outcome scores[1]

Baseline	GAF (1 yr)	GAF (2 yrs)	SC (1 yr)	SC (2 yrs)
CVLT	0.151 (n = 88)	0.119 (n = 59)	0.040 (n = 82)	0.257 (n = 49)
WCST PE	–0.30** (n = 83)	–0.17 (n = 53)	–0.19 (n = 76)	–0.32* (n = 45)
Trails A	–0.208* (n = 93)	–0.230 (n = 60)	–0.246* (n = 86)	–0.469** (n = 49)
Trails B	–0.196 (n = 92)	–0.259* (n = 60)	–0.187 (n = 85)	–0.411** (n = 49)
WMS (immediate)	0.188 (n = 92)	0.289* (n = 60)	0.153 (n = 86)	0.383** (n = 49)
WMS (delayed)	0.131 (n = 93)	0.30* (n = 60)	0.083 (n = 86)	0.348** (n = 49)
Digit Span	0.093 (n = 93)	0.140 (n = 60)	0.022 (n = 86)	0.362** (n = 49)
NES	–0.192 (n = 88)	–0.337** (n = 57)	–0.057 (n = 82)	–0.390** (n = 45)

Note.—CVLT = California Verbal Learning Test; DUI-pro = duration of untreated illness—prodrome (wks); DUI-psy = duration of untreated illness—psychosis (wks); GAF = Global Assessment of Functioning scale; NES = Neurological Evaluation Scale (average of the cognitive and motor subscale items); PE = perseverative errors; SC = Strauss-Carpenter scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.

[1] Values represent r values with p values in parentheses.

* $p \leq 0.05$; ** $p \leq 0.01$.

scores for the subset of patients that had these data available at baseline (n = 28). As may be seen in table 4, DUI-pro highly significantly predicted both GAF and SC scores at 2 years, and also the 1-year GAF scores. GAF (4 weeks) predicted the 1-year GAF scores; Trails A moderately predicted GAF at 1 year and SC scores at year 2. PAS strongly predicted SC scores at year 2.

Both the above analyses were also carried out using DUI-pro (square root transformed) as a continuous measure. The findings were largely similar, with DUI-pro showing a significant predictive value for both GAF (R^2 = 0.16; p = 0.006) and SC scores (R^2 = 0.21; p = 0.004) at 2 years (figure 1).

We also examined whether the observed relation between DUI-pro and outcome might be confounded by the inclusion of patients with nonaffective psychotic disorders. When only schizophrenia and schizoaffective patients were included in the multiple regression analyses, the predictive value of DUI-pro for 2-year outcome remained significant (R^2 = –0.43; n = 34; p = 0.00002 for GAF and R^2 = –0.40; n = 29; p = 0.01 for SC scores) for the analysis of the entire data set; for the analysis of the data set that included PAS measures, the results were R^2 = –0.51; n = 23; p = 0.0002 for GAF and R^2 = –0.50; n = 20; p = 0.01 for SC scores.

It is possible that choice of global SC scores might confound traitlike characteristics (e.g., social functioning) with episodic exacerbations (e.g., hospital admissions). For this reason, we repeated the multiple regression analyses to include the SC social subscale (instead of the SC total score) as the dependent variable. DUI-pro showed a trend for a predictive value for the SC social subscale at 2 years in the total sample n = 40 (R^2 = 0.28; p = 0.07). In the subset with PAS data, the predictive value of DUI-pro remained significant as a predictor in this analysis (n = 27; R^2 = 0.33; p = 0.043).

Table 5 shows the results of the hierarchical regression analysis, with the predictor variables being entered in order of their appearance (see above). As seen in table 5, DUI-pro continued to show a robust contribution to the 2-year outcome in GAF as well as SC scores that was highly significant (p = 0.00005 and p = 0.001, respectively).

Discussion

The main findings in our study are that DUI-pro can predict outcome in first episode psychotic disorders independent of clinical factors such as diagnosis, baseline func-

Table 4. Stepwise multiple regression analyses of the data using predictor variables significant at $p < 0.01$ from tables 2 and 3[1]

	All Subjects						Subset With PAS Data				
	Predictor measure	R^2	R^2 change	F to enter/remove	p		Predictor measure	R^2	R^2 change	F to enter/remove	p
GAF 1 yr	GAF (4 wks)	0.20	0.20	16.23	0.0001	**GAF 1 yr**	DUI-pro	0.15	0.15	5.34	0.028
(*n* = 68)	WCST PE	0.28	0.08	7.63	0.007	**(*n* = 34)**	GAF (4 wks)	0.29	0.12	4.88	0.035
	Diagnosis	0.31	0.03	3.1	0.083		Trails A	0.37	0.11	4.72	0.038
	Trails A	0.33	0.01	1.10	0.297		PAS	0.39	0.02	1.18	0.287
GAF 2 yrs	DUI-pro	0.41	0.41	29.7	0.00001	**GAF 2 yrs**	DUI-pro	0.52	0.52	29.87	0.000
(*n* = 45)	WMS (delayed)	0.49	0.08	6.87	0.012	**(*n* = 31)**	GAF (4 wks)	0.57	0.05	3.45	0.074
	GAF (4 wks)	0.51	0.02	1.67	0.204		PAS	0.60	0.03	1.98	0.171
	Trails A	0.53	0.02	1.62	0.211		Trails B	0.62	0.02	1.37	0.253
							Digit span	0.67	0.05	3.88	0.061
SC 1 yr	GAF (4 wks)	0.13	0.13	9.05	0.004	**SC 1 yr**	PAS	0.09	0.09	2.96	0.095
(*n* = 64)	Trails A	0.21	0.09	6.75	0.012	**(*n* = 34)**	GAF (4 wks)	0.15	0.06	2.20	0.148
	DUI-pro	0.24	0.03	2.07	0.156		Trails A	0.18	0.03	1.09	0.305
							NES	0.21	0.03	1.01	0.324
							DUI-pro	0.25	0.04	1.43	0.243
							Trails B	0.28	0.03	1.12	0.299
SC 2 yrs	DUI-pro	0.23	0.23	10.97	0.002	**SC 2 yrs**	PAS	0.32	0.32	11.28	0.003
(*n* = 38)	Trails A	0.44	0.20	12.58	0.001	**(*n* = 27)**	Trails A	0.46	0.14	5.83	0.024
	WCST-PE	0.51	0.07	4.94	0.033		DUI-pro	0.62	0.17	9.72	0.005
	WMS (immediate)	0.54	0.04	2.58	0.118		Diagnosis	0.66	0.03	1.95	0.178
							WMS (immediate)	0.70	0.04	2.70	0.116
							WCST PE	0.73	0.03	2.10	0.163

Note.—DUI-pro = duration of untreated illness—prodrome (wks); GAF = Global Assessment of Functioning scale; NES = Neurological Evaluation Scale (average of the cognitive and motor subscale items); PAS = Premorbid Adjustment Scale (child and early adolescence subscales combined); PE = perseverative errors; SC = Strauss-Carpenter scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale.

[1] DUI-pro was categorized by a median split (< or > 97 wks).

Figure 1. Scatterplots showing the relationship between illness duration from prodromal onset (weeks, square root transformed) and 2-year outcome as measured by (A) GAF scores and (B) SC scores.

Figure 1a

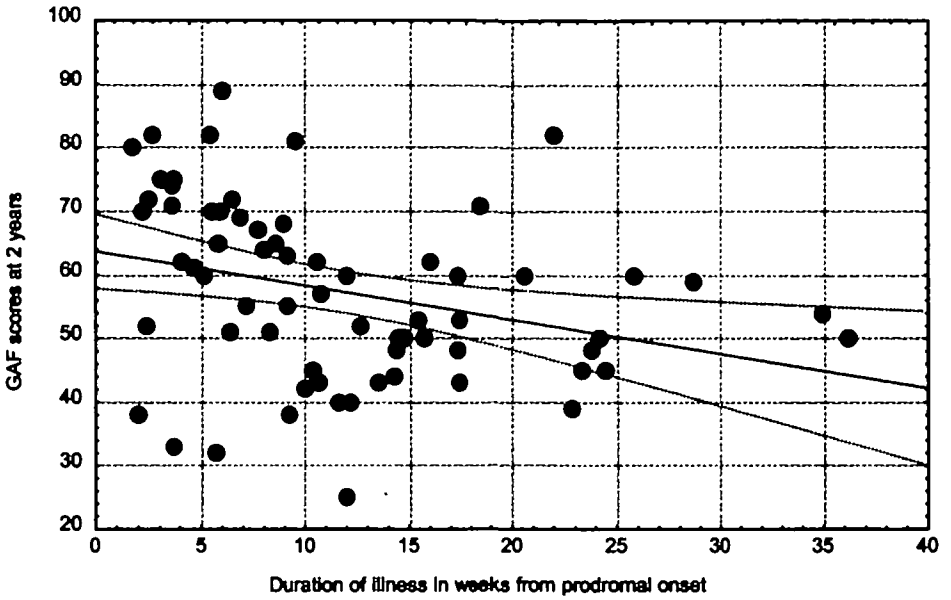
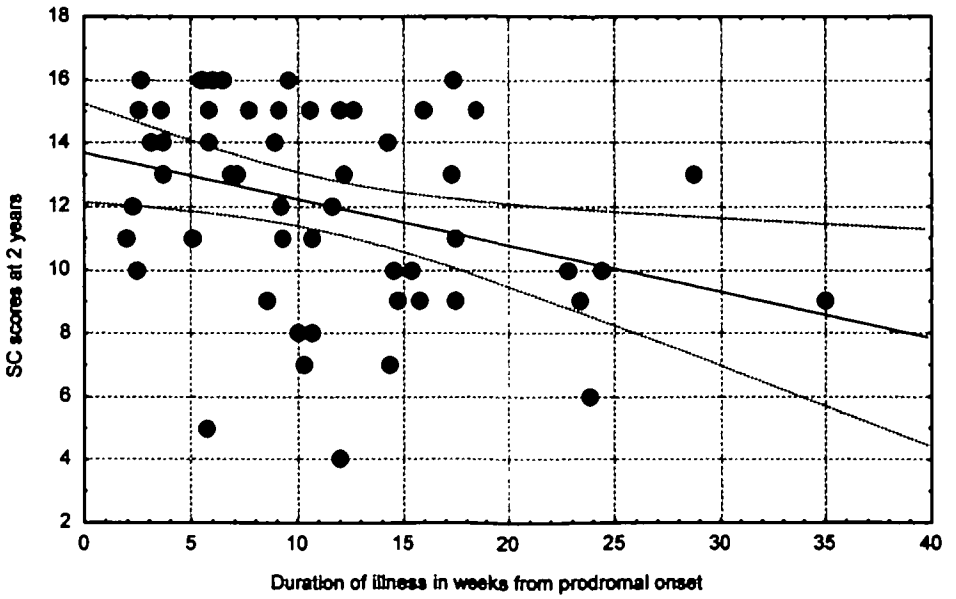


Figure 1b



Note.—GAF = Global Assessment of Functioning scale; SC = Strauss-Carpenter scale.

tioning, and neurocognitive deficits. In a subset of our sample, we also observed an independent effect of DUI-pro on the 2-year outcome after conjointly examining the potential confounding effect of premorbid adjustment. These observations provide support for the view that an independent relationship exists between DUI and outcome in first episode psychotic patients.

While studies on the relationship between DUI and outcome have led to a significant body of literature, relatively few studies have examined this question using longitudinal prospective designs. Haas et al. (1998) reported a relationship between duration of psychosis and inpatient treatment response for both first episode and longer ill schizophrenia patients. They also observed that premorbid

Table 5. Hierarchical regression analyses of the data[1]

	GAF 1 yr			GAF 2 yrs		
	Adjusted R^2	**F**	***p***	**Adjusted R^2**	**F**	***p***
PAS	0.04	1.98	0.17	0.26	10.03	0.004
DUI-pro	0.1	2.45	0.1	0.63	22.04	0.00005
Neuropsychological/ neurological measures	–0.1	0.76	0.66	0.57	4.65	0.004
GAF baseline	0.1	1.25	0.33	0.57	4.34	0.005
Diagnosis	0.06	1.14	0.4	0.54	3.68	0.01
	SC 1 yr			**SC 2 yrs**		
	Adjusted R^2	**F**	***p***	**Adjusted R^2**	**F**	***p***
PAS	0.12	4.55	0.04	0.29	11.28	0.002
DUI-pro	0.15	3.23	0.06	0.38	8.74	0.001
Neuropsychological/ neurological measures	0.03	1.08	0.43	0.48	3.63	0.01
GAF (4 wks)	0.01	1.02	0.46	0.47	3.2	0.02
Diagnosis	0.04	0.91	0.55	0.53	3.62	0.01

Note.—DUI-pro = duration of untreated illness—prodrome (wks); GAF = Global Assessment of Functioning scale; PAS = Premorbid Adjustment Scale (child and early adolescence subscales combined); SC = Strauss-Carpenter scale.

[1] DUI-pro was categorized into < or > median (97 wks).

functioning (measured using the PAS) was superior for subjects with a longer duration of untreated psychoses. Loebel et al. (1992) reported the first longitudinal study examining outcome in relation to psychosis duration in first episode patients with schizophrenia or schizoaffective disorder during a 3-year followup. Time to remission was significantly predicted by psychosis duration independent of gender and diagnosis. A larger data set from the same group, however, found only a tendency for prediction of outcome by psychosis duration (Robinson et al. 1999). McGorry et al. (1996) reported a followup study of 200 first episode patients treated in Melbourne, Australia; prolonged duration of the prodromal phase predicted worse outcome at 12-month followup on the Brief Psychiatric Rating Scale and the SANS, GAF, and quality of life scales. Szymanski et al. (1996) examined 36 neuroleptic-naïve schizophrenia patients over a 6-month followup period and observed that longer duration of psychosis was associated with less change in positive symptoms but not negative symptoms. Linszen et al. (1998) reported that psychosis duration was unrelated to the likelihood of relapse during a 12-month followup treatment. On the other hand, Craig et al. (2000) found no relationship between psychosis duration and 24-month outcome as measured by positive and negative symptoms and GAF scores. Ho et al. (2000), in a 6-month followup examination, also found no significant relationship between psychosis duration and either the level of remission of symptoms or the quality of life at 6-month followup.

Our study has attempted to address several of the limitations that may have accounted for variable findings in previous studies, and it has several strengths. First, our study included a longitudinal prospective design in first episode psychotic patients. The advantages of this first episode strategy are that estimates of illness duration, unlike those in retrospective studies, are from the recent past, and the prospective design ensures that patients are followed up over time to measure outcome. Second, we chose composite measures of outcome such as the GAF and SC scales and used more than one followup time point. Third, we examined well-documented evidence of the patient's initial clinical features (e.g., premorbid adjustment, baseline symptoms, and cognitive deficits) that could potentially confound or mediate the influence of illness duration on outcome variables. Finally, to our knowledge, only a few previous studies (e.g., McGorry et al. 1996; Harrigan et al. 2003) have examined the relationship between illness duration as defined by prodromal onset and outcome. We examined two measures of illness duration: the duration as measured by prodromal onset and that measured by onset of psychotic symptoms. Our observation that DUI-pro was more robustly predictive of outcome suggests that this may be a more informative measure for examining the

predictive value of the duration of illness. However, one should be cautious in making this interpretation because the difference between DUI-pro and DUI-psy in the strength of correlation with outcome measures was subtle. Studies showing an association between untreated psychosis duration and unfavorable outcome have suggested that this may reflect a neurotoxic process because of continued psychosis, perhaps mediated by the effects of dopaminergic excess (Wyatt 1991; Loebel et al. 1992). Our data suggest that if untreated psychosis duration has an effect on outcome, the prodromal phase might contribute to this as well. The absence of a correlation between baseline cognitive or neurological deficits and illness duration to some extent argues against the notion that continued untreated illness somehow led to a decline in brain function. It is possible that prolonged untreated prodromal and psychotic symptoms might lead to unfavorable outcome by psychosocial mechanisms such as reduced self-esteem, loss of educational and vocational possibilities, and shrinkage of environmental support systems (Ho et al. 2003).

Our finding of a lack of relationship between illness duration and outcome at 1 year but the emergence of such a relationship at the 2-year time point is of interest. Our data indicated that this difference between 1- and 2-year data could not have been simply the result of attrition of the sample. We noted that baseline function as measured by GAF scores at 4 weeks was a strong predictor of outcome at the 1-year time point and that this might therefore be an important confounding factor to consider in studies examining short-term outcome. However, our observations of an effect of DUI-pro at 2 years independent of baseline functioning suggests that illness duration may be more of a "traitlike" predictor of outcome in psychotic disorders. Interestingly, GAF scores at 4 weeks were highly correlated with SC and GAF scores at 1 year but not at 2 years. This suggests that at 1 year, the patients may still be having continuing effects of the initial episode, and the assessment at 2 years may be a more "true" measure of outcome independent of the first episode of the illness.

The observed association between baseline neuropsychological performance and poor outcome is also consistent with prior studies (Grawe and Levander 2001). Impaired attention and memory were significantly related to outcome; problem-solving ability as measured by the WCST also showed a trend to be related to outcome. None of the neuropsychological measures were correlated with DUI-pro, suggesting that cognitive deficits and illness duration might serve independently to predict outcome. Again, the persistence of the relationship between cognitive performance and outcome at 2 years suggests that cognitive measures are more likely to be trait related.

There were several limitations of our study. First is the reliance on history for assessments of prodromal and psychosis onset. However, we used multiple sources of information and a best estimate, consensus approach to determining onset to improve reliability. Future studies need to use standardized methods of assessing onset timing such as Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Hafner et al. 1992) and the Royal Park Instrument (McGorry et al. 1990). Instruments that tap into the more subtle aspects of psychopathology seen in the prodromal phase (e.g., Beiser et al. 1993) are likely to be of particular value. Second, global outcome measures (the GAF and SC scales) are somewhat coarse. It is possible that selection of these scales might confound traitlike characteristics (e.g., social functioning) with episodic exacerbations (e.g., hospitalizations). More finely grained and comprehensive measures of functional outcome might explain contradictions in the prodromal literature and should be used in future studies. Third, it is possible that treatment type and adherence patterns, and other factors such as family support and insight, might have affected the relationships between the predictor and outcome measures. Ours was not a treatment study, and therefore we did not have systematic data to adequately address these issues. Fourth, our sample size is relatively small; thus, the results of the multivariate analyses need to be interpreted with caution.

It is an important question whether prolonged DUI-pro reflects a causal mechanism for poor outcome, a consequence of pre-illness factors such as premorbid impairment, or simply a confound of a more severe illness running a protracted, insidious course. Our observation of a strong relationship between DUI-pro and outcome even after accounting for baseline and premorbid deficits suggests that the causal mechanism explanation deserves serious consideration. Our data cannot conclusively determine whether such a causal relationship, if it exists, is determined by neurobiological factors, nonbiological factors, or both. Future studies need to examine the neurobiology of psychotic illnesses prospectively in carefully defined patients with prodromal as well as early psychotic phases of schizophrenia and related disorders. Clearly, such studies will have pivotal implications for early diagnosis and intervention efforts, and mental health policy.

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