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Does treatment delay in first-episode psychosis really matter?[1]

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ABSTRACT

Background. Relatively few predictors of outcome in first-episode psychosis are potentially malleable and duration of untreated psychosis (DUP) is one. However, the degree to which DUP is mediated by other predictors of outcome is unclear. This study examines the specific effects of DUP on 12-month outcome after adjusting for effects of potential confounders and moderating variables.

Method. The sample comprised 354 first-episode psychosis patients followed up 12-months after remission/stabilization of their psychotic symptoms. Outcome measures included functional outcome, severity of positive symptoms and negative symptoms. Hierarchical multiple regression assessed whether DUP significantly predicted 12-month outcome after adjusting for other predictors. Contrast analysis further clarified the differential effects of DUP on 12-month outcome.

Results. DUP remained a significant predictor of outcome after adjusting for the effects of other variables. This finding remained robust for the subset of patients with schizophrenia or schizophreniform disorder. Functional outcome appeared to decline substantially even after very short treatment delays (>7 days), with more gradual deterioration in functioning until very long DUP (>1 year). Good outcome was variably associated with good pre-morbid adjustment, female gender, diagnosis of affective disorder, short duration of prodromal symptoms, and treatment within the Early Psychosis Prevention and Intervention model in contrast to other models of care.

Conclusions. DUP consistently predicts outcome independently of other variables, and is not simply a proxy for other factors. As one of the few potentially malleable factors influencing outcome, DUP could prove to be a target for secondary preventive efforts in early psychosis.

INTRODUCTION

It is highly likely that an association exists between duration of untreated psychosis (DUP) and outcome in first-episode psychosis (Helgason, 1990; Wyatt, 1991; Loebel *et al.* 1992; Beiser *et al.* 1993; Larsen *et al.* 1996; Scully *et al.* 1997; Haas *et al.* 1998; McGlashan, 1999; Bottlender *et al.* 2000; Drake *et al.* 2000; Larsen *et al.* 2000; Quinn *et al.* 2000; Meagher *et al.* 2001; Norman & Malla, 2001), though this is not beyond dispute (Barnes *et al.* 2000; Craig *et al.* 2000; Ho *et al.* 2000; Ho & Andreasen, 2001). Moreover, DUP is one of the few risk factors for poor outcome that has some potential for malleability through early detection strategies. Timing of treatment is not the only malleable factor influencing outcome; quality of treatment has also been associated with improved outcomes (McGorry *et al.* 1996) although evidence suggests that its capacity to influence outcome may be limited where treatment delays are very short or very long (Carbone *et al.* 1999). Identification of these potentially malleable risk factors for poor outcome contrasts with the relatively fixed nature of most predictors such as gender, age of onset of

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psychotic symptoms, pre-morbid adjustment and diagnosis.

If the association between DUP and outcome is direct and causal in nature, then the prospects of favourably influencing patient outcome by reducing DUP via early detection programs appear promising. However, it is not sufficient to simply establish an association between DUP and outcome. DUP may be confounded to a greater or lesser extent by other predictors of outcome, such as pre-morbid adjustment, family psychiatric history, level of education, mode of onset and gender (Loebel *et al*. 1992; Verdoux *et al*. 1998, 2001; Larsen *et al*. 2000; Birchwood *et al*. 1998; Haas *et al*. 1998). The extent of such confounding is of critical importance (Norman & Malla, 2001), as it has implications for the viability of early detection programmes in early psychosis. If DUP is merely a proxy for other predictors of outcome, then establishing programmes to reduce the duration of untreated psychosis would be of dubious value in improving outcome. On the other hand, if it can be established that prolonged DUP influences patient outcome independently of other factors, then it becomes imperative to develop strategies for early detection of psychosis.

One of the factors consistently associated with good outcome in first-episode psychosis is good pre-morbid adjustment (Larsen *et al*. 2000; Haas & Sweeney, 1992; Johnstone *et al*. 1990). DUP appears to be consistently associated with both patient outcome and pre-morbid adjustment, with debate surrounding the question of whether DUP is simply an epiphenomenon of pre-morbid adjustment (Larsen *et al*. 2000; McGorry, 2000). It is possible that poor pre-morbid functioning could result in a reduced likelihood of detection and appropriate treatment, thus resulting in longer DUP. DUP, according to this perspective, has only a spurious association with outcome, a view seemingly supported by some studies (Verdoux *et al*. 1998, 2001) but not others (Haas *et al*. 1998; Larsen *et al*. 2000). The other possibility is that pre-morbid adjustment and DUP each exert a distinct and separate influence on outcome, in addition to sharing a component of outcome variance. Similarly, the prodromal phase is defined as an intermediate stage or prelude to the emergence of frank psychosis. It is uncertain whether DUP is a correlate only of a more proximal and intrinsic feature, such as mode of onset or duration of prodrome, or whether the influence of DUP is independent of these factors. The critical question is whether DUP is a significant and important predictor of outcome after adjusting for the effects of pre-morbid adjustment, duration of prodrome and other predictors of outcome. As Norman & Malla (2001) note, taking potential confounds into account is critical in assessing the independent influence of DUP on patient outcomes.

This paper will provide evidence that pre-morbid adjustment, duration of prodrome and other factors thought to be associated with outcome do not fully account for the apparent effects of DUP on outcome, and that inherent negative effects on patient outcome linked to delayed treatment probably exist. The validity of this finding in first-episode psychosis as a whole and also within the schizophrenia/schizophreniform subsample will be established, and evidence produced for the positive impact of quality of treatment, as represented by model of care, on functional outcome.

METHOD

Context and sample

The initial sample consisted of 565 patients who had experienced their first psychotic episode. Of this sample, 200 patients were treated within the Aubrey Lewis Unit for First Episode Psychosis, Melbourne (the 'pre-EPPIC' model), between March 1989 and April 1992. The other 365 patients were treated at the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, between January 1993 and September 1997. The EPPIC programme evolved from the specialized model of care offered by the Aubrey Lewis Unit (Edwards *et al*. 1994; McGorry *et al*. 1996) and doubled the original catchment area to around 800,000 people (Jackson *et al*. 1998; Carbone *et al*. 1999). EPPIC is the only facility in the catchment area for the target population, with virtually no private psychiatrists and little, if any, leakage to private facilities located outside the catchment area; therefore the study group is a truly epidemiologically based sample.

Included in the sample were consecutively admitted patients who consented to being assessed over the course of their first psychotic episode and to follow-up assessment over the 12 months

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Table 1. *Means (with standard deviations in parentheses) or percentages, for demographic and illness-related variables for the completer and non-completer groups*

	Completer group ($N=354$)	Non-completer group ($N=211$)	P
Age at admission, years	22·7 (4·6)	24·0 (5·8)	**
Age at onset, years	22·2 (4·7)	23·4 (5·7)	**
Gender, % Male	71·2	63·5	NS
DSM-III-R Diagnosis, %			NS
Sz/Schizophreniform	57·3	51·0	
Bipolar/Depressive	23·7	27·1	
Schizoaffective	11·6	9·0	
Delusional/NOS/Brief reactive psychosis/ Induced psychosis	7·3	12·9	
Duration untreated psychotic symptoms in days†	180·9 (379·9)	193·2 (573·7)	NS
Median	49·5	32·0	
Duration prodrome in days†	394·6 (655·0)	299·5 (553·7)	NS
Median	136·5	115·0	
Marital status, % never married	86·2	73·9	***
Education, % post-secondary	29·4	26·2	NS
Pre-morbid functioning	0·31 (0·189)	0·32 (0·169)	NS
Positive symptoms at admission	10·5 (3·8)	10·0 (3·9)	NS
Negative symptoms at admission	23·5 (15·3)	22·2 (15·8)	NS
Positive symptoms at stabilization	3·3 (3·5)	3·2 (3·4)	NS
Negative symptoms at stabilization	19·0 (15·3)	16·2 (14·0)	*

† Due to extreme positive skewness, these variables were log-transformed, but untransformed scores are displayed here.
* $P\leqslant 0{\cdot}05$; ** $P\leqslant 0{\cdot}01$; *** $P\leqslant 0{\cdot}001$; NS, not significant.

after their recovery or stabilization. Another group of patients failed to consent to any assessment, and available data indicate that the refusal rate was $\leqslant 25\%$ for both pre-EPPIC and EPPIC cohorts. In order to establish that subjects who consented to research were a representative first-episode psychosis sample, demographic and diagnostic data on study refusers were collected for selected time periods within each of the pre-EPPIC and EPPIC cohorts. A comparison of participant and refuser groups collected within these targeted study periods revealed only minor and clinically unimportant differences on demographic and diagnostic characteristics (McGorry *et al.* 1996; Krstev *et al.* 2002). For the crucial DUP variable, an independent samples t test performed on the log-transformed data showed that the participant group ($N=98$; mean DUP = 278·6 days; S.D. = 459·4, median = 96·5) was representative when compared with the refuser group ($N=22$; mean DUP = 224·5 days; S.D. = 467·3; median = 68·0; $P=0{\cdot}90$). These results indicate that subjects who consented to research constituted a broadly representative first-episode psychosis sample. Eligibility criteria common to both EPPIC and pre-EPPIC services were that the patient had to be experiencing their first psychotic episode and not have previously received substantial treatment (>6 months) for a psychotic illness. Any treatment received prior to entry to the service was not included in the calculation of DUP. Patients were excluded if they were diagnosed with an organic disorder or if they were clearly of below-normal intelligence. EPPIC patients were aged between 16 and 30 years, whereas the pre-EPPIC patients were aged between 16 and 45 years.

Data were collected at three assessment points, which included an assessment on admission to the service (T1), an assessment around the time of episode stabilization (T2), and a final assessment (T3) at 12 months after T2. Of the initial sample of 565, 73·5% (415) completed the 12-month assessment, but a number of these subjects were excluded because of missing data on a number of scales used in the primary analyses. This left 354 subjects (62·7%) in the final study sample.

The representativeness of these 354 subjects was assessed on a range of sociodemographic and illness-related variables, the results of which are reported in Table 1. Differences between the completers and non-completers on categorical variables were tested using χ^2 tests of significance,

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while differences on continuous data were examined using independent samples *t* tests. Highly skewed data such as DUP and duration of prodromal symptoms were log-transformed to approximate normality prior to analysis. It is particularly important to note that the final sample were comparable to the non-completers on duration of untreated psychosis (DUP) ($P=0{\cdot}649$). Furthermore, no statistically significant differences were detected in education, gender, diagnosis, pre-morbid functioning, positive and negative symptoms on admission (T1), positive symptoms at stabilization of illness (T2), nor differences in duration of prodrome. However, the final sample were slightly, but significantly, younger at age of admission than non-completers, had an earlier age of onset of active psychotic symptoms and had slightly more severe negative symptoms at stabilization of illness (T2). Even so, these differences were unimportant, and represent only small effect sizes as defined by Cohen's terminology (Cohen, 1992).

Assessment

Duration of illness, diagnosis and sociodemographic variables

Subjects were assessed with the Royal Park Multidiagnostic Instrument for Psychosis (RPMIP) (McGorry *et al*. 1990 *a*, *b*), which features meticulous measurement of the duration of untreated psychosis and prodromal phases of illness according to carefully operationalized criteria. Onset of psychosis is defined as the emergence of the first sustained psychotic symptom of any type at threshold level, and is dated as precisely as possible to the nearest day, week or month. Duration of untreated psychosis (DUP) is defined as the number of days between the onset of psychosis and initiation of treatment. The onset of prodrome is defined as the earliest deviation from the patient's pre-morbid personality, behaviour or level of functioning prior to the onset of psychotic symptoms. The duration of prodrome is the period of time between the onset of the prodrome and the onset of the psychotic symptoms. The RPMIP includes detailed guidelines that systematize the process of establishing dates of onset of prodromal and psychotic symptoms, a process which helps safeguard the reliability of duration of illness ratings. Multiple sources of information were obtained by interviewing patients and close relatives and then merged to produce an accurate record of the onset, evolution and duration of the illness. DSM-III-R diagnosis, sociodemographic information and severity of drug use, which was rated on a five-point scale of problem use, were also assessed using the RPMIP.

Reliability

Specially trained research psychologists conducted the assessments for the EPPIC and pre-EPPIC cohorts. Formal interrater reliability studies were carried out for 50 subjects in the pre-EPPIC cohort. Very good to excellent interrater reliability was established for specific components of the RPMIP (McGorry *et al*. 1990 *b*), including DSM-III-R diagnosis of schizophrenia ($\kappa=0{\cdot}92$), and the onset and duration of symptoms (mean $\kappa=0{\cdot}79$). While serial interrater measurements were not carried out across the whole study period, interrater reliability over time was safeguarded by the comprehensive set of definitions for symptom ratings and for establishing the illness onset and duration of symptoms provided by the glossary and manual for the RPMIP, and monitored in the context of the extensive training provided for new raters and careful calibration and standardization procedures.

Twelve-month functional outcome and psychopathology

Scales used as 12-month outcome measures included the Quality of Life Scale (QLS) (Heinrichs *et al*. 1984), the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Brief Psychiatric Rating Scale (Nursing modification) (Overall & Gorham, 1962; McGorry *et al*. 1988) from which a positive symptoms subscale was derived (BPRS-PS). The BPRS-PS included four items measuring conceptual disorganization, hallucinatory behaviour, unusual thought content and suspiciousness. The SANS and BPRS-PS were also measured at admission (T1) and episode stabilization (T2).

Pre-morbid functioning

The pre-morbid functioning of the patient was measured using the Pre-morbid Adjustment Scale (PAS) (Cannon-Spoor *et al*. 1982). To avoid potentially confounding pre-morbid functioning

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with the patient's prodromal phase of illness, the pre-morbid adjustment of the patient during the period immediately preceding the prodromal phase was used as an estimate of true pre-morbid functioning.

Statistical analysis

Data transformations

Due to the very high positive skewness of DUP, it was necessary to transform this variable prior to analysis. To facilitate interpretability, two types of transformation were performed. First, a log-transformation of DUP was performed, which produced a normal distribution suitable for use in parametric procedures, and secondly, DUP was cut into five pre-defined categories to facilitate clinical and statistical interpretability. These categories were as follows: 0 to 7 days; 8 days to 4 weeks; over 4 weeks up to 3 months; over 3 months up to 1 year; and over 1 year. Both log-transformed DUP and categorical DUP produced very similar results in the regression analyses, but only the results for the five-levels of DUP are reported here. Duration of prodromal symptoms was log-transformed to normality prior to use in all analyses, and a square-root transformation was applied to the moderately skewed BPRS positive symptoms subscale.

Is DUP an epiphenomenon or does it independently predict 12-month outcome?

A series of hierarchical multiple linear regressions were performed to assess the relative contribution of hypothesized predictors to 12-month outcome, which was represented by the QLS, SANS and BPRS-PS. Separate analyses were conducted for each of these measures as the dependent variable. The predictors were entered in a number of distinct blocks based on the sequence and malleability of the variables. The primary aim was to test whether DUP independently predicts 12-month outcome after incorporating the *a priori* effects of potentially confounding variables. A secondary aim was to estimate the relative contribution of each predictor after controlling for preceding predictors.

Therefore, predictors of 12-month outcome that precede DUP chronologically, including gender, age of onset of psychotic symptoms, pre-morbid functioning, level of education and duration of prodrome, were entered in the model in hierarchical blocks, with DUP entering the model after these. The effects of posterior predictors such as severity of drug use, treatment model and DSM-III-R diagnosis were assessed after accounting for the effects of DUP. The predictive utility of DUP was also reported after controlling for the effects of all predictors in the model.

The multiple regression analyses were based on the total sample of 354 subjects, and subsequently repeated with a subsample of 203 patients who were diagnosed with schizophrenia or schizophreniform disorder. In this way, comparisons could be made with other studies that have focused specifically on schizophrenia-spectrum disorders (Barnes *et al.* 2000; Craig *et al.* 2000; Ho *et al.* 2000). Effect sizes were used to support results obtained in multiple regression analyses, with bivariate linear variances converted to Cohen's f^2 effect sizes according to the equation for multiple partial correlation described in Cohen (1992). Effect sizes were defined as small ($f^2 = 0{\cdot}02$), moderate ($f^2 = 0{\cdot}15$) and large ($f^2 = 0{\cdot}35$).

Is there a clear point at which delayed treatment is linked to poor outcome?

Following the hierarchical multiple regression models, further analyses were performed to examine and further clarify the actual impact of DUP on outcome. In linear regression, the impact of DUP on outcome is assumed to be constant across the various categories of DUP. This is unlikely, however, to be the case. For example, it is possible that the difference between a long and very long DUP on outcome is of a different magnitude to the difference between a very short and a short DUP. Such disparities will not be reflected in the DUP regression coefficients, which measure only average change. Therefore, oneway analysis of covariance (ANCOVA) was employed to clarify the impact of DUP on outcome. Each of three ANCOVA models included DUP as a five-level independent factor, with all of the predictors used in the multiple regression models included as covariates. Simple contrasts compared the DUP category of over 1 year with each of the other DUP categories and repeated contrasts compared adjacent DUP categories. These analyses were performed

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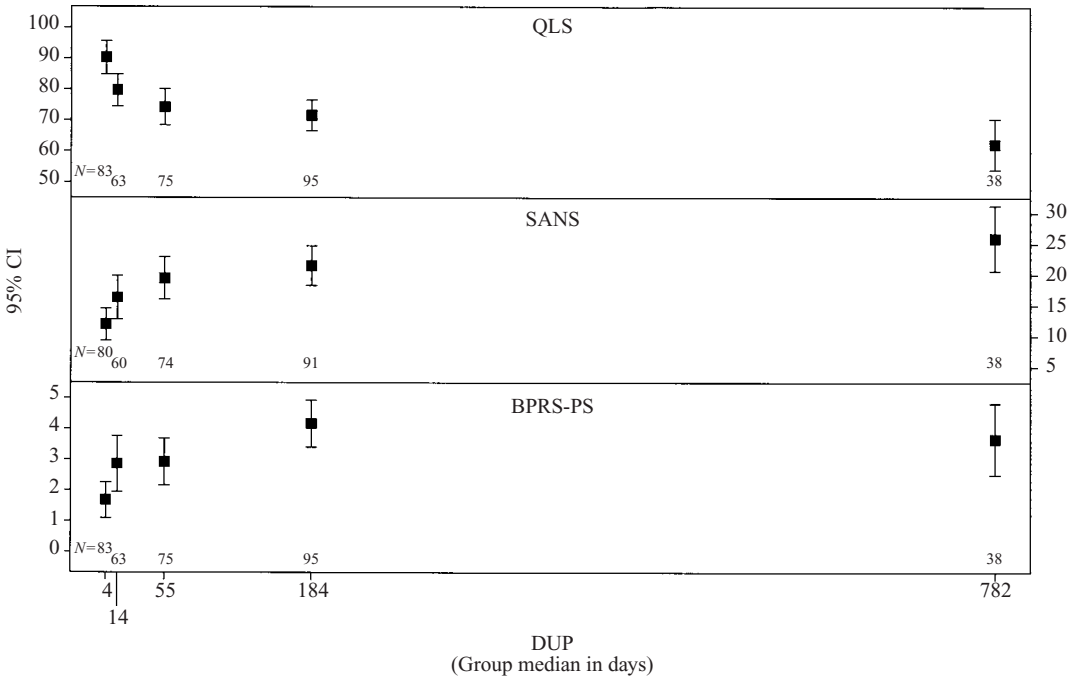


FIG. 1. Twelve-month QLS, SANS and BPRS-PS symptomatology worsen as levels of DUP increase.

for the total sample of 354 subjects and repeated for the schizophrenia-spectrum subsample.

RESULTS

DUP and 12-month outcome

The mean duration of untreated psychosis in the sample was 180·9 days (S.D. = 379·9), but the median was 49·5 days. Pearson correlations between log-transformed DUP and 12-month outcome indicated that prolonged DUP is associated with poor outcome; it was moderately correlated with 12-month QLS ($r = -0{\cdot}33$; $P < 0{\cdot}0001$), and to a lesser extent with negative symptoms ($r = 0{\cdot}29$; $P < 0{\cdot}0001$) and positive symptoms ($r = 0{\cdot}26$; $P < 0{\cdot}0001$). Even when the analyses were restricted to the subsample of 203 patients with a diagnosis of schizophrenia or schizophreniform, the magnitude of these associations remained relatively constant. In the schizophrenia-spectrum subsample, DUP was moderately correlated with 12-month QLS ($r = -0{\cdot}29$; $P < 0{\cdot}0001$), and less so with negative symptoms ($r = 0{\cdot}24$; $P = 0{\cdot}001$) and positive symptoms ($r = 0{\cdot}22$; $P = 0{\cdot}001$).

The frequency of patients in each of the five DUP categories together with the median DUP of each category is as follows: DUP category 0–7 days: $N = 83$ (23·4%, median = 4 days); 8–28 days, $N = 63$ (17·8%, median = 14 days); 29–90 days, $N = 75$ (21·2%, median = 55 days); 3 months–1 year, $N = 95$ (26·8%, median = 184 days); >1 year, $N = 38$ (10·7%, median = 782 days).

The association between categorical DUP and outcome is evident in Fig. 1. Each graph displays the means and 95% confidence intervals of the 12-month outcome measures, plotted at the median of each DUP category for the 354 subjects. A monotonic decrease in 12-month QLS outcome can be observed for each successive level of DUP. Similar patterns are apparent for negative symptoms (SANS) and positive symptoms (BPRS-PS) at 12-months, with increasing severity of symptoms associated with longer DUP levels.

DUP, pre-morbid adjustment and prodrome

Pearson correlations between DUP, pre-morbid adjustment and duration of prodrome indicated

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Table 2. *Summary of hierarchical regression model for predictors of* 12*-month QLS for the total sample* (N = 354) *and for the schizophrenia-spectrum subsample* (N = 202)

	Model	R^2	R^2 change	*P*
All diagnoses (*N* = 354)	Intercept + Gender + Age onset	0·046	0·046	***
	+ Pre-morbid adjustment	0·136	0·090	***
	+ Education level	0·151	0·014	*
	+ Prodrome duration†	0·175	0·025	***
	+ DUP‡	0·232	0·057	***
	+ Severity of drug use	0·233	<0·001	NS
	+ EPPIC *v.* pre-EPPIC	0·251	0·019	**
	+ Diagnosis	0·274	0·022	*
Schizophrenia-spectrum subsample (*N* = 202§)	Intercept + Gender + Age onset	0·052	0·052	**
	+ Pre-morbid adjustment	0·178	0·125	***
	+ Education level	0·187	0·010	NS
	+ Prodrome duration†	0·221	0·034	**
	+ DUP‡	0·287	0·066	***
	+ Severity of drug use	0·288	0·001	NS
	+ EPPIC *v.* pre-EPPIC	0·307	0·019	*

† Log-transformed.
‡ Transformed into categories.
§ Single highly influential case removed from analysis.
* $P \leqslant 0{\cdot}05$; ** $P \leqslant 0{\cdot}01$; *** $P \leqslant 0{\cdot}001$.

modest but statistically significant associations between these variables. DUP correlated weakly with pre-morbid adjustment ($r = 0{\cdot}14$; $P = 0{\cdot}007$) and marginally more with duration of prodrome ($r = 0{\cdot}22$; $P < 0{\cdot}001$). Only a weak relationship was evident between duration of prodrome and pre-morbid adjustment ($r = 0{\cdot}13$; $P = 0{\cdot}016$).

Is DUP an epiphenomenon or does it independently predict 12-month outcome?

Functional outcome at 12 *months* (*QLS*)

To assess whether DUP is simply an epiphenomenon or whether DUP independently predicts outcome, a series of hierarchical multiple regressions were performed. Table 2 summarizes the effect of each additional sequence of predictors on 12-month QLS outcome for the total sample of 354 and for the schizophrenia-spectrum subsample. For the total sample of 354, about 27% of total outcome variance was accounted for by these predictors, with an adjusted R^2 of 25·1%. Inspection of Table 2 shows that after the effects of gender, age of onset of illness, pre-morbid adjustment, education and duration of prodrome are taken into account, DUP explains an additional 5·7% of outcome variance, a contribution that is statistically significant ($F = 25{\cdot}8$; df = 1,347; $P < 0{\cdot}001$). The magnitude of this effect size is defined as small-to-moderate, ($f^2 = 0{\cdot}060$) according to Cohen's terminology (Cohen, 1992). Model of care, as defined by the EPPIC *v.* pre-EPPIC treatment model, accounted for only 1·9% of additional variance after all predictors (except diagnosis) were accounted for, but this contribution was also statistically significant and non-trivial, as discussed below. These results remained robust when the regression analysis was restricted to the schizophrenia-spectrum subsample, with DUP accounting for 6·6% of outcome variance, which is a small-moderate effect size ($f^2 = 0{\cdot}071$). Approximately 31% of the variance in outcome was explained jointly by all predictors.

Table 3 shows that for the total sample of 354, the four strongest predictors of QLS outcome are DUP, pre-morbid adjustment, diagnosis and model of care, with DUP marginally more powerful than pre-morbid adjustment. The unstandardized coefficients (B) reveal that QLS outcome declines by an average of 4·3 points for each increment in DUP level, whereas EPPIC treatment increases QLS by an average of 8·6 points compared to pre-EPPIC treatment. Hence, the evidence indicates that both time to treatment (DUP) and quality of treatment (pre-EPPIC *v.* EPPIC) are clinically important independent predictors of functional outcome. QLS outcome scores for patients with schizophrenia-spectrum disorders were, on average, 9·5 points lower than for patients with affective disorders.

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Table 3. *Standardized regression coefficients (betas), presented in order of importance, indicate that DUP and pre-morbid adjustment are the principal predictors of 12-month QLS outcome*

		B	S.E.	Beta	*t*	*P*
All diagnoses ($N=354$)	DUP†	−4·3	1·0	−0·224	−4·3	***
	Pre-morbid adjustment	−29·5	6·6	−0·218	−4·5	***
	Diagnosis: schizophrenia-spectrum‡	−9·5	3·2	−0·184	−3·0	**
	Pre-EPPIC *v.* EPPIC	8·6	2·9	0·156	2·9	**
	Gender: female	7·7	2·7	0·137	2·8	**
	Diagnosis: schizoaffective‡	−10·9	4·3	−0·137	−2·5	*
	Prodrome duration§	−2·3	1·1	−0·104	−2·1	*
	Diagnosis: mixed disorders‡	−10·0	5·0	−0·103	−2·0	*
	Education level	−3·9	2·7	−0·069	−1·4	NS
	Age of onset	0·16	0·27	0·029	0·58	NS
	Severity of drug use	−0·52	0·93	−0·029	−0·56	NS
Schizophrenia-spectrum subsample ($N=202$¶)	Pre-morbid adjustment	−38·3	7·6	−0·311	−5·0	***
	DUP†	−5·2	1·1	−0·284	−4·6	***
	Prodrome duration§	−3·8	1·3	−0·182	−2·9	**
	Gender: female	8·9	3·4	0·164	2·6	**
	Pre-EPPIC *v.* EPPIC	7·8	3·4	0·155	2·3	*
	Education level	−7·0	3·4	−0·128	−2·1	*
	Age of onset	−0·09	0·31	−0·019	−0·29	NS
	Severity of drug use	−0·26	1·1	−0·016	−0·24	NS

† Transformed into categories.
‡ Reference category is affective diagnosis (comprising psychotic bipolar disorder and psychotic depression).
§ Log-transformed due to severe positive skewness.
¶ Single highly influential case removed from analysis.
* $P\leqslant 0{\cdot}05$; ** $P\leqslant 0{\cdot}01$; *** $P\leqslant 0{\cdot}001$; NS, not significant.

The strongest predictors of good outcome in the schizophrenia-spectrum subsample, after statistically adjusting for the effects of all other predictors, were good pre-morbid adjustment and short DUP. It is noteworthy that the effects of all predictors became stronger when the sample was restricted to patients with schizophrenia-spectrum diagnoses, compared with the effects observed in the total sample.

Severity of negative and positive symptoms at 12 months

The predictors yielded more conservative results when used to predict severity of negative and positive symptoms at 12 months. When SANS was used as the dependent variable, the predictors explained just over 21% of its variation. DUP accounted for almost 5% of variance, which represents a small-to-moderate effect size ($f^2=0{\cdot}051$) but model of care accounted for only a minor, non-significant amount of variance (R^2 change $=0{\cdot}005$; $P=0{\cdot}145$) which equated to an average 2·7 point decrease for EPPIC. When all predictors were considered simultaneously, diagnosis was the strongest of the significant predictors, followed by DUP, then pre-morbid adjustment and gender. Duration of prodrome failed to predict significantly severity of negative symptoms. When analysis was restricted to the schizophrenia-spectrum subsample, DUP remained a powerful and significant predictor of negative symptoms ($P=0{\cdot}001$) even when the effects of all other predictors were taken into account.

Severity of positive symptoms (BPRS-PS) at 12 months was somewhat less well predicted by the combined variables, with just over 15% of the variation in positive symptomatology accounted for. Nevertheless, DUP accounted for 3·8% of variance ($P<0{\cdot}001$), which represents a small effect size ($f^2=0{\cdot}040$) slightly diminished from its impact on QLS and SANS. A significant effect was also detected for model of care, which accounted for 1·4% of variance ($P=0{\cdot}005$), however this was in the opposite direction to that hypothesized, with the EPPIC treatment group performing more poorly on severity of positive symptoms than the group who did not receive the EPPIC model of care, although this difference was small (a one-point difference). Diagnosis was the only other significant predictor of positive symptoms, and was the most powerful. Pre-morbid adjustment failed to significantly predict the severity of positive symptoms. When analysis was restricted to the schizophrenia-spectrum subsample, DUP accounted for a significant

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proportion of variance (2·3%; $P=0·026$) after covarying for the effects of the preceding variables, but failed to attain statistical significance ($P=0·071$) when the effects of treatment model were factored into the model.

These regression models demonstrate that for the overall sample, DUP is a strong and consistent predictor of the three outcome measures after accounting for the effects of other predictors, and comprises between 21–25% of the total explained variance. In terms of explanatory power, DUP was more potent than pre-morbid adjustment as a predictor of both functional outcome and severity of negative symptoms, and furthermore, DUP remained an important and significant predictor of positive symptoms while pre-morbid adjustment was not. Evidence also indicates that the model of care positively impacts on outcome, as measured by the QLS, although its effect appears somewhat less consistent than that of DUP. The findings were equally compelling in the total first-episode psychosis sample and the schizophrenia-spectrum subsample.

Do other prognostic variables explain the DUP effect?

Severity of negative symptoms and positive symptoms at admission

The stability of these findings was tested in secondary regression analyses which included the effects of severity of negative symptoms at admission, which could be regarded as an intrinsic feature or alternatively, a consequence of prolonged DUP. The severity of positive symptoms at admission was also taken into account. DUP remained a statistically significant predictor of the three 12-month outcome measures after adjusting for the effects of SANS and BPRS-PS scores at admission, with little impact on the coefficients and probability levels. Under this model, DUP accounted for 5·0% of the variance of 12-month QLS (compared with 5·7% in the previous model), 3·3% of the variance of 12-month SANS (previous model 4·9%) and 4·5% of the variance of 12-month BPRS-PS (previous model 3·8%). The results in the schizophrenia-spectrum group also remained robust (QLS 5·0%; SANS 2·8%; BPRS-PS 3·1%), and DUP significantly predicted all 12-month outcome measures.

Medication compliance

Adherence to medication at 12-month follow-up was also taken into account in a subsample of 255 subjects. Subjects were categorized as being fully compliant ($N=132$), reasonably compliant ($N=36$), or non-compliant ($N=23$), and a fourth group ($N=64$) were not on a medication regime. This latter group, who had discontinued their medication regime under the supervision of their treatment team, were significantly less impaired at 12-month follow-up (20·9 QLS points, $P<0·001$; 11·2 SANS points, $P<0·001$; 1·1 BPRS-PS point, $P=0·004$) and had a significantly shorter median DUP (14 days) compared with patients who were on a medication regime (53 days). Treatment compliance *per se* did not appear to be associated with 12-month outcome as indicated by oneway ANOVAs on 12-month QLS ($F=0·52$; df=2,188; $P=0·595$) SANS ($F=0·71$; df=2,181; $P=0·492$) and BPRS-PS ($F=1·36$; df=2,188; $P=0·259$). The effects of DUP on the three 12-month outcome measures remained statistically significant after covarying for medication compliance and the other predictors in this subsample of 191, with DUP accounting for 7·3% of the variance of QLS, 6·9% of SANS and 1·9% of BPRS-PS.

Is there a clear point at which delayed treatment is linked to poor outcome?

DUP appears to be an important predictor of 12-month outcome, however further analyses were performed to ascertain if a clear point exists at which delayed treatment leads to deterioration in outcome. Three ANCOVAs, one each outcome measure, were specified to assess the impact of prolonged DUP after adjusting for the effects of the other predictors, and these analyses were repeated for the schizophrenia-spectrum subsample. The adjusted QLS means for each DUP category are presented in Fig. 2 for the total sample and the schizophrenia-spectrum subsample, having covaried for the effects of age of onset, gender, pre-morbid adjustment, education, duration of prodrome, illicit drug use, treatment model and, for the total sample, diagnosis.

Repeated contrasts indicated that for the total sample, the largest decline in QLS outcome occurred for subjects with a DUP of 8–28 days, with a 9·0 point decrease in functioning ($P=0·019$) relative to subjects with DUP of 0–7 days.

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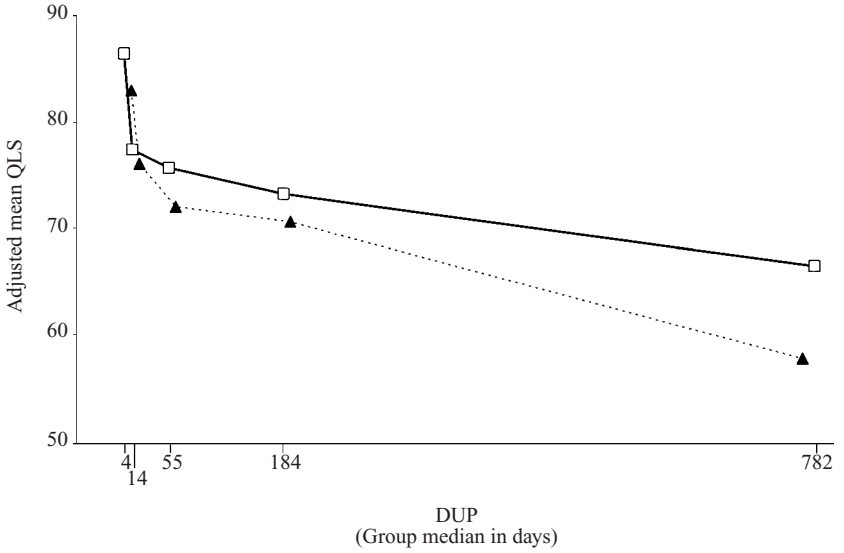


FIG. 2. Estimated QLS means (ANCOVA) for the total sample (□——□, $N=354$) and schizophrenia-spectrum subsample (▲---▲, $N=202$) indicate the differential impact of DUP increments on outcome.

Subjects with a DUP of more than 1 year fared significantly worse on QLS outcome than did subjects in most other DUP categories, as indicated by simple contrasts. For example, subjects with a DUP of >1 year were 19·7 QLS points worse than subjects with a DUP of 0–7 days ($P<0·001$), 10·7 points worse than subjects with a DUP of 8–28 days ($P=0·025$) and 9·0 points worse than subjects with a DUP of 29–90 days ($P=0·048$). Results obtained for the schizophrenia-spectrum subsample were even stronger. Subjects with a DUP of >1 year were 24·9 QLS points poorer, on average, than subjects with a DUP of 0–7 days ($P<0·001$), 18·1 points poorer than subjects with a DUP of 8–28 days ($P=0·001$), 14·0 points poorer than subjects with a DUP of 29–90 days ($P=0·004$) and 12·7 points poorer than subjects with a DUP of 3 months to 1 year ($P=0·004$).

The impact of successive levels of DUP on 12-month severity of negative symptoms was also evaluated. The adjusted means of SANS for each category of DUP are presented in Fig. 3 for the total sample and the schizophrenia-spectrum subsample, having covaried for the effects of all other predictors.

The effects of increasing DUP on severity of negative symptoms were more moderate, and there was no clear point apparent at which delayed treatment led to a substantial increase in severity of symptoms. However, subjects with a DUP of >1 year fared significantly worse on SANS outcome than did subjects with a DUP of 0–7 days (9·3 points; $P=0·002$) and 8–28 days (6·0 points; $P=0·043$). Results for the schizophrenia-spectrum subsample were stronger. Significant differences were apparent between subjects with a DUP of >1 year and subjects in all other DUP categories, with the exception of those subjects with a DUP of 3 months to 1 year. Examination of the impact of DUP on severity of positive symptoms for both the total and schizophrenia-spectrum subsample failed to reveal any clear point of deterioration in symptoms.

DISCUSSION

In this large study of first-episode subjects, we tested whether DUP predicted 12-month outcome independently of the effects of potential confounders. The impact of model of care on outcome was also examined. The most robust finding was that DUP remained a moderate yet consistent predictor of functional and symptomatic outcome even after controlling for age of onset of symptoms, gender, pre-morbid adjustment, education, duration of prodromal symptoms, severity of illicit drug use and diagnosis. These results remained robust in secondary

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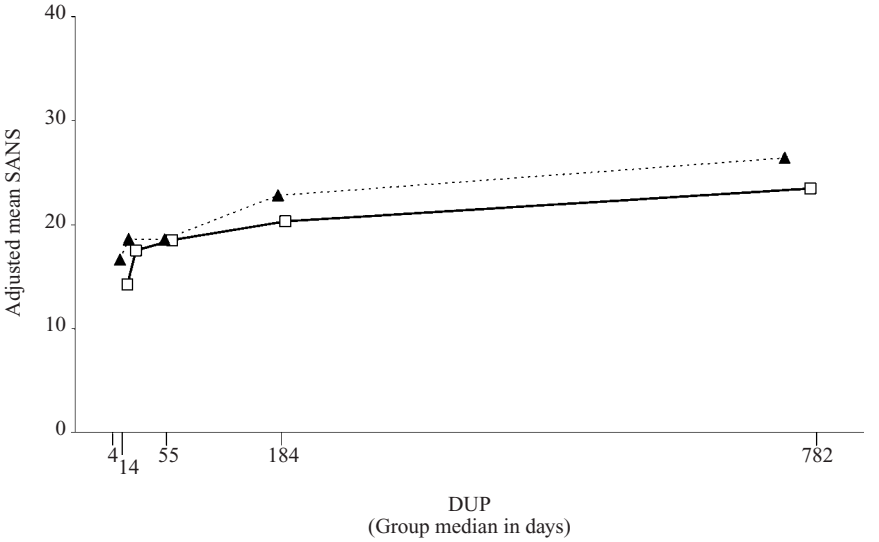


FIG. 3. Estimated SANS means (ANCOVA) for the total sample (□——□, $N=343$) and schizophrenia-spectrum subsample (▲---▲, $N=198$) indicate the differential impact of DUP increments on severity of negative symptoms.

analyses which adjusted for the effects of severity of negative and positive symptoms at admission to the service and treatment adherence at 12-month followup. This finding supports other research indicating that DUP is not simply a proxy for other factors (Haas *et al*. 1998; Larsen *et al*. 2000), and supports the notion that DUP has direct effects on outcome.

These findings contrast with those of Ho *et al*. (2000) and Verdoux *et al*. (2001) but are not inconsistent with previous data of Verdoux *et al*. (1998). The latter found that DUP was correlated with a number of other clinical variables and prematurely concluded that the effect of DUP on outcome could be principally explained by confounding. Our data show that the likely situation is one of partial confounding, but with an independent and hence malleable influence of DUP on at least short-term outcome. These alternatives have been discussed in detail elsewhere (McGorry, 2000).

Another key finding is that the robust albeit modest association between DUP and outcome is sustained even when the sample is confined to patients with schizophrenia and schizophreniform disorder. This finding contrasts with recent research (Barnes *et al*. 2000; Craig *et al*. 2000; Ho *et al*. 2000), which failed to find any evidence for an association between DUP and outcome for patients with schizophrenia-spectrum disorders. One potential explanation for this discrepancy could be that the statistical power of some of these studies might be too low to detect associations of this magnitude. For example, the numbers of subjects in both the Ho *et al*. study ($N=74$) (Ho *et al*. 2000) and the Barnes study ($N=53$) (Barnes *et al*. 2000) are unlikely to provide sufficient power to detect the small to moderate effect sizes that characterize the relationship between DUP and the numerous measures of outcome studied. However, small to moderate effect sizes can be clinically important, and failure to achieve statistical significance may simply reflect small sample size and inadequate power. While the sample size in the study of Craig *et al*. (2000) was larger, it is likely that, over the 2-year period of the study in a diffuse service system of variable quality, treatment effects are likely to dilute the initial DUP effect. The current data underscore this point in that treatment model appears to influence 12-month outcome.

A third finding is the evidence suggesting that the model of care positively impacts on outcome, although this relationship appears to be specific to functional outcome and is less potent than that of DUP. The EPPIC model of service delivery, specifically tailored to promoting recovery in early psychosis, accounted for an increase of nearly nine points on the QLS, after adjusting for the effects of the other predictors. This increase

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represents a clinically important improvement in level of functioning, although a small increase in severity of positive symptoms (of minor clinical importance) seems to be a cost of this improvement. The model of care provided by EPPIC is one of the four strongest factors influencing functional outcome, and is surpassed only by DUP, pre-morbid functioning and diagnosis.

The strengths of this study include the large numbers of representative first-episode subjects which helps to ensure generalizability and the systematic exploration of the impact of a large number of potential confounders on the association between DUP and outcome. A further strength is that, unlike other studies in which DUP seems to be poorly operationalized, we have carefully and rigorously measured onset and endpoint dates according to well-defined, standardized criteria in the RPMIP and used multiple sources of information which help to establish reliable records of the onset and duration of the prodromal and psychotic phases of illness. As Norman & Malla have pointed out in their review of this area (Norman & Malla, 2001), there is a good deal of inconsistency among studies in defining the onset and endpoint of DUP. Differences in the operationalization of DUP could account for results that are seemingly inconsistent with the findings of our study. Finally, the large sample size allowed us to test the robustness of the results in subjects with schizophrenia-spectrum disorders, while maintaining sufficient statistical power.

The key methodological weakness of the study is that the design is correlational in nature. While this approach can assist in determining whether evidence of partial or total confounding exists between DUP and other predictors, it provides only supportive, but not conclusive, evidence of the detrimental effects of DUP. The causal link between prolonged DUP and poor outcome can only be finally established by experimental or, at the very least, quasi-experimental designs (McGlashan & Johannessen, 1996). However, even quasi-experimental research is not without its complexities, as a number of methodological problems have emerged in recent research (Johannessen *et al*. 1999; McGlashan, 1999), that render interpretation of the findings more difficult than initially thought (McGlashan & Johannessen, 1996). It has been suggested that a randomized controlled trial may be the only way to collect the evidence to clarify/determine the causal link and could be considered ethically justified as long as liberal dropout criteria were in place to ensure safety (McGorry *et al*. 2000). However, it can be argued (Lieberman & Fenton, 2000) that the issue is so clear-cut, in a clinical and logical sense, that a RCT is neither necessary nor ethical. If this view is accepted, then further ambivalence about the development of early detection strategies and services should be actively dispelled.

There are a number of implications arising from the findings of this study. If it is true that DUP is an independent causal contributor to outcome, then there appears to be a very limited window of opportunity for treatment to be sought and initiated (up to 7 days), after which a significant decline in functioning occurs. In fact, as many as 83 of the 354 subjects had a DUP of up to 7 days. While at first glance these cases might be suspected to be brief or self-limiting psychoses, the final 'episode' diagnoses reveal that this is not the case. Thirty ultimately received a diagnosis of schizophrenia or schizophreniform disorder, 10 schizoaffective disorder and 37 affective psychosis, with only six having a diagnosis of psychotic disorder NOS, and no brief psychoses. For DUP of longer than 28 days, a more gradual deterioration in functioning becomes apparent, until DUP becomes very long (over 1 year) when functioning becomes more seriously impaired. Other studies have also shown evidence of a negative effect for very prolonged DUP, which has been associated with increasing impairment in social-adaptive functioning (Quinn *et al*. 2000) and severity of negative symptoms (Meagher *et al*. 2001). Our finding that DUP also impacts substantially on outcome in the very early phase of illness lends support to the importance of pre-psychotic intervention and high-risk strategies such as those offered by specialist programmes within EPPIC, for example, the Personal Assessment and Crisis Evaluation clinic (PACE) (Yung *et al*. 1996 *a*, *b*, 1998; McGorry *et al*. 2001). Rapid assessment for first presentations, such as that offered by the Youth Access Team (YAT) within EPPIC (Edwards & McGorry, 1998; Yung *et al*. 1999) may also be critical, given the substantial decline in outcome after just 1 week of untreated psychosis. Also implicit in these findings is the

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notion that, notwithstanding the limited opportunities for influencing outcome via very rapid detection and treatment of patients, a lengthy period exists (29 days to 1 year) in which outcome is relatively stable. This time may provide a period of 'grace' in which to detect and treat patients before DUP becomes very long and further deterioration occurs. This is also important since it may be unrealistic in the short-term to reduce DUP below a median threshold of 1–2 months or a mean of 5–6 months (Carbone *et al*. 1999).

In conclusion, the potential significance of DUP as a malleable and prognostically important target variable is emphasized. DUP consistently predicts outcome independently of other variables and does not appear to be simply a proxy for other factors, as suggested by Verdoux *et al*. (Verdoux, 2001; Verdoux *et al*. 2001, 1998). As one of the few potentially malleable factors influencing outcome, and coupled with evidence indicating that the negative effects of DUP manifest early in this phase of illness, we believe DUP is a 'best bet' as the focus for early intervention strategies. Indeed, even academic critics of the early intervention paradigm do not argue for delayed intervention, and most argue that efforts to reduce treatment delays are justified in order to prevent much unnecessary misery and suffering (McGlashan, 1999; Lieberman & Fenton, 2000; Ho & Andreasen, 2001; Ho *et al*. 2001; Verdoux, 2001). We therefore conclude that early detection and high-risk strategies should be implemented while awaiting elusive conclusive proof that DUP really matters, and equal efforts devoted to enhancing the quality of care in the early phases of treatment (McGorry & Jackson, 1999).

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