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Duration of untreated psychosis: impact on 2-year outcome

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ABSTRACT

Background. The duration of untreated psychosis has been postulated to be a predictor of clinical outcome in schizophrenia. Although several prospective studies support the relationship, some studies do not. These differences may be due to a number of methodological issues. The objectives of this study are: (*i*) to address many of the methodological limitations of earlier studies such as variations in sample size and selection, type of treatment provided, differences in measurement of DUP and outcome, and length of follow-up; and (*ii*) to examine the relationship between DUP and outcome in a prospective longitudinal study.

Method. The DUP of 200 consecutive admissions to a first-episode programme was determined. The sample was followed over 2 years and pre-morbid functioning, symptoms, social and cognitive functioning and substance use were assessed longitudinally.

Results. Two years after admission to the programme, longer DUP was significantly associated with high levels of positive symptoms and poor social functioning. Independently of other variables, DUP predicted positive symptoms and social functioning at 1 and 2 years.

Conclusions. There is evidence that long DUP continues to have an influence on outcome up to 2 years. These results support ongoing efforts for early detection and intervention.

INTRODUCTION

The period of untreated psychosis, commonly referred to as the duration of untreated psychosis (DUP), is an important variable, as unlike other prognostic factors, it can be reduced through changes in health service delivery (Larsen *et al.* 2001). Several studies (Loebel *et al.* 1992; Drake *et al.* 2000; Larsen *et al.* 2000; Black *et al.* 2001; Malla *et al.* 2002; Harrigan *et al.* 2003) support an association between long DUP and a range of poor outcome factors, while others do not (Barnes *et al.* 2000; Craig *et al.* 2000; Ho *et al.* 2000). The inconsistency in findings may be related to variations in sample size and selection, type of treatment provided, the fact that those who refuse to engage often have longer DUPs, differences in measurement of DUP and outcome, and length of follow-up (Norman & Malla, 2001). Alternatively, DUP may be a proxy for other predictors of outcome (Verdoux *et al.* 1998).

The majority of longitudinal studies have followed samples for $\leqslant$12 months (Drake *et al.* 2000; Ho *et al.* 2000; Larsen *et al.* 2000; Malla *et al.* 2000; Harrigan *et al.* 2003). To date two studies have follow-ups of 2 years (Craig *et al.* 2000; Verdoux, 2001). Craig *et al.* (2000), reporting on a large sample over 2 years did not find any association between DUP and outcome. In this study DUP was defined as beginning with the occurrence of the first psychotic symptom and ending with hospitalization. Since this sample had a relatively low rate of remission, results of this study may be related to a selection bias by including only hospitalized patients. In their 2 year follow-up Verdoux *et al.* (2001) reported that the effect size of the association between DUP and chronicity of psychotic

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symptoms was reduced over the 2 years and confounded by poor pre-morbid functioning. This was, however, a smaller sample of only in-patient admissions that generally seemed older than most first-episode samples reported in the literature. Furthermore, assessment of pre-morbid functioning was limited in that it was determined by the best global functioning score in the year preceding hospital admission and only for a subsample of 38 who had a DUP of <12 months.

The purpose of this study was to examine prospectively the impact of DUP on longitudinal outcome in a large representative sample of first-episode patients and to address a number of the methodological limitations of earlier studies. First, the sample, described in detail below, includes the majority of potential incidence cases and thus permits generalizability. This is accomplished by including all those attending a first episode programme available to the whole community. Secondly, the sample is a first contact for treatment for a first episode of psychosis and not a first admission to hospital. Thirdly, we have a clear definition of DUP and have standardized the assessment of DUP, which is conducted at admission to the programme and reviewed 1 year later. Fourthly, we examine longitudinal, prospective, comprehensive and standardized follow-up data that can explore potential confounders on associations of DUP and outcome. This can address the issue of pre-morbid functioning, which is potentially a key candidate as a variable to explain DUP. Finally, our follow-up is for 2 years in a significantly large sample.

METHOD

Sample

Subjects were 278 individuals who had been consecutively admitted to the Calgary Early Psychosis Program (EPP), a comprehensive treatment programme that serves an urban population of 930 000 (Addington & Addington, 2001). These individuals were experiencing their first episode of psychosis and had not received more than 3 months of previous adequate treatment (Larsen *et al*. 1996). Since Calgary has a population of 930 000 and we admit approximately 100 new cases per year it is likely that the majority, perhaps 85–90%, of all new cases in Calgary are being referred to this specialized programme.

An initial assessment was completed upon admission to the programme, and follow-up assessments were conducted at 12 and 24 months. Two hundred patients completed the 12-month assessment and 164 the 24-month assessment. On average, of those not completing an assessment, 47% were drop-outs, 37% had moved away for legitimate reasons and were obtaining treatment elsewhere and 16% were attending the programme but failed to attend the assessment. Additionally, approximately 13% of those who completed the symptom and functional assessments did not complete the 12-month and 24-month cognitive assessments. Thus, this study reports on the 200 patients (136 men, 64 women) who completed the 1-year assessment. The majority of the sample was single ($N=172$, 86%), with a mean age of 24·79 (S.D. = 8·49) years, had completed grade 12 ($N=120$, 60%), lived at home ($N=161$, 80·6%), and was Caucasian ($N=154$, 77·3%). Average age at onset was 23·18 (S.D. = 7·76) years. Twenty-eight per cent (56) had been admitted to EPP as in-patients, the remainder as out-patients.

Subjects were diagnosed according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer *et al*. 1992). All subjects met criteria for a schizophrenia spectrum disorder. Diagnoses were conducted at the initial assessment and confirmed at the 1-year assessment. At the 1-year assesment of the 200 who completed the year, 67·5% (135) had a diagnosis of schizophrenia, 16·5% (33) schizophreniform disorder, 4% (8) schizoaffective disorder, 2% (4) delusional disorder, 2·5% (5) brief psychotic disorder and 7·5% (15) psychotic disorder NOS. After complete description of the study to the subjects, written informed consent was obtained.

Measures

Symptoms and functioning

Pre-morbid functioning was assessed with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor *et al*. 1982). Since the majority of individuals experience onset in their late teens and very early adulthood, and in order to minimize any potential overlap with the onset of

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prodromal and psychotic symptoms, we chose to use only the first three developmental periods of the PAS (Malla *et al*. 2002; Harrigan *et al*. 2003). These are childhood (up to age 11), early teen (12–15 years) and late teen (16–18 years). Positive and negative symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay *et al*. 1987). Social outcome was assessed using the Quality of Life Scale (QOL) (Heinrichs *et al*. 1984). The Case Manager Rating Scale for Substance Use, a short checklist, was used to determine the level of substance use (Drake *et al*. 1990).

Cognitive functioning was assessed with a comprehensive battery that included verbal fluency (Controlled Oral Word Association Test & Category Instances), immediate and delayed verbal memory (logical memory subtests of the Wechsler Memory Scale-Revised, Rey Auditory Verbal Learning Test), visual memory (Rey Complex Figure), working verbal memory (Letter–Number Span), executive functioning (Wisconsin Card Sorting Test), visual attention (degraded stimulus CPT; Nuechterlein, 1991), early information processing (Span of Apprehension; Asarnow *et al*. 1991), visual–constructional ability (copy of the Rey Complex Figure), visuomotor sequencing (Trails A & Trails B), and psychomotor speed (Grooved Pegboard).

Duration of untreated psychosis

DUP was first determined at the initial assessment. Relevant questions from the Interview for the Retrospective Assessment for the Onset of Schizophrenia (IRAOS), which is an instrument for the assessment of the onset and early course of schizophrenia (Häfner *et al*. 1992) was used to elicit initial information. Probes for items on the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Prodromal Symptoms (SOPS) (Miller *et al*. 2002) were given to determine the first appearance of prodromal, positive, and negative symptoms.

Using all available information, DUP was determined by assessing the point at which the first positive symptom was present and then the length of time in weeks until the first effective treatment was initiated. Criteria for the presence of positive symptoms was the presence of any one positive symptom (hallucinations, delusions or thought disorder) rated $\geqslant 4$ on the PANSS. The symptom(s) must have lasted throughout the day for several days or several times a week, not being limited to a few brief moments. Ratings of DUP were based on interviews with the patients and family members and hospital records. Inter-rater reliability was assessed from observed interviews with 10 patients: the intraclass correlation was 0·90.

DUP was reviewed and confirmed by a second clinician within 2–3 weeks and confirmed with the family in approximately 72% of the cases by an independent rater. DUP was reviewed at the 1-year assessment. Changes to the length of DUP at the 1-year assessment occurred in approximately 10% of the cases and was due to additional information being given by the patient. All changes were discussed among the principal investigator and raters and were consensually agreed.

Procedures

Pre-morbid functioning was assessed at the initial assessment. Both DUP and diagnosis were assessed initially and confirmed at 12 months. Symptoms, social functioning, substance use and cognitive functioning were assessed intially, and at 12 and 24 months. Raters of DUP were blind to results of follow-up symptom and social and cognitive functioning assessments.

Effort was made to ensure a consistent and professional level of reliability of measurement across subjects in this study. Raters were experienced research clinicians who routinely used all of these measures and who demonstrated adequate reliability at routine reliability checks as part of the ongoing Early Psychosis Program evaluation. Criteria for reliability are that the scoring of each item on the PANSS and QOL is within one point and there is at least 80% agreement on total scores and subscale scores for all measures. Agreement was calculated as the number of ratings within one point divided by the total number of ratings. The DSM-IV diagnoses were made using the SCID-I by J.A. and D.A. Inter-rater reliability was determined by 100% agreement on the diagnosis and at least 80% agreement for symptom presence.

Data analysis

In order to use parametric statistics, DUP was normalized by taking the logarithm to base

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10 (log_{10}DUP). Using DUP as a continuous variable we examined longitudinal associations between DUP and demographics, symptoms, substance use, and social and cognitive functioning. Secondly, a series of hierarchical multiple linear regression analyses were conducted to determine if DUP independently predicted 12- and 24-month symptom outcome and QOL, and if so to determine the relative contribution of DUP.

Table 1. *Correlations between log_{10}DUP and symptoms and Quality of Life (QOL)*

	Initial ($N=200$)	12 months ($N=200$)	24 months ($N=164$)
Positive symptoms Log_{10}DUP	0·28***	0·29***	0·17*
Negative symptoms Log_{10}DUP	−0·03	0·11	−0·11
QOL Log_{10}DUP	−0·18*	−0·21**	−0·20*

* $P<0·05$; ** $P<0·01$; *** $P<0·001$.

RESULTS

Duration of untreated psychosis

The mean DUP was 84·2 weeks (S.D. = 139), median 28 weeks and ranged from 1–780 weeks. Mean of log_{10}DUP was 1·41, which corresponds to a DUP of 26 weeks. There was no gender or level of education differences in DUP. Those with longer DUPs were significantly older ($r=0·34$, $P<0·001$).

Subjects lost to follow-up

There were no differences between those ($N=200$) who completed the 1-year assessment and those who were lost to follow-up at 1 year ($N=78$) on any of the demographic, symptom, functional or cognitive measures. However, those who were lost to follow-up had a significantly shorter DUP (log_{10}DUP) ($P<0·01$) of 20 weeks compared with 36 weeks of those who remained in the study and they were significantly younger (22 years *v.* 24 years, $P<0·05$). Since young age and short DUP are associated we controlled for age. There were no differences in DUP between those who completed the 1-year follow-up and those who did not. There were no differences on any variables between those who completed the 12- but not the 24-month follow-up ($N=36$) and those who completed both follow-ups ($N=164$).

Correlates of DUP at each assessment period

Pearson correlations were used to determine the associations of DUP (log_{10}DUP). There were no associations between log_{10}DUP and pre-morbid functioning at any of the three developmental stages. At the initial, 12-month and 24-month assessments there were no associations between log_{10}DUP and any of the cognitive tests or level of substance use. Tables of non-significant results are available on request. At all three assessments poorer scores on QOL were significantly associated with longer DUP. There were no associations with negative symptoms at any time. High levels of positive symptoms were associated with longer DUP (log_{10}DUP) at all three assessments. Results of symptoms and Quality of Life are presented in Table 1.

Predictors of outcome

Significant associations were observed between DUP and both positive symptoms and the QOL. Thus, a series of hierarchical multiple linear regressions were conducted to determine if DUP independently predicted positive symptoms and quality of life, and to determine the relative contribution of DUP to these outcome variables. In this study the only potentially confounding variable was age but we also included pre-morbid functioning since there has been concern that this may be a proxy for DUP. Age was entered first, then the three developmental pre-morbid functioning scores, with DUP entering last in hierarchical blocks. The effect of the sequence of predictors on symptoms and QOL at 12 and 24 months are presented in Table 2. All four models were significant. After controlling for the effects of age and pre-morbid functioning, DUP explained an additional 4% and 5% of the variance in QOL at 12 and 24 months, respectively. For positive symptoms, DUP explained 11% and 5% at 12 and 24 months, respectively. Although the magnitude of these effect sizes is small to moderate, it is a statistically significant contribution. These results are presented in Table 2.

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Table 2. *Hierarchical regression model for predictors of outcome*

Measure	Model	R^2	R^2 change
Positive symptoms			
12 month	Age	0·012	0·012
	+ Pre-morbid functioning	0·084	0·072**
	+ Log_{10}DUP	0·189	0·105***
Model is significant: ($F(5, 179) = 9·13$, $P < 0·0005$)			
24 month	Age	0·028	0·028*
	+ Pre-morbid functioning	0·093	0·065**
	+ Log_{10}DUP	0·143	0·050***
Model is significant: ($F(5, 151) = 5·43$, $P < 0·0005$)			
QOL			
12 month	Age	0·001	0·001
	+ Pre-morbid functioning	0·167	0·166***
	+ Log_{10}DUP	0·207	0·040***
Model is significant: ($F(5, 180) = 8·22$, $P < 0·0005$)			
24 month	Age	0·008	0·008
	+ Pre-morbid functioning	0·109	0·102**
	+ Log_{10}DUP	0·156	0·047***
Model is significant: ($F(5, 153) = 4·99$, $P < 0·0005$)			

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

Table 3. *Hierarchical regression model for predictors of outcome including adherence to medication*

Measure	Model	R^2	R^2 change
Positive symptoms			
12 month	Age	0·012	0·012
	+ Pre-morbid functioning	0·086	0·073**
	+ Medication adherence	0·110	0·025*
	+ Log_{10}DUP	0·204	0·093***
Model is significant: ($F(6, 178) = 6·48$, $P < 0·0005$)			
24 month	Age	0·028	0·028*
	+ Pre-morbid functioning	0·093	0·066*
	+ Medication adherence	0·210	0·117***
	+ Log_{10}DUP	0·239	0·029*
Model is significant: ($F(6, 150) = 7·75$, $P < 0·0005$)			
QOL			
12 month	Age	0·001	0·001
	+ Pre-morbid functioning	0·172	0·166***
	+ Medication adherence	0·172	0·000
	+ Log_{10}DUP	0·213	0·040**
Model is significant: ($F(6, 179) = 6·90$, $P < 0·0005$)			
24 month	Age	0·008	0·008
	+ Pre-morbid functioning	0·112	0·104***
	+ Medication adherence	0·181	0·069***
	+ Log_{10}DUP	0·208	0·027*
Model is significant: ($F(6, 152) = 6·39$, $P < 0·0005$)			

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

Examination of the level of adherence to medication

It is possible that increased symptoms and poor functioning are a function of non-adherence to medication and not long DUP, in that longer DUP might interfere with insight and willingness to take medication. We therefore repeated the hierarchical regression analyses with medication compliance entered prior to DUP. We have published previously on adherence to medication in this sample based on retrospective ratings (Coldham *et al*. 2002). There are limitations to this method of determining adherence. However, no one method of adherence has been found to be good (Verdoux *et al*. 2000) and our rates were comparable to those reported in the literature for both first-episode psychosis patients as well as those with a more chronic course of the illness (Coldham *et al*. 2002). In this current sample, there were no differences at 1 year in length of DUP between those who were rated as adherent to medication and those who were not. At 2 years, those who were adherent to medication actually had longer DUPs than those who were non-adherent ($P < 0·01$, $t = 3·46$). Again all four models were significant. After controlling for the effects of age, pre-morbid functioning and adherence to medication, DUP explained an additional 4% and 3% of the variance in QOL at 12 and 24 months, respectively. For positive symptoms, DUP explained 9% and 3% at 12 and 24 months, respectively. Although the magnitude of these effect sizes is small, it remains a statistically significant contribution. These results are presented in Table 3.

DISCUSSION

In this study of first-episode subjects, we examined the longitudinal relationship of the duration of untreated psychosis (DUP) to several outcome variables and tested whether DUP predicted outcome independently of the effects of potential confounders. The most robust findings were that DUP was significantly associated with positive symptoms at 1 year. These findings support those of other studies (Loebel *et al*. 1992; Drake *et al*. 2000; Larsen *et al*. 2000; Malla *et al*. 2002; Harrigan *et al*. 2003). More importantly, DUP was a significant predictor of positive symptoms after controlling for other factors. This suggests that DUP has an independent role in determining symptomatic outcome and is not a proxy for other factors (Harrigan

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et al. 2003). Long DUP was also associated with poor scores on the Quality of Life Scale (QOL). Although poor pre-morbid functioning was clearly a significant predictor of QOL, DUP did make a small independent contribution. The additional analyses examining medication adherence suggested that these results were not a function of non-adherence to medication, although controlling for medication adherence reduced the effect size of DUP on positive symptoms and quality of life. At 2 years those with longer DUP demonstrated increased adherence.

The absence of significant associations between DUP and several other correlates of outcome has been replicated elsewhere. These correlates include gender (Barnes *et al*. 2000; Drake *et al*. 2000; Hoff *et al*. 2000; Malla *et al*. 2002), substance use (Drake *et al*. 2000) and cognitive functioning (Barnes *et al*. 2000; Hoff *et al*. 2000; Norman *et al*. 2001; Ho *et al*. 2003). The lack of an association of cognitive functioning with DUP is not surprising as there is evidence that cognitive deterioration is present during childhood (Jones *et al*. 1994) and at onset (Addington & Addington, 2002; Addington *et al*. 2003). Although Amminger *et al*. (2002) report an association; they were considering an estimate of cognitive deterioration rather than measures of current cognitive functioning. We did not find any association between DUP and negative symptoms, which is consistent with many of the studies. Larsen *et al*. (2000) suggest that their observed relationship between DUP and negative symptoms was partly spurious and probably due to a common relationship with poor pre-morbid functioning in adolescence, which results in a long DUP and poor clinical course. The other exception is Edwards *et al*. (2002) who reported an association with enduring negative symptoms even when controlling for pre-morbid functioning. Since negative symptoms often develop during the prodrome (Häfner *et al*. 1993) it is less likely that an association with DUP would be found. However, it may be that either enduring negative symptoms or the deficit syndrome predate onset and hinder help-seeking, or alternatively, that DUP leads to the possibility of enduring negative symptoms (Edwards *et al*. 2002).

There are concerns as to whether DUP is an epiphenomenon of pre-morbid adjustment and that poor pre-morbid functioning reduces the likelihood of earlier detection and ultimately appropriate treatment. Results of this study support other findings that suggest that DUP and pre-morbid adjustment have a separate influence on outcome as well as sharing a component of outcome variance (Larsen *et al*. 2000; Harrigan *et al*. 2003).

In contrast to the findings of the other 2-year studies, we found an enduring relationship between DUP and two major outcome measures. Currently, we do not know the potential impact of DUP on the medium to long-term course of a psychotic illness. Over the course of 2 years post-treatment factors such as treatment compliance, range of available treatments, and social environment may dilute the effect of DUP. The strength of this study is that it used a combination of a large sample, a long follow-up, an incidence cohort from a geographically circumscribed area, a standardized assessment of DUP and standardized, longitudinal, prospective and comprehensive follow-up data. A limitation of the study is that it remains correlational in nature and as such the results do not offer conclusive evidence about the effects of DUP.

In conclusion this study demonstrates a significant impact of DUP on symptom and functional outcome up to 2 years. Furthermore in controlling for potential confounders it suggests a moderate independent contribution of DUP towards symptom outcome, and a small independent contribution towards QOL up to 2 years. These results are supportive of a continued focus on reducing DUP both through timing and quality of treatment (Harrigan *et al*. 2003). They highlight the value of early recognition and the necessity for prompt delivery of early, appropriately designed and effective intervention programmes for those with a recent onset of psychosis. The concept of early intervention is more than an earlier start of antipsychotic medications (Edwards & McGorry, 2002). It includes treatment with a specific model of service delivery that is tailored to promoting recovery in early psychosis. Such a programme offers not only optimal pharmacotherapy but also a range of individual, group and family interventions, designed to address the psychological and social damage that may result from a psychotic illness and a long DUP.

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REFERENCES

Addington, J. & Addington, D. (2001). Early intervention for psychosis: the Calgary Early Psychosis Treatment & Prevention Program. *Canadian Psychiatric Association Bulletin* **33**, 11–16.

Addington, J. & Addington, D. (2002). Cognitive functioning in first-episode schizophrenia. *Journal of Psychiatry and Neuroscience* **27**, 188–192.

Addington, J., Brooks, B. & Addington, D. (2003). Cognitive functioning in first episode psychosis: initial presentation. *Schizophrenia Research* **62**, 59–64.

Amminger, G. P., Edwards, J., Brewer, W. J., Harrigan, S. & McGorry, P. (2002). Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. *Schizophrenia Research* **54**, 223–230.

Asarnow, R. F., Granholm, E. & Sherman, T. (1991). Span of apprehension in schizophrenia. In *Handbook of Schizophrenia, Vol. 5: Neuropsychology, Psychophysiology and Information Processing* (ed. S. R. Steinhauer, J. H. Gruzelier and J. Zubin), pp. 335–370. Elsevier: Amsterdam.

Barnes, T. R. E., Hutton, S. B., Chapman, M. J., Mutsatsa, S., Puri, B. K. & Joyce, E. M. (2000). West London first-episode study of schizophrenia: clinical correlates of duration of untreated psychosis. *British Journal of Psychiatry* **177**, 207–211.

Black, K., Peters, L., Rui, Q., Milliken, H., Whitehorn, D. & Kopala, L. C. (2001). Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophrenia Research* **47**, 215–222.

Cannon-Spoor, H. E., Potkin, S. G. & Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin* **8**, 470–484.

Coldham, E. L., Addington, J. & Addington, D. (2002). Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatrica Scandinavica* **106**, 286–290.

Craig, T. J., Bromet, E. J., Fennig, S., Tanenberg-Karant, M., Lavelle, J. & Galambos, N. (2000). Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *American Journal of Psychiatry* **157**, 60–66.

Drake, R. E., Osher, F. C., Noordsy, D. L., Hurlbut, S. C., Teague, G. B. & Beaudett, M. S. (1990). Diagnosis of alcohol use disorders in schizophrenia. *Schizophrenia Bulletin* **16**, 57–67.

Drake, R. J., Haley, C. J., Akhtar, S. & Lewis, S. W. (2000). Causes and consequences of duration of untreated psychosis in schizophrenia. *British Journal of Psychiatry* **177**, 511–515.

Edwards, J. & McGorry, P. (2002). *Implementing Early Intervention in Psychosis*. Martin Dunitz: London.

Edwards, J., Harrigan, S., McGorry, P. & Amminger, P. G. (2002). DUP and enduring positive/negative symptoms in first episode schizophrenia. *Psychological Medicine* **32**, 563–564.

Häfner, H., Maurer, K., Loffler, W. & Riecher-Roessler, A. (1993). The influence of age and sex on the response and early course of schizophrenia. *British Journal of Psychiatry* **162**, 80–86.

Häfner, H., Riecher-Rossler, A., Hambrecht, M., Maurer, K., Meissner, A., Schmidtke, B., Fatkenheuer, W., van der Heiden, L. & van der Heiden, W. (1992). IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research* **6**, 209–233.

Harrigan, S. M., McGorry, P. D. & Krstev, H. (2003). Does treatment delay in first episode psychosis really matter? *Psychological Medicine* **33**, 97–110.

Heinrichs, D. W., Hanlon, T. E. & Carpenter, W. T. (1984). The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin* **10**, 388–398.

Ho, B. C., Andreasen, N. C., Flaum, M., Nopoulous, P. & Miller, D. (2000). Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *American Journal of Psychiatry* **157**, 808–815.

Ho, B. C., Alicata, D., Ward, J., Mosere, D. J., O'Leary, D. S., Arndt, S. & Andreasen, N. C. (2003). Untreated initial psychosis: relation to cognitive deficits and brain morphology in first episode schizophrenia. *American Journal of Psychiatry* **160**, 142–148.

Hoff, A. L., Sakuma, M., Heydebrand, G., Csernansky, J. G. & DeLisi, L. E. (2000). Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *American Journal of Psychiatry* **157**, 1824–1828.

Jones, P., Rodgers, B., Murray, R. & Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* **344**, 1398–1402.

Kay, S. R., Fiszbein, A. & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Larsen, T. K., McGlashan, T. H. & Moe, L. C. (1996). First-episode schizophrenia: I. Early course parameters. *Schizophrenia Bulletin* **22**, 241–256.

Larsen, T. K., Moe, L. C., Vibe-Hansen, L. & Johannessen, J. O. (2000). Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Schizophrenia Research* **45**, 1–9.

Larsen, T. K., McGlashan, T. H., Johannessen, J. O., Friis, S., Guldberg, C., Haahr, U., Horneland, M., Melle, I., Moe, L., Opjordsmoen, S., Simonsen, E. & Vaglum, P. (2001). Shortened duration of untreated first-episode of psychosis: changes in patient characteristics at treatment. *American Journal of Psychiatry* **158**, 1917–1919.

Loebel, A. D., Lieberman, J. A., Alvir, J. M. J., Mayerhoff, D. L., Geisler, S. H. & Szymanski, D. O. (1992). Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry* **149**, 1183–1188.

Malla, A. K., Norman, R. M. G., Manchanda, R., Ahmed, M. R., Scholten, D., Harricharan, R., Cortese, L. & Takhar, J. (2002). One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophrenia Research* **54**, 231–242.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K. & Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predicative validity. *American Journal of Psychiatry* **159**, 863–865.

Norman, R. M. G. & Malla, A. K. (2001). Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychological Medicine* **31**, 381–400.

Norman, R. M., Townsend, L. & Malla, A. K. (2001). Duration of untreated psychosis and cognitive functioning in first-episode patients. *British Journal of Psychiatry* **179**, 340–345.

Nuechterlein, K. H. (1991). Vigilance in schizophrenia and related disorders. In *Handbook of Schizophrenia, Vol. 5: Neuropsychology, Psychophysiology and Information Processing* (ed. S. R. Steinhauer, J. H. Gruzelier and J. Zubin), pp. 397–433. Elsevier: Amsterdam.

Spitzer, R. L., Williams, J. B., Gibbon, M. & First, M. B. (1992). The Structured Clinical Interview for DSM-III-R SCID, I. History, rationale, and description. *Archives of General Psychiatry* **49**, 624–629.

Verdoux, H., Bergey, C., Assens, F., Abalan, F., Gonzales, B., Pauillac, P., Fournet, O., Liraud, F., Beaussier, J. P., Gaussares, C.,

Etchegaray, B., Bourgeois, M. & Van Os, J. (1998). Prediction of duration of psychosis before first admission. *European Psychiatry* **13**, 346–352.

Verdoux, H., Lengronne, J., Liraud, F., Gonzales, B., Assens, F., Abalon, F. & Van Os, J. (2000). Medication adherence in psychosis: predictors and impact on outcome. A 2 year follow-up of first-admitted subjects. *Acta Psychiatrica Scandinavica* **102**, 203–210.

Verdoux, H., Liraud, F., Bergey, C., Assens, F., Abalan, F. & Van Os, J. (2001). Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first admitted patients. *Schizophrenia Research* **49**, 231–241.