Psychological Medicine, 2001, **31**, 381–400. Printed in the United Kingdom

REVIEW ARTICLE

Duration of untreated psychosis: a critical examination of the concept and its importance

ROSS M. G. NORMAN[1] AND ASHOK K. MALLA

From the Department of Psychiatry, University of Western Ontario, London, Ontario, Canada

ABSTRACT

Background. The concept of duration of untreated psychosis (DUP) has recently attracted much interest because of its possible relationship to treatment outcome and implications for preventive efforts with reference to psychotic disorders, especially schizophrenia. In this paper we review critically the literature concerning the concept and its importance.

Methods. Articles concerned with measuring DUP and those that have been suggested to provide indirect or direct evidence of the effect of DUP on treatment outcome are reviewed.

Results. Evidence thus far suggests that DUP may be related to ease of reducing psychotic symptoms once treatment begins for first episode patients, but there is no evidence of a relationship to likelihood of relapse. There has been little investigation of the relationship of DUP to other long-term outcomes such as negative symptoms and cognitive functioning neither have the possible confounds of DUP been widely investigated or controlled.

Conclusions. It is important that there should be more thorough investigations of DUP, its correlates, and the extent to which it does mediate any advantages of earlier intervention.

INTRODUCTION

Many authors have recently argued that reducing the time between the onset of psychosis and initiation of treatment may result in substantially improved outcomes for schizophrenia and related disorders (Wyatt, 1991; McGlashan & Johannessan, 1996; McGorry *et al.* 1996; Malla *et al.* 1999). In particular, it has been suggested that psychosis itself may have toxic effects on the brain and, as a result, increased periods of initially untreated psychosis could result in less complete recovery, greater vulnerability to future episodes of psychosis and/or more compromised functioning (Grace, 1991; Wyatt, 1991; Olney & Farber, 1995; Lieberman *et al.* 1997; Keshavan, 1999). Central to this possibility is the concept of duration of untreated psychosis (DUP). The purpose of this paper is to review critically the DUP concept and evidence concerning its relationship to outcomes. Articles were identified for inclusion in this review on the basis of computerized searches on MEDLINE and PsycINFO databases using search terms such as 'duration of untreated psychosis', 'delay in treatment', 'treatment delay' or 'initiation of treatment' cross referenced with the terms 'psychosis', 'psychoses', 'psychotic disorders', 'schizophrenia', 'schizoaffective' or 'schizophreniform'. Additional references were included as a result of citations in examined articles, and suggestions by others familiar with the field. Because of the current emphasis on the

[1] Address for correspondence: Dr Ross M. G. Norman, Department of Psychiatry, London Health Sciences Centre – SSC, 392 South Street, London, Ontario N6A 4G5, Canada.

importance of untreated psychosis in particular, we have elected to focus our review on DUP rather than duration of untreated illness (DUI) which includes time between the onset of any psychiatric symptom and initiation of treatment.[1]†

We have organized our review in terms of three issues. The first concerns conceptual and measurement issues related to the definition of DUP; the second examines the evidence concerning a relationship between DUP and treatment outcome, and the third addresses the implications of the literature reviewed for further research and clinical practice related to early intervention.

MEASUREMENT OF DUP

Initially the concept of DUP seems simple enough – referring to a time interval anchored at the beginning by onset of psychosis and at the end by initiation of treatment. Upon further consideration, however, it becomes clear that the identification of both time points defining this interval can be complex.

Potential challenges in identifying the onset of psychosis include inconsistency in the types of symptoms used to define psychosis (e.g. restricted to hallucinations and delusions or including disorganization of thought form); the subtlety and, perhaps, arbitrariness of some judgements as to whether, or when, an individual's experience or behaviour has crossed the boundary from the eccentric or unusual into the psychotic; and the essentially private nature of some initial aspects of psychotic symptoms, which can result in patients identifying a different time of onset from observers (Häfner *et al.* 1993; Browne *et al.* 2000). Perhaps the onset of subjective symptoms such as hallucinations or delusions may be best identified by the patient, while family members or other observers may provide the most valid reports of behavioural changes (McGorry *et al.* undated). Difficulties commonly associated with retrospective recall of events, can be compounded by any difficulties being experienced by the patient at the time of appraising DUP. For instance, if the patient is still experiencing psychotic symptoms or compromised cognition, he, or she, may not be able to recall the onset accurately. Observers' recall of onset of psychosis will be influenced by their perceptiveness, possible denial, tolerance for eccentricity and/or the extent to which the onset is accompanied by bizarre behaviours.

Onset of treatment is usually operationalized in terms of administration of antipsychotic medication. Because a prescription is generally well-documented, one might assume that the end point of DUP is more readily identified than its onset. Nevertheless, the literature reveals significant differences between studies in whether DUP is considered to have ended with the initiation of any level of antipsychotic treatment or only when such treatment meets some criterion for adequacy (cf. Larsen *et al.* 1996, 1998; Edwards *et al.* 1998; Haas *et al.* 1998; Craig *et al.* 2000). Disagreements can also occur between those who attempt to define adequacy, for instance Loebel *et al.* (1992) allow previous treatment up to 12 weeks within their operational definition of DUP, whereas Larsen *et al.* (1996) consider adequate treatment to have occurred for patients who have received 3 weeks of appropriate medication. Furthermore, such criteria typically do not take into consideration the patients' adherence to the prescribed medication.

If the experience of psychosis is an important determinant of long-term outcome it could be argued that it is the length of such psychosis *per se* that is critical regardless of whether it is being treated. Nevertheless, time of initiation of any medication or adequate medication rather than time of resolution of psychosis is used as the end points for DUP. One merit of ending DUP by time of initiation of treatment is that it is not intrinsically confounded with time to remission once treatment is begun (sometimes used as an outcome measure) and which, in turn, might be expected to relate to long-term outcome (Breier *et al.* 1991). This means that any relationship of DUP to outcome is less likely to reflect general treatment 'refractoriness' than would total length of psychosis.

Many studies do not report specific reliability indices of their measures of DUP. Some researchers have used instruments designed to provide standardized methods of assessing the onset and early course of psychiatric disorders such as the Royal Park Instrument (McGorry *et al.* 1990), the CASH (Andreasen *et al.* 1992), the IRAOS (Häfner *et al.* 1992) and the interview

† The notes will be found on pp. 397–398.

for establishing the onset of psychosis developed by Beiser *et al*. (1993). While information is available on the interrater or test–retest reliability of these instruments, we do not know the comparability of estimates of DUP across these methods. It is likely that there would be inconsistency given that there is considerable variation in the breadth of symptoms used in these instruments for identifying the onset of psychosis (cf. Carbone *et al*. 1999; Ho *et al*. 2000). While an interview such as that developed by Beiser *et al*. (1993) would yield valuable information concerning many aspects of onset, it is of questionable value, in itself, as a measure of DUP given that mood symptoms are included in the definition of psychosis and it appears to focus on initiation of 'treatment seeking' behaviour rather than initiation of actual treatment.

Table 1 summarizes studies that report indices likely to reflect DUP.[2] We have endeavoured to reproduce the description of the observations used to establish DUP in each of the studies, but, often detailed descriptions are not provided. Furthermore, definitions of length of untreated psychosis do not generally address whether psychotic symptoms have been present constantly or sporadically in the period between initial onset and treatment or the severity of such symptoms when present. To facilitate comparisons across studies, all estimates from the relevant papers have been converted to weeks.

There is a remarkable range in average DUPs being reported in Table 1. The range of means is from 22 weeks (Linszen *et al*. 1998) to 166·4 weeks (Szymanski *et al*. 1996). There are no clear relationships between the definitions of DUP, nature of the sample, or geographic location and estimated length of DUP. It is worth noting, however, that the two reports showing lowest average DUP (Linszen *et al*. 1998 and Carbone *et al*. 1999) were both from treatment programmes with a particular interest in identification of psychosis at an early stage.

Table 1 also indicates that when mean, median and an index of variability of DUP are provided for a study, they suggest the presence of a positively skewed distribution (median substantially lower than mean) with a concentration towards the shorter DUPs and a comparatively small number of extremely long DUPs.

DUP AND TREATMENT OUTCOME

Research concerning a relationship between DUP and treatment outcome can be classified on the basis of whether a study provides indirect or direct evidence. Indirect evidence comes from studies wherein DUP is not directly assessed (or manipulated), but outcomes are compared on groups for whom it might be assumed that there are differences in DUP. In studies providing direct evidence, DUP is carefully estimated for individuals and related to variation in outcome.

INDIRECT EVIDENCE

A seminal article by Wyatt (1991) reviewed several bodies of research that could indirectly reflect the importance of DUP in determining treatment outcome. These included mirror image, neuroleptic discontinuation and controlled trial follow-up studies.

Mirror image studies

Mirror image studies compare long-term outcomes for patients in the historical period before the availability of neuroleptics (pre-neuroleptic era) with outcomes for supposedly similar groups of patients treated in the post-neuroleptic era. Can such studies be interpreted as reflecting anything other than the well documented efficacy of neuroleptics in reducing psychotic symptoms and likelihood of relapse? Yes, but only if neuroleptics were being used in the latter patients solely for the treatment of acute symptoms and not used on a maintenance basis as a prophylaxis for relapse and if the long-term outcomes (e.g. likelihood of relapse after discharge) rather than short-term responses to treatment (such as time to reduction of acute symptoms) are assessed. Finding that pre- and post-neuroleptic era patients differed in time to resolution of acute symptoms would simply reflect the efficacy of antipsychotic medications. Differences between the two groups in likelihood of relapse once the psychotic symptoms had remitted, however, could reflect the effect of a more prolonged initial duration of the untreated psychosis.

Although some of these studies indicate a better long-term outcome for those patients whose symptoms were presumably treated more rapidly in the post-neuroleptic era (e.g.

Table 1. *Operationalizations of DUP and findings regarding DUP length*

Study	Sample	Beginning of DUP	End of DUP	Average DUP (weeks)	Variability in DUP
Browne *et al.* (2000)	53 individuals meeting DSM-IV criteria for schizophrenia or schizophreniform psychosis experiencing a first-ever episode or having had a previous episode, but not having been treated for > 30 days before referral for service	Time of emergence of psychotic symptoms as dated by patient on basis of SCID interview	Initiation of treatment	Mean = 90·8 Median = 26	S.D. = 157 Range = 4 to 1040
Carbone *et al.* (1999)	250 patients with first-episode psychosis for whom data were available over a 12 month follow-up. One half were diagnosed as schizophrenia or schizophreniform psychosis, one-third schizoaffective, bipolar or depression and the remainder with other psychotic disorders. Figures regarding DUP are reported separately for two early intervention programmes (EPPIC and Pre-EPPIC)	Time of onset of first psychotic symptoms using Royal Park Multidiagnostic Instrument for Psychosis	Entry into treatment programme that includes administration of antipsychotic medication	EPPIC*: Mean = 25·0 Median = 7·4 Pre-EPPIC: Mean = 32·4 Median = 4·3	EPPIC: S.D. = 55·1 Pre-EPPIC: S.D. = 102·0
Craig *et al.* (2000)	155 patients with schizophrenia or schizoaffective disorder, 199 with bipolar disorder, with psychotic features and 75 with major depressive disorder with psychotic features	Occurrence of first clear psychotic symptom as derived from information from SCID interview, medical records and significant others	First psychiatric hospitalization and initiation of antipsychotic medication	Schizophrenia and schizoaffective: Median = 14 weeks Bipolar disorder: Median = 1·3 weeks Psychotic depression: Median = 3·1 weeks	Schizophrenia and schizoaffective: 95% CI = 5·2–22·8 Bipolar disorder: 95% CI = 0·8–1·8 Psychotic depression: 95% CI = 0·9–5·3
Haas & Sweeney (1992)	71 first-episode patients with schizophrenia, schizophreniform disorder or schizoaffective disorder	Time of onset of first psychotic symptoms (unspecified)	Time of first antipsychotic medication	Mean = 98·8 weeks†	Not available
Haas *et al.* (1998)	103 patients representing consecutive admissions to a psychiatric clinic who met DSM-III-R criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder	A review of all available sources (interviews with patients, family members, treating clinicians and medical records) were used by two senior clinicians in order to provide a best estimate of time of onset of first psychotic episode	Time of first antipsychotic medication	Mean = 74·4 weeks (derived from Table 2, p. 154 of Haas *et al.* 1998)	78% had DUP < 52 weeks 22% had DUP of ⩾ 52 weeks

Häfner *et al.* (1993)	267 first-admission patients with schizophrenia (ICD-9 broad definition), admitted to psychiatric hospital or unit	Onset of first-rank symptoms or meeting criteria for a syndrome based on IRAOS interview of patient	Hospitalization	Mean = 109·2 weeks (as reported by Larsen *et al.* 1996)	Not available
Ho *et al.* (2000)	74 first-episode, neuroleptic naive patients with DSM-IV diagnosis of schizophrenia	Occurrence of any one of delusions, hallucinations, bizarre/disorganized behaviours, formal thought disorder, or catatonic motor behaviour at moderate or greater severity as assessed by CASH interview	Initiation of neuroleptic treatment	Mean = 60·8 Median = 13·5	Interquantile range = 45·0
Larsen *et al.* (1996)	43 first-episode patients with non-affective psychosis (DSM-III-R). Members of an early identification and treatment programme	Onset of psychosis defined as score of $\geqslant 4$ on PANSS positive subscale with presence of delusions, hallucinations, thought disorder or inappropriate or bizarre behaviour with duration of several weeks	Hospitalization for psychosis or initiation of an antipsychotic drug for sufficient time and dosage that would lead to clinical response in average non-chronic patient (e.g. haloperidol 5 mg/day for 3 weeks)	Mean = 114·2 weeks Median = 26 weeks	s.d. = 173·6 weeks
Linszen *et al.* (1998)	76 patients with a DSM-III-R criteria diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder or atypical psychoses. Patients were not included if judged to have primary alcohol dependence, drug dependence and/or brief drug-related psychosis	Onset of psychotic illness (hallucinations, delusions and/or thought disorder)	Entry into treatment protocol involving administration of neuroleptics.	Mean = 23·4 weeks	s.d. = 47·6 weeks
Robinson *et al.* (1999*a*) more extensive report on enlarged data overlapping with that of Loebel *et al.* 1992	104 patients with RDC criteria diagnosis of schizophrenia or schizoaffective disorder based on SAPS, with total life time exposure to antipsychotic of $\leqslant 12$ weeks	After 'explaining psychosis in clear language' patient (or family member) was asked when psychotic symptoms were first experienced or noticed. When patients and family members disagreed, research staff reached consensus	Entry into protocol for open standardized treatment using standardized protocol for administration of neuroleptics	Mean = 64 weeks	s.d. = 146 weeks

Table 1 (*cont.*)

Study	Sample	Beginning of DUP	End of DUP	Average DUP (weeks)	Variability in DUP
Szymanski *et al.* 1996	36 individuals with DSM-III-R criteria of schizophrenia or schizophreniform disorder	The first time at which psychotic symptoms were noticed by the patient, family or others in the context of a decline in functioning	Entry into research study involving administration of neuroleptics based on clinical judgement of treating physician. Prior treatment with one or two doses was permitted	Mean = 166·4 weeks	S.D. = 223·6 weeks

*McGorry *et al.* (1996), Edwards *et al.* (1998) provide generally comparable figures for slightly smaller samples that substantially overlap with those reported by Carbone *et al.* (1999).
†This figure differs from that cited by Larsen *et al.* (1996). Our estimate is based on data presented in Table 2 of Haas & Sweeney's article regarding age at onset of psychotic symptom and age of first administration of neuroleptic. The estimate by Larsen *et al.* appears to reflect difference in age of onset *versus* age of first hospitalization.
EPPIC, Early Psychosis Prevention and Intervention Centre.

McWalter *et al.* 1961; Watt *et al.* 1983), others do not (Ødegaard, 1964; Peterson & Olson, 1964; Pritchard, 1967*a*, *b*). Furthermore, comparison between eras are often difficult to interpret given possible changes in diagnostic practices and/or hospital admission/discharge policies (McWalter *et al.* 1961; Ødegaard, 1964; Peterson & Olson, 1964); the efficacy of non-neuroleptic somatic therapies such as ECT and insulin coma therapy, which were widely used in many of the pre-neuroleptic era patients (Freyhan, 1955; Achte, 1967; Markowe *et al.* 1967) and which remained dominant forms of treatment for at least some of the post-neuroleptic era patients (e.g. McWalter *et al.* 1961); evidence that a historical trend towards improved outcome had begun prior to the introduction of neuroleptics (McWalter *et al.* 1961; Ødegaard, 1964; Pritchard, 1967*a*, *b*; Watt *et al.* 1983); different patterns of change between the eras for males and females (McWalter *et al.* 1961; Watt *et al.* 1983); and the finding in at least one analysis that better outcomes for post-neuroleptic patients characterized those patients who did not receive pharmacological or other physical treatment as well as those who did (Pritchard, 1967*a*, *b*). In addition, post-neuroleptic patients in at least one of the mirror image studies were receiving maintenance medication (Watt *et al.* 1983).

Neuroleptic discontinuation studies

Indirect evidence relevant to the possible effects of DUP on long-term prognosis has also been obtained from studies in which medication is deliberately discontinued in order to investigate the value of maintenance medication. Any differential long-term effects for patients who did *versus* did not experience discontinuation once treatment has been reestablished, might be attributable to the discontinuation group having experienced increased exposure to psychosis. Data from such studies are likely to reflect the impact of total rather than initial DUP on long-term outcome.

Curson *et al.* (1985) report a long-term follow-up (average of seven years) of 64 of the patients in a drug discontinuation trial originally reported by Hirsch *et al.* (1973). All patients had been stabilized on depot medications after completion of the discontinuation trial and were not considered to present problems in com-

pliance with treatment. Given that differences in relapse rates (and, therefore, presumably, length of psychosis) had earlier occurred between continuation and discontinuation groups, one might anticipate some differences between the two groups in likelihood of relapse over the post-trial follow-up. No difference in relapse rates over follow-up was found, although patients who had experienced discontinuation showed poorer social adjustment in the long-term follow-up. These were chronic patients, and so there may have been minimal impact of the controlled trial on cumulative experience of psychosis.

Johnson *et al*. (1983), in an 18-month follow-up of 60 patients who had discontinued medication after being stable on depot medication and 56 matched patients who continued on medication reported higher relapse rates for the discontinuation group. In general, medication was reinstituted after any relapse. Wyatt (1991) noted that the results showed a high proportion (62%) of patients continuing on medication showing good social functioning at 18 months in comparison to those in the discontinuation group (38%). There are, however, mitigating considerations. Ratings of social and work functioning were not carried out by individuals blind to the patient's status regarding earlier continuation of medication. Ancillary analyses reported by Johnson *et al*. (1983, p. 347–348) also showed that when non-relapsing patients in the discontinuation and maintenance groups were compared, the percentages of patients showing good overall social adjustment (33% and 60% respectively) parallel the differences for all subjects in each group. This suggests that differential experience of psychosis was not the mediator of differences between the groups in social functioning at 18 months.

Controlled trial follow-up studies

These studies involved patients randomly assigned to treatment conditions which differed significantly in effectiveness in reducing psychotic symptoms. Long-term follow-ups of such patients can be of relevance to the issue of the relationships of DUP to outcome if: (*i*) there were substantial differences in length of psychosis as a result of treatment condition in the initial trial; (*ii*) groups did not significantly differ on other prognostic indicators; (*iii*) subsequent to the initial clinical trial, there were no significant differences in the treatment received by patients during follow-up; and (*iv*) there were no differences between original treatment conditions in proportions of patients available for long-term follow-up.

Wyatt (1991) reviewed several studies of this type. There appear to be conflicting results regarding long-term outcomes for those initially assigned to receive different interventions (cf. Greenblatt *et al*. 1965; Simon *et al*. 1965; Carpenter *et al*. 1977; Rappaport *et al*. 1978). Difficulties related to the interpretation of findings include: inconsistent results when using different long-term outcome indicators such as time in hospital *versus* clinical ratings (Greenblatt *et al*. 1965); non-random assignment to treatment conditions (Pritchard, 1967*b*); differences between groups in prognostic indicators (Carpenter *et al*. 1977), drop-out rate (Schooler *et al*. 1967), or availability to follow-up (Rappaport *et al*. 1978); and/or long-term outcome indices being completed by individuals who were not blind concerning treatment assignment (Greenblatt *et al*. 1965). Furthermore, if DUP is influenced by the effectiveness of the randomly assigned conditions and DUP is the presumed mediator of later long-term outcome, one would expect direct parallels between speed of initial treatment response and long-term outcomes. Such parallel patterns do not always occur (e.g. Simon *et al*. 1965).

A study by May *et al*. (1981), frequently cited for its relevance to the influence of DUP, reports a long-term follow-up of patients initially treated in a randomized control trial. A total of 228 first admission schizophrenic patients were randomly assigned to receive psychotherapy alone; antipsychotic drugs; psychotherapy plus antipsychotics; ECT; or milieu treatment. Those who, during this 6–12 months of the assigned treatment, improved to a point to be discharged were considered treatment successes, whereas those who did not were assigned to a second treatment (psychotherapy plus medication). Those receiving drugs or ECT were discharged from hospital earlier and presumably experienced shorter DUP. Several years later, those patients who had been assigned to receive medication or ECT were showing advantages in terms of days in hospital and ratings on clinical and social indicators.

Table 2. *Summary of studies relating DUP to outcome*

Authors	Type of study retrospective *v.* longitudinal	Patient sample	Definition of DUP	Length of follow-up for outcome	Evidence regarding relation of DUP to outcome
Craig *et al.* (2000)	Longitudinal	155 patients with schizophrenia or schizoaffective disorder, 119 with bipolar disorder with psychotic features and 75 with major depressive disorder with psychotic features as diagnosed after 24 months follow-up. All had not been treated prior to first hospitalization and had first hospitalization within 6 months of entry into study	Time between occurrence of the first clear psychotic symptoms and first psychiatric hospitalization based on SCID, medical records and information from significant others	24 months	DUP (based on tertile split in each diagnostic group) was not related to likelihood of remission, global assessment of functioning, positive or negative symptoms at 24 months
Edwards *et al.* (1998)	Longitudinal	227 patients with first-episode psychosis (primarily schizophrenia, schizophreniform, affective or schizoaffective), 146 males and 81 females	Time between onset of psychotic symptoms as assessed using Royal Park Multidiagnostic Instrument for Psychosis and entry into treatment programme	12 months	15 patients showing prolonged recovery (failure to demonstrate sustained remission by 12 months) had longer DUP than 212 patients showing shorter recovery
Haas *et al.* (1998)	Retrospective	103 patients with DSM-III-R diagnosis of schizophrenia, schizophreniform or schizoaffective psychosis, 60 males and 43 females	Two senior clinicians reviewed all available information, including interviews with patient and family and clinicians and records to get best estimates and consensus regarding date of first psychotic symptoms and initiation of anti-psychotic treatment. DUP was divided at 1 year point for further analysis	Mean of 6·4 years	DUP unrelated to subsequent number of hospitalizations and to severity of positive symptoms at most recent hospitalization. Longer DUP related to greater negative symptoms at most recent hospitalization and less improvement in GAS during hospitalization

Ho *et al.* (2000)	Longitudinal	74 first-episode, neuroleptic-naive patients with DMS-IV diagnosis of schizophrenia: 46 males and 28 females	Two definitions were used: (1) time from onset of first symptom (psychotic or prodromal) to the initiation of antipsychotic medication; or (2) time from presence of first positive symptom (delusions, hallucinations, bizarre/disorganized behaviour, formal thought disorder or catatonic motor behaviour) at severity of moderate or worse to the initiation of antipsychotic treatment	6 months	No relation found between either definition of DUP and time to remission, or quality of life or level of symptoms at 6 month follow-up
Linszen *et al.* (1998)	Longitudinal	76 patients with a diagnosis of schizophrenia, schizophreniform and related psychotic disorders. Age range restricted to 15 to 26 year and living with or in close contact with family. 57% of sample were first episode, 53 males and 23 females	Time between onset of psychotic symptoms and onset of treatment (medication) using parents, patients and case records as sources and reaching resolution of any inconsistencies between data sources	12 months	Likelihood of relapse during 12 months of out-patient treatment was not related to DUP
Loebel *et al.* (1992); Robinson *et al.* (1999 *a*, *b*)	Longitudinal	70 patients with meeting RDC criteria for schizophrenia or schizoaffective disorder, 39 males and 31 females	Duration from onset of psychotic symptoms to initiation of study treatment protocol. Previous treatment of up to 12 weeks was permissible (90% of sample were neuroleptic naive)	Up to 3 years	Loebel *et al.* (1992) concluded that DUP predicted time to treatment response. Also DUP was related to level of remission achieved Robinson *et al.* 1999 *b* in larger sample concluded that there was no relation of DUP to likelihood of relapse
McGorry *et al.* (1996)	Longitudinal	200 patients with first-episode psychosis. 122 males and 78 females. Over half had a diagnosis of either schizophrenia or schizophreniform psychosis; one-third schizoaffective, bipolar or depression and the remainder with other psychotic disorders	Time between onset of psychotic symptoms as assessed using Royal Park Multidiagnostic Instrument for Psychosis and entry into treatment programme	12 months	Longer DUP was associated with longer duration of psychotic symptoms during first hospitalization and worse scores at 12 month follow-up on BPRS, SANS, GAF and Quality of Life Scale

Table 2 (*cont.*

Authors	Type of study retrospective *v.* longitudinal	Patient sample	Definition of DUP	Length of follow-up for outcome	Evidence regarding relation of DUP to outcome
Szymanski *et al.* (1996)	Longitudinal	36 first-episode patients mostly DSM-III-R criteria for schizophrenia or schizophreniform disorder, 21 males and 15 females	Time between onset of psychotic symptoms in context of decline in functioning and entry into treatment protocol. Prior treatment with one or two doses of antipsychotics was permitted	6 months	Longer DUP associated with less reduction in positive symptoms during 6 months of treatment
Waddington *et al.* (1995); Scully *et al.* 1997	Retrospective	88 patients mean age of 62·6 with range from 25 to 89 years of age. Patient satisfied Feighner's criteria for schizophrenia: 50 males and 38 females	Age at first prescription of neuroleptics minus age at first admission to a psychiatric hospital	Variable, average not reported but likely to be several decades	Longer DUP was associated with muteness, greater negative symptoms and lower scores on Mini-Mental Status examination. There was no relationship of DUP to level of positive symptoms at time of assessment
Wiersma *et al.* (1998)	Longitudinal	63 patients with first-ever onset of psychotic illness of a non-affective type using ICD criteria. Approximately 50% males and 50% females	The time between onset of psychosis and initiation of any form of treatment (almost always involving medication). Estimates were based on Life Chart Schedule (Sartorius *et al.* 1996) and WHO Past and Follow-up History (Jablensky *et al.* 1980)	15 years	Longer DUP associated with longer first episode (including initial untreated period) but not subsequent course (length of remission or likelihood of relapse)

In a further follow-up of the above study, Wyatt *et al.* (1997) examined case records to estimate days in hospital and functioning (blind retrospective Global Assessment of Functioning (GAF)) for those who had been considered treatment successes during the original trial. Of these, 71 had and 25 had not received medication during the assigned treatment phase. Although patients who had achieved remission in the non-medication group could be regarded as 'naturally' having a more positive prognosis: over the first 2 years of follow-up patients in the medication groups who had improved showed significantly fewer days in hospital and better functioning than those who had improved without medication. While these results suggest the possible advantages of early treatment with medication, they do not directly demonstrate the role of DUP as a mediator of this effect given that the patients from medication and non-medication conditions in the Wyatt *et al.* (1997) follow-up study had not differed on number of days in hospital during the index admission, which (in the absence of a direct measure) is the variable most likely to reflect DUP.

One of the most difficult problems in the evaluation of controlled trial follow-ups is the possibility of differences in treatment of patients once the original trial had ended. The possibility that those who were originally assigned to differing treatment conditions may have continued on them during follow-up periods is critical in determining whether any differences in long-term outcome are due to DUP or to continuing differences in treatment over the follow-up period (Greenblatt *et al.* 1965; Wyatt, 1991, p. 336). May *et al.* (1976) noted, a tendency for patients to continue to receive the same treatment over such follow-ups.

DIRECT EVIDENCE

Several studies have been reported in which comparisons have been made of outcome for patients in the same historical period, similar or same facilities and who were treated using treatment protocols that were unlikely to differ as a function of DUP.[3] In addition, DUP is estimated for each individual and is unlikely to be confounded with temporal changes in recruitment, diagnostic practices or the nature of follow-up treatment.

In retrospective studies, patients are followed up at a single point in time and their symptoms and treatment history as then assessed are related to estimates of DUP reconstructed for an often distant past. In longitudinal studies, patients are assessed for DUP near the time of their first presentation for treatment and then followed over time and assessed for outcomes. The latter design has two potential advantages for examining possible effects of DUP: (*i*) reports of DUP are likely to be more accurate because they are being collected with reference to a more recent time period; and (*ii*) there is more likely to be well documented evidence concerning other correlates of the patient's initial presentation (e.g. pre-morbid adjustment or presenting symptoms), which means that one could estimate the influence of DUP on future outcomes while controlling for possible confounds. Summaries of the following studies are presented in Table 2.

RETROSPECTIVE STUDIES

Haas *et al.* (1998) studied 103 consecutive admissions to the Payne–Whitney Clinic in New York. All patients met DSM-III-R criteria for diagnosis of schizophrenia, schizoaffective or schizophreniform psychosis. Compared to patients with DUP < 1 year those with DUP $\geqslant 1$ year had more negative symptoms (especially flat affect/anhedonia) at the time of their most recent admission, but the two groups did not differ on positive symptoms. Those with shorter DUP also showed greater improvement in Global Assessment Scale (GAS) scores (Endicott *et al.* 1976) during the most recent hospitalization. The two groups did not differ on number of psychiatric hospitalizations since their illness onset. Those with apparently longer DUP had higher level of negative symptoms as well as high residual hallucinations and delusions at the time of discharge from their most recent admission. These findings were similar for first and multiple admission patients and were not mediated by current age, age of onset, gender, marital status, or duration of treatment with antipsychotic as the two groups did not differ on these variables.

Waddington *et al.* (1995) examined the relationships of DUP to current clinical status in

a sample of 88 in-patients. DUP was defined as length of time between age at first admission to a psychiatric hospital and age when first receiving neuroleptics. Many of the patients were quite elderly and had developed their illness in the pre-neuroleptic era resulting in quite lengthy estimated DUPS (mean = 17·1 years, range 0–51 years). The measure of DUP might be considered contentious, given that it does not account for psychotic symptoms prior to hospital admission, or admissions precipitated by non-psychotic symptoms; but given the unusual circumstances of this population, it seems likely that the estimates would largely reflect DUP.

Longer DUP was related to higher likelihood of muteness in patients independently of age and history of neuroleptic treatment. Additional data on 48 of these patients showed longer DUP to be associated with higher levels of negative symptoms and poorer scores on the Mini-Mental State Examination (Scully *et al.* 1997). While noteworthy, interpretation of these results as showing the independent contribution of DUP to outcome is compromised because of the inability to control for important characteristics at the time of initial onset (e.g. negative symptoms and pre-morbid adjustment). Generalizability of findings from a sample consisting solely of long-term in-patients in a psychiatric hospital could also be problematical.

LONGITUDINAL DESIGNS

Loebel *et al.* (1992) report the first longitudinal study regarding DUP and outcomes in 70 in-patients with a diagnosis of schizophrenia or schizoaffective disorder. Although 70% of the subjects were neuroleptic naive, others were entered into the study with up to 12 weeks of previous neuroleptic treatment. DUP was calculated by individuals blind as to treatment outcome. All patients received an open label standardized treatment with antipsychotics.

Remission was defined on the basis of a reduction in scores on SADS-C and Psychosis and Disorganization Scale items to at least a mild level persisting for a minimum of 8 weeks. Time to remission (calculated over periods ranging from a minimum of 8 weeks to 3 years) was significantly predicted by DUP (see also Lieberman *et al.* 1992) independent of gender and diagnosis. DUP was also a significant predictor of level of remission at the end of the prescribed treatment.

The significance of the findings reported by Loebel *et al.* are mitigated, however, by two subsequent reports. Robinson *et al.* (1999*a*) analysed data from 118 patients who were eventually recruited into the above study, and concluded that while there was a tendency for those with shorter DUP (dichotomized at 1 year) to be more likely to achieve remission within 1 year after initiation of treatment, it did not reach statistical significance.[4] Robinson *et al.* 1999*b* showed that among patients who remitted, DUP was unrelated to likelihood of relapse during a follow-up of up to 5 years.

McGorry *et al.* (1996) report a follow-up of 200 first episode patients treated in Melbourne, Australia. The majority of patients had a diagnosis of schizophrenia or schizophreniform disorder, one-third had schizoaffective or affective psychosis diagnoses and the remainder psychotic disorder NOS, drug induced psychosis or brief reactive psychosis. McGorry *et al.* found longer DUP to be significantly correlated with longer duration of psychotic symptoms during the first hospitalization ($r = 0{\cdot}33$), and worse scores at 12 month follow-up on the BPRS, SANS, GAF and Heinrichs *et al.*'s (1984) Quality of Life Scale (QLS) (Spearman's rho varied between 0·26 and 0·38). While duration of prodromal phase and diagnosis (schizophrenia/schizophreniform *v.* psychotic mood disorder *v.* other psychotic disorders) were also related to QLS, DUP appeared able to predict 15% of the variance.

In a slightly different approach to analysis on a largely overlapping sample, Edwards *et al.* (1998) compared 15 patients who showed a carefully defined pattern of delayed recovery from a first episode of psychosis with 212 patients who did not show such prolongation. DUP was significantly greater in the prolonged recovery group. Diagnosis of schizophrenia and schizophreniform (*versus* affective and schizoaffective) diagnosis were more common in the delayed prolonged recovery group. Contrasts between groups on DUP while controlling for other differences were not reported.

Szymanski *et al.* (1996) include follow-up data on 36 neuroleptic naive patients with a DSM-

III-R diagnosis of schizophrenia. Onset of DUP was defined by psychotic symptoms being noticed in the context of a decline in functioning. In a longitudinal follow-up, longer DUP was associated with less change in positive, but not negative symptoms over 6 months of treatment, and this relationship appeared to be independent of gender, age or baseline severity of symptoms.

Linszen *et al.* (1998) report the results of a trial assessing the impact adding an intensive family intervention to other treatments during a 12-month period of out-patient care. Although all of the 76 patients were considered to be at early stages of their illness, 43% were not first episode patients. No relation was found between duration of untreated psychosis and symptom course or likelihood of relapse during the 12 months of treatment. The authors note that the average length of untreated psychosis for their sample (5·4 months) was quite short in comparison with those in many other studies and suggest that this may be responsible for the failure to find DUP predicting relapse. Although 74% of the sample had a DUP of 6 months or less, 12 had suffered from psychosis for at least 12 months prior to initiation of treatment.

Wiersma *et al.* (1998) found that time between onset of psychosis and initiation of any form of treatment was a significant predictor of the length of the first acute episode of psychosis for 63 patients who had been assessed as part of a WHO collaborative study. Such a finding is to be expected, of course, given that length of first episode included the time between onset and initiation of treatment (Wiersma, personal communication) resulting in substantial common variance. Perhaps more noteworthy, is the finding that delay in treatment did not predict likelihood of subsequent episodes or length of first remission over a 15 year follow-up.

Craig *et al.* (2000) examined the relation between DUP (defined as time between first 'clear psychotic' symptom and first hospitalization and administration of antipsychotics) and clinical course during the 24 months after first admission to one of the several psychiatric facilities. For all patients this would have represented their first psychiatric admission or the first admission would have occurred within the past 6 months. Approximately 44% of the sample had a diagnosis of schizophrenia or schizoaffective psychosis, 34% bipolar disorder with psychotic features and 22% depressive disorder with psychotic features.

Those with a diagnosis of schizophrenia or schizoaffective disorder had longer DUPs and lower rates of complete remission than those with affective disorders. When patients within each diagnostic group were split into three groups on the basis of increasing length of DUP, in no case was DUP found to be significantly related to likelihood of attaining remission over the 24 months, neither was it significantly related to ratings at follow-up of positive symptoms, negative symptoms, GAF scores or scores on BPRS items reflecting thought disorder, grandiosity or excitement.

Ho *et al.* (2000) reported a 6 month follow-up evaluation on 74 first episode, neuroleptic naive patients with a DSM-IV diagnosis of schizophrenia. DUP was defined in two ways. The first method involved estimating the length of time between the first symptom and initiation of antipsychotic medication and the second reflected the time between the presence of one or more of five positive symptoms at moderate or greater level. The former definition appears to be reflecting DUI. The latter definition comes closest to the concept of DUP as generally used, although it did include the presence of such symptoms as disorganized behaviours or catatonic motor behaviour in addition to hallucinations, delusions and formal thought disorder.

No significant relation was found between either of the above estimates and *post hoc* estimates of time to remission or level of symptoms or quality of life at a 6 month follow-up. This report differs from most other longitudinal studies in its relatively short follow-up period, methods of assessing remission and definition of DUP.

STATISTICAL ISSUES

As noted earlier, DUP typically shows a positively skewed distribution. Among studies that have treated it as a continuous variable, some have performed a log transformation or used non-parametric analyses (Loebel *et al.* 1992; McGorry *et al.* 1996; Edwards *et al.* 1998; Carbone *et al.* 1999; Craig *et al.* 2000; Ho *et al.* 2000) while others appear not to have done so (Waddington *et al.* 1995; Szymanski *et al.* 1996). Loebel *et al.* (1992) report that performing such

a log transformation of DUP had no significant effect on their results. Nevertheless, given a reasonably consistent pattern of positive skewedness in distributions of DUP, it is important that the effect of such transformations continue to be investigated.

There are no strong *a priori* grounds for suggesting a particular initial level or 'cut-off' for DUP although some authors have suggested that the first 2–3 years is a 'critical period' in which most deterioration occurs in the course of psychotic disorders (e.g. McGlashen, 1996; Birchwood *et al*. 1998). Several reports have chosen to examine a dichotomy around the greater or less than 1 year level (e.g. Haas *et al*. 1998; Robinson *et al*. 1999*a*, *b*), but other reports have suggested that initiating treatment within a period of 6 months from onset of psychosis may be critically associated with better outcomes (McGorry *et al*. 1996; Carbone *et al*. 1999). Reports of substantial differences between diagnostic groups in DUP (e.g. McGorry *et al*. 1996; Craig *et al*. 2000) suggest that application of a single cut-off would risk confounding any association between DUP and outcome with diagnosis. Certainly, more systematic data collection and detailed analyses concerning critical periods in the relationship between DUP and outcome would be valuable.

ARE THERE CONFOUNDS OF THE RELATIONSHIP BETWEEN DUP AND RESPONSE TO TREATMENT?

It is important to remember that the current interest in DUP comes primarily from the postulate that it is a potentially modifiable factor that has an independent influence on outcome. Several authors have noted many positive prognostic indicators may be associated with shorter DUP (McGorry *et al*. 1996; Vaglum, 1996; Falloon *et al*. 1998; McGlashan, 1999). For instance, a pattern of insidious onset with social withdrawal, poor functioning and prominent negative symptoms might well lead to increased DUP and could also help explain variation in negative symptoms and psychosocial functioning at follow-up.

Unfortunately, there is little evidence concerning possible confounds of any relationship between DUP and treatment outcome. Most studies have found DUP unrelated to age of onset of psychosis (Haas & Sweeney, 1992; Loebel *et al*. 1992; Beiser *et al*. 1993; Häfner *et al*. 1993; Larsen *et al*. 1996; Haas *et al*. 1998), except when a very broad definition of onset of psychosis is used (Ho *et al*. 2000). There is less and inconsistent evidence with reference to possible correlations between DUP and other prognostic indicators such as gender (cf. Loebel *et al*. 1992; Beiser *et al*. 1993; Larsen *et al*. 1996; Haas *et al*. 1998; Craig *et al*. 2000; Ho *et al*. 2000); pre-morbid adjustment (cf. Loebel *et al*. 1992; Larsen *et al*. 1996; Haas *et al*. 1998; Verdoux *et al*. 1998; Browne *et al*. 2000; Ho *et al*. 2000) and acuity of onset (cf. Loebel *et al*. 1992; Larsen *et al*. 1996). Single studies have found longer DUP related to increased severity of negative symptoms and deficit symptoms in initial presentation (Larsen *et al*. 1996; Browne *et al*. 2000) and poor social support and social withdrawal (Larsen *et al*. 1996). In a sample of 40 patients Verdoux *et al*. found that family history of psychiatric hospitalization, lower level of education, global severity of illness, and low level of functioning prior to hospitalization each predicted longer DUP. Each of these correlates could in turn be a predictor of treatment outcome.

Taking such potential confounds into account will be critical in assessing the independent influence of DUP on outcomes even when no single one shows a statistically significant relationship to DUP (Rhodes *et al*. 1999). Among the studies which have attempted to control for possible confounds, Loebel *et al*. (1992) present evidence that the relationship of DUP to time to remission is independent of diagnosis and gender and McGorry *et al*. (1996) found DUP related to deficit symptoms at 12 month outcomes even when diagnosis, gender and age have already been entered into a multiple regression. Szymanski *et al*. (1996) found the power of DUP to predict change in positive symptoms was independent of gender and baseline symptoms. Future reports concerning DUP and outcome certainly need to carefully assess for possible confounding with other outcome predictors.

Given evidence that substance use and/or assiduity in taking prescribed medication can have a substantial impact on treatment outcome (e.g. Helgasson, 1989; Cantwell *et al*. 1999), it is

unfortunate that no data has been reported on the relationship of these variables to DUP. It is conceivable that medical help will be sought later (and DUP extended) if symptoms are partially attributable to substance use. Furthermore, it is possible that denial, embarrassment and distrust of medical treatment might underlie both delay in treatment and reluctance in taking medication.

WHAT CAN BE CONCLUDED ABOUT DUP AND COURSE OF PSYCHOSIS?

Is DUP related to initial response to treatment?

Reports from five databases have provided evidence concerning the relationship of DUP to rapidity or completeness of recovery from the initial episode once treatment is initiated. Two were collected in New York (Loebel *et al*. 1992; Robinson *et al*. 1999*a*; Craig *et al*. 2000), and one in each for Melbourne (McGorry *et al*. 1996; Edwards *et al*. 1998); Philadelphia (Szymanski *et al*. 1996); and Iowa (Ho *et al*. 2000). Three of the five databases provide some evidence of DUP being related to either time to remission (Loebel *et al*. 1992; McGorry *et al*. 1996; Edwards, 1998; Robinson *et al*. 1999*a*) or level of remission achieved (Szymanski *et al*. 1996). Although the conclusions drawn by Loebel *et al*. (1992) and Robinson *et al*. (1999*a*) are somewhat inconsistent with respect to their largely common database, the results of a proportional hazards analysis for both sets of data regarding the predictive power of DUP are similar, the conclusions differ only in respect to willingness to accept a 0·03 significance level.

Neither Craig *et al*. (2000) nor Ho *et al*. (2000) found DUP to be related to likelihood of remission. No single factor is clearly implicated as the reason to explain these discrepancies in findings. One possibility that must be considered is that both of these studies examined DUP and outcome within the context of samples with relatively homogenous diagnoses. Ho *et al*. raise the possibility that findings of a relationship between DUP and time to remission in other studies such as McGorry *et al*. (1996) may reflect a confound with differences in diagnosis. Such an explanation seems unlikely to account for reports by Loebel *et al*. (1992) and Szymanski *et al*. (1996) both of which found DUP related to initial treatment response in samples with restricted diagnoses and McGorry *et al*. (1996) finding DUP to predict outcome independently of diagnosis. Further complicating such comparisons in Ho *et al*.'s use of a definition of DUP that includes catatonic motor behaviour or disorganized behaviour as the basis for identifying the onset of psychosis and the remarkably low rate of remission (14%) achieved over a 2 year period by patients followed by Craig *et al*. In addition, both Craig *et al*. (2000, p. 63) and Ho *et al*. (2000, p. 811) report extreme groups analyses which provide some non-significant, but suggestive findings of a possible trend for DUP being related to likelihood of achieving remission.

On balance, it seems fair to say that there is evidence suggesting a relationship between DUP and initial response to treatment although the robustness of such findings and their independence from all potential confounding variables is yet to be established.

Is DUP related to long-term outcome?

There is currently no evidence of a relationship of DUP to longer term outcomes such as likelihood of relapse. All four studies examining DUP and likelihood of relapse (or rehospitalization) have failed to find a relationship (Haas *et al*. 1998; Linszen *et al*. 1998; Weirsma *et al*. 1998; Robinson *et al*. 1999*b*).

Robinson *et al*. (1999*b*) have remarked that 'either the pathologic mechanisms of relapse differ from those of acute treatment response, or – if common mechanisms initially underlie treatment response and relapse – that the pathologic process changes over time because of a "deteriorative" component, the effects of prolonged anti-psychotic medication exposure, or both' (p. 246). Robinson *et al*. (1999*b*) found no significant relationship between time to remission of an initial episode and likelihood of relapse, although others have (e.g. Breier *et al*. 1991).

The failure to find a relationship between DUP and likelihood of relapse is not necessarily inconsistent with degree of past experience of psychosis having an influence on future course. If the duration of past psychosis has a cumulative effect on likelihood of future psychosis regardless of whether the individual is in treatment while

experiencing the psychotic symptoms, then we might well expect the predictive power of initial DUP to weaken over time. Time to remission after initiation of treatment, presence of residual psychotic symptoms, and subsequent episodes of florid psychosis would have cumulative effects and DUP would become only one part of the pool of factors contributing to past experience of psychosis. Consistent with this possibility are findings by Szymanski *et al.* (1996) that length of time since initial onset of psychosis was equally predictive of reduction in positive symptoms in both neuroleptic naive first-episode patients and chronic patients who had gone through a washout period and Scully *et al.* (1997) who found duration of antipsychotic free periods after initiation of treatment was predictive of subsequent negative symptoms and mental status in long-term patients. Studies that more directly assess cumulative exposure to psychosis and its relationship to long-term outcomes would be valuable.

A third possibility is that any potential influence of DUP on likelihood of relapse is being masked by other more powerful predictors of relapse such as medication compliance, patterns of substance use, nature of the treatment provided or environmental stress. Such factors are likely to be less variable in patients upon entry into acute treatment protocols (particularly involving in-patient hospitalization) than during long-term follow-up.

Finally, before concluding that DUP is unrelated to long-term outcomes, there should be more thorough investigation using indices of outcome other than relapse into psychotic symptoms (McGlashan, 1996). Many studies have shown that patterns of change over time in positive symptoms, negative symptoms and community functioning are not parallel (Loebel *et al.* 1992; Tohen *et al.* 1992; Gupta *et al.* 1997; Birchwood *et al.* 1998). Of particular relevance to the 'toxic effects' hypothesis, are findings that compromised neurocognitive functioning is generally more strongly related to level of negative symptoms than to psychotic symptoms (Bilder *et al.* 1985; Shtasel *et al.* 1992; Censitis *et al.* 1997; Norman *et al.* 1997). Might DUP be found to be more strongly related to levels of negative symptoms, cognitive disorganization and/or community functioning than to psychotic relapse in the long-term? Support for this possibility can be found in the retrospective studies of Waddington *et al.* 1995, Scully *et al.* (1997) and Haas *et al.* (1998). In each of these retrospective reports subsequent indices of negative symptoms are found to be related to DUP. Only two prospective studies of DUP have examined relationships of DUP to negative symptoms at follow-ups of one year or greater. McGorry *et al.* (1996) found DUP to predict scores on the SANS, GAF, total BPRS and a measure deficit symptoms at 12 month follow-up. Craig *et al.* (2000) found no relation between DUP and negative symptoms at 2 year follow-up. While not consistent, the overall pattern of findings suggest the need to expand the range of long-term outcomes that are assessed.

If the future yields additional evidence of DUP being more strongly related to initial treatment response, but not likelihood of relapse, there are several possible explanations as noted above, including the masking effects of other variables, the importance of cumulative indices of experienced psychosis, and/or neurotoxic effects being displayed in outcomes other than likelihood of or time to relapse. If any clinical effects of duration of psychosis weaken over time, this could also imply the operation of a mechanism that gradually serves to restore homeostasis, which has been disturbed by psychosis rather than a permanent effect on brain functioning.

The nature and permanence of any effects of DUP on brain function is an important issue best addressed through studies examining its relationship to indices based on brain imaging and/or neurocognitive functioning. In one study of relevance, Madsen *et al.* (1999) have reported a relationship between DUP and CT measures of frontal sucal enlargement at first admission.

IMPLICATIONS FOR EARLY INTERVENTION

There are two primary reasons for favouring earlier detection and intervention for psychotic disorders. This first is immediate reduction in unnecessary suffering. While there will undoubtedly be much debate about appropriate symptom severity and duration thresholds for administering such treatment and the possible risks of inappropriate diagnosis and treatment (e.g. Bjorklund, 1998), as Table 1 attests, large

numbers of individuals are unnecessarily suffering for prolonged periods of time because of lengthy delays between onset of psychosis and initiation of treatment.

A second reason for favouring early intervention is the possibility that it will improve long-term outcome. If DUP does influence the course of psychosis, by intervening earlier, we may be able to improve long-term outcome beyond the level that would be accomplished by comparable interventions initiated later (McGlashan & Johannessen, 1996; McGorry *et al*. 1996; Birchwood *et al*. 1997; DeQuardo, 1998). The challenges of implementing and evaluating such early intervention programmes are considerable (Falloon *et al*. 1996; McGorry *et al*. 1996; Malla *et al*. 1999) and it is too early to tell what, if any, long-term benefits earlier intervention will yield. Data concerning such benefits will have to come from historical control designs (McGorry *et al*. 1996) or comparisons between geographical areas that differ in their ability to detect cases early (see Johannessen, 1998; McGlashan, 1999). Among other concerns, it is important to ensure that any apparent benefits in outcome are not illusory – for instance, a reflection of differences in the types or severity of patients being seen or the nature of the treatment being provided (McGorry *et al*. 1996; McGlashan, 1999). In addition, we should not focus narrowly on the effects of earlier intervention on resolution of psychosis or likelihood of psychotic relapse, but also examine effects on negative symptoms, cognitive functioning, community living, and risk of co-morbid psychiatric conditions or suicide.

Early detection and intervention programmes represent an extremely important innovation in the treatment of psychosis. There are many reasons for optimism about their benefits for patients, families and society as a whole, but careful, comprehensive and balanced appraisal of their benefits is not yet possible. There are several routes by which such programmes could bring about true improvement in outcome. It is possible that the resources provided by such programmes could effect the quality of treatment provided and the enthusiasm and optimism with which it is delivered in addition to the rapidity of its delivery. Shorter duration of psychosis and/or other symptoms might reduce likelihood of feeling of personally engulfed by the illness and lessen damage to self-esteem, family relations and other social supports (Crow *et al*. 1986; Erickson *et al*. 1989, 1998; Aguilar *et al*. 1997). Such factors has been found to predict outcome in other disorders, but have not been widely investigated with reference to psychosis. Given biological and social disadvantages potentially associated with longer DUP, great importance should be attached to more thorough investigations of this variable, its correlates and the extent to which it does mediate any advantages of earlier intervention.

Preparation of this paper was partly supported by an operating grant from the Medical Research Council of Canada to both authors and a Senior Research Fellowship in Mental Health Services Research from the Ontario Mental Health Foundation to Dr Malla.

NOTES

[1] There is the potential for confusion between DUI and DUP, particularly given that some studies use the term 'duration of illness' to refer to DUP (e.g. Szymanski *et al*. 1996) and some studies (e.g. Crow *et al*. 1986) are occasionally cited by others as investigating DUP when they actually assess DUI.

[2] Several studies that elsewhere have been cited as addressing issues related to DUP, upon close inspection appear to be assessing time from onset of any psychiatric symptoms or behavioural anomalies, rather than psychosis in particular. These reports are not included in Table 1 (Lo & Lo, 1977; Crow *et al*. 1986; Rabiner *et al*. 1986). Beiser *et al*. (1993) although cited by Larsen *et al*. (1996) as reflecting on DUP was not included as it assessed time between onset of psychotic symptoms and initiation of treatment seeking by patient, family, etc., rather than initiation of treatment.

[3] In his review Wyatt (1991) included such studies in a category referred to as 'early intervention'. The three such studies reviewed at that time (Aritome, 1978; Crow *et al*. 1986; Anzai *et al*. 1988) will not be included here because they appear to have been assessing length of time from onset of any symptoms of psychiatric illness rather than focusing specifically on onset of psychosis.

[4] The significance level associated with the relationship of DUP to likelihood of remission is the same (0·03) in both Loebel *et al*. (1992, p.

1186) and Robinson *et al*. (1999*a*, p. 547). The differences in conclusions in the two papers appear to reflect willingness to reject the null hypothesis on the basis of that *P* value.

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