Duration of Untreated Psychosis and Clinical Outcome 1 Year after First-episode Psychosis

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Abstract

Objective: The effectiveness of early intervention for patients with first-episode psychosis is uncertain. This study aimed to explore the association of duration of untreated psychosis and short-term clinical outcome.

Patients and Methods: Ninety four patients receiving treatment from an early intervention programme in Hong Kong (the Early Assessment Service for Young People with First-episode Psychosis) were retrospectively assessed using a standardised survey to examine the relationship between duration of untreated psychosis and 1-year outcome variables such as treatment adherence, time to treatment response, and academic and occupational functioning.

Results: Patients with a shorter duration of untreated psychosis had better treatment adherence and responded to treatment more quickly than patients with a longer duration of untreated psychosis. However, patients with a shorter duration of untreated psychosis were more likely to be admitted to hospital during their first psychotic episode. Duration of untreated psychosis was not related to the level of occupational functioning and the risk for relapse after stabilisation of first-episode psychosis.

Conclusions: These findings suggest that patients with a shorter duration of untreated psychosis tend to present more acutely, yet have a faster rate of recovery, than patients with a longer duration of untreated psychosis. Duration of untreated psychosis has a significant effect on treatment adherence in the initial recovery phase. However, further studies are required to evaluate the relationship between duration of untreated psychosis and long-term outcome, as well as the impact of duration of untreated psychosis on the subsequent utilisation of health services.

Key words: *Hong Kong, Psychotic disorders, Treatment outcome*

Introduction

Patients with psychosis tend to present for medical treatment a substantial time after the onset of symptoms. This delay may be influenced by a number of factors, some of which cannot be altered (e.g., a patient's sex) and some of which can. Studies have demonstrated that a delay to initial treatment of first-episode psychosis (FEP) plays a critical role in influencing the outcome of psychotic disorders.[1-9] This period of delay is referred to as the duration of untreated psychosis (DUP) and is usually extremely long. Studies from the USA, Canada, and Europe have consistently reported a mean DUP of 1 to 2 years.[10]

Several studies[1-4,6-8] have shown a significant relationship between DUP and several domains of outcome, while others[5,11] have failed to demonstrate this, especially when addressing long-term outcomes. One study reported that 83.7% of patients with a short DUP (<22 weeks) were in remission at the end of the first year compared with patients with a longer DUP (≥22 weeks; 65.7%).[1] Patients with a shorter DUP achieved a higher rate and level of remission after the first year, even after results were controlled for onset age, length of prodromal period, diagnosis, and sex.

The extent to which DUP affects the outcome of patients with psychosis remains controversial. This study contributes

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to the debate by examining whether a relationship exists between DUP and treatment outcome for patients with FEP in Hong Kong. This study evaluated patients with FEP who presented to the Early Assessment Service for Young People with First-episode Psychosis (EASY) programme in Hong Kong, and determined whether DUP is related to outcomes such as relapse rates and treatment adherence.

Patients and Methods

Patients

The study recruited patients with psychotic disorders who had received the initial diagnosis more than 1 year previously. The study period ranged from 1 July 2001 to 31 December 2002. Patients who defaulted follow-up were also included, as non-engagement was a possible outcome. Patients with psychoses aged from 15 to 25 years from a catchment population of approximately 1.5 million (Hong Kong Island, Kwun Tong, and the outlying islands) were assessed by the EASY programme. The diagnosis was made according to the *International Statistical Classification of Diseases and Related Health Problems-10*,[12] and was based on interviews with patients and their relatives. Case records with incomplete data from the first 6 months after stabilisation of patients with FEP were excluded. Patients with an organic disorder causing psychosis (including those with primary substance-induced disorders), or with accompanying severe mental retardation were excluded from the study. Ninety four patients met the inclusion criteria and were enrolled in the study.

Treatment Setting

All patients included in the study attended the EASY programme. The EASY programme caters for young people aged from 15 to 25 years who are experiencing FEP, and provides a 2-year follow-up service. The multidisciplinary approach involves both medical and social support. Treatment is tailored-made for each patient, and includes family education to establish closer relationships between patients and their families.

Survey Instrument

Retrospective case note review of patients with FEP enrolled in the EASY programme was done by 10 medical students. Inter-rater reliability was conducted on 10 separate case notes using κ agreement. The information collected included patients' demographic data, treatment adherence, episode relapse, self-harm behaviour, academic and occupational functioning, treatment history, and mental health service utilisation. Average agreement of the instrument was 0.83. In particular, the κ agreements for treatment adherence, episode relapse, self-harm behaviour, and academic and occupational functioning were 0.81, 0.79, 0.98, and 0.88, respectively.

Demographic information, including migration status; presence of any comorbidities such as affective disorder substance abuse and personality disorders; smoking status; and body weight and height, was recorded. The DUP was defined as the number of days from when the psychotic symptoms first appeared to the date that treatment was given.

The study also investigated several important outcome measures. The types of medication given during FEPs and after recovery were recorded, along with the efficacy (in terms of positive and negative symptoms), side effects, and adherence. Additionally, the occurrence of risk-related behaviour, including suicide attempt, deliberate self-harm, violence, and law-breaking behaviour, was recorded within each of the 3 periods of pre-DUP (PDUP), DUP, and the first year after recovery. Whether these risk-related behaviours were associated with a genuine intention of death was also explored; this aspect was checked by examining key words in the case notes. The cause, nature, and consequence of these behaviours were also recorded. Academic and occupational functioning was assessed during the 3 periods. The functional status was grouped into 5 categories of inpatient, rehabilitation, unemployed, part-time employment, and full-time employment.

The short-term outcomes of the patients were operationally defined as follows:

- time to treatment response (TTR) was calculated from the time when treatment was first given to the time when the psychotic symptoms were stabilised
- treatment adherence after recovery was categorised as good (regularly taking oral or depot medication) or poor (missing prescribed medication >5 times per month)
- episode relapse was defined as the need for a change of medication to control a significant increase in positive symptoms. The pre- and postepisodic symptoms (divided into active, partial, and symptom-free), life events occurring 6 months before relapse, and need for admission to hospital for such an episode were recorded.

Data Analysis

Data were analysed using the Statistical Package for the Social Sciences. Descriptive statistics were used to describe the demographic data and clinical profile of the study group. Mann-Whitney *U* and *t* tests were used to analyse the data, depending on the distribution of the data. The Chi squared test was also used to analyse the categorical data. Finally, correlation analysis was used to explore any relationship between DUP and other clinical data. The DUP was further divided into 3 DUP groups of 0 to 90 days, 91 to 180 days, and more than 180 days. A DUP of more than 180 days is usually considered long.[1,4,5,10,11] These ranges were applied to subsequent analysis of DUP with other clinical outcomes.

Results

Patients' Characteristics

The case notes of 94 patients were reviewed, including those of patients who defaulted follow-up. There were 45 men (48%) and 49 women (52%). The mean age was 21.0 years (SD, 3.5 years). The majority of patients (76%) were born in Hong Kong. For those who were born overseas,

the mean duration of residency in Hong Kong was 12.0 years (SD, 7.0 years). Twenty six patients (27.7%) had schizophrenia, 41 (43.6%) had unspecified psychosis, 11 (11.8%) had acute and transient psychotic disorder, 1 (1.1%) had schizoaffective disorder, 11 (11.8%) had affective disorder, 2 (2.1%) had delusional disorder, and 2 (2.1%) had mental and behavioural disorder due to the use of stimulants. The mean DUP was 240.0 days (SD, 283.1 days; median, 90.0 days; range, 1 to 1100 days), and the mean TTR was 87.0 days (SD, 91.6 days; median, 54 days; range 3 to 365 days).

Clinical Profile

Fifty one patients (54%) required admission to hospital for treatment of FEP. Fifty nine patients (63%) had good treatment adherence during the first year after stabilisation. Twenty patients (21%) had 1 episode of relapse in the first year after stabilisation; half of these patients required admission to hospital. Only 1 patient had a second relapse during the first year.

Medical Therapy

The medications prescribed were classified into 4 categories: typical antipsychotic agents; atypical antipsychotic agents (including risperidone, olanzapine, quetiapine, and amisulpride); clozapine; and adjunctive medications such as antidepressant agents. At the start of the first episode, 81 patients (86%) were given typical antipsychotic agents, 3 (3%) were given atypical antipsychotic agents, no patients were given clozapine, and 10 (11%) were given only adjunctive medication. During the remission period, 71 patients (76%) were given typical antipsychotic agents, 20 patients (21%) were given atypical antipsychotic agents, no patients were given clozapine, and 3 patients (4%) were given adjunctive medication.

Academic and Occupational Functioning

The different occupations of the patients are shown in Table 1. Most patients were employed during the PDUP period. Nevertheless, there was a general decline in academic and occupational functioning across the 3 time intervals. In particular, nearly 50% of students dropped out of school between the PDUP and the end of the first year after recovery.

Relationship of Duration of Untreated Psychosis to Demographic and Clinical Data

Forty nine patients (52%) had a DUP of 0 to 90 days, 11 (12%) had a DUP of 91 to 180 days, and 34 (36%) had a DUP of more than 180 days. These ranges were applied to subsequent analysis of DUP for other clinical outcomes.

Both Pearson's correlation coefficient and Spearman's correlation coefficient were used to analyse the relationship between DUP and different age groups. No significant associations were found among these variables. DUP was also not significantly associated with sex and migration (using both parametric *t* test and non-parametric Mann Whitney *U* test). DUP did not have a significant overall effect on violence or law-breaking behaviour, and there was no significant association between DUP and suicide attempt.

Table 1. Academic and occupational functioning of patients attending the Early Assessment Service for Young People with First-episode Psychosis programme during the 3 periods of pre-duration of untreated psychosis (PDUP), duration of untreated psychosis (DUP), and the first year after recovery.

	PDUP (%)	DUP (%)	1 Year (%)
Skilled industrial worker	2 (2.1)	1 (1.1)	1 (1.1)
Unskilled office worker	2 (2.1)	5 (5.3)	4 (4.3)
Skilled office or administrative worker	6 (6.4)	4 (4.3)	2 (2.1)
Unskilled worker in service or business	15 (16.0)	10 (10.6)	20 (21.3)
Trained worker in service or business	4 (4.3)	1 (1.1)	2 (2.1)
Employed or independent academic or administrator	3 (3.2)	2 (2.1)	2 (2.1)
Housewife	1 (1.1)	1 (1.1)	2 (2.1)
Unemployed	12 (12.8)	32 (34.0)	21 (22.3)
Active student	45 (47.9)	33 (35.1)	27 (28.7)
Other	4 (4.3)	4 (4.3)	4 (4.3)
Total	94 (100.2)	93 (99.0)*	85 (90.4)†

* *One patient missing data.*
† *Nine patients missing data.*

Relationship of Duration of Untreated Psychosis to Time to Clinical Response

The variable TTR was also divided into 3 groups of 1 to 60 days, 61 to 120 days, and more than 120 days. Forty four patients (46%) took 1 to 60 days to respond to treatment, 29 (30%) took 61 to 120 days, and 19 (20%) took more than 120 days. Two patients were missing data for TTR. There were significant differences between the different ranges of DUP and TTR (χ^2[4], 13.988; p = 0.009) [Table 2]. Shorter DUP was associated with a shorter time to clinical response.

Table 2. Relationship between duration of untreated psychosis (DUP) and time to treatment response.

DUP (days)	Time to treatment response (days)			Total*
	1-60	61-120	≥121	
0-90	31	9	8	48
91-180	5	4	2	11
≥181	8	16	9	33
Total	44	29	19	92

* *Two patients missing data.*

Relationship of Duration of Untreated Psychosis to Treatment Adherence

Chi squared test indicated a significant difference for DUP and treatment adherence during the first year after stabilisation of disease (χ^2[2], 10.653; p = 0.005); a long DUP was associated with poor treatment adherence. Only 14 of 34 patients (41%) with a DUP of more than 180 days, 37 of 49 patients (76%) with a DUP of 0 to 90 days, and 8 of 11 patients (73%) with a DUP of 91 to 180 days had good treatment adherence.

Relationship of Duration of Untreated Psychosis to Need for Inpatient Management

Short DUP was significantly associated with inpatient management during FEP (χ^2[4], 14.265; p = 0.006). A greater proportion of patients with a DUP lasting 0 to 90 days (60%) required hospital admission when compared with patients who had a DUP lasting 91 to 180 days (10%) and more than 180 days (29%).

Risk-related Behaviour

Before treatment, 8 patients (8%) had attempted suicide with intent to die, 5 (5%) attempted suicide without intent to die, 4 (4%) had violent behaviour, and 2 (2%) had law-breaking behaviour.

In the year following stabilisation, 4 patients (4%) attempted suicide with intent to die, 5 (5%) attempted suicide without intent to die, 5 (5%) had violent behaviour, and 3 (3%) had law-breaking behaviour. Only 2 patients committed risk-related behaviour both before and after treatment. Therefore, there seems to be no association between risk-related behaviours and DUP.

Discussion

The findings of this study suggest that DUP has predictive value for certain outcomes of patients with FEP who are in the initial recovery phase. Patients with shorter DUP had greater need for inpatient treatment at first presentation. Many factors may hinder disease recognition for patients with long DUP and therefore their presentation to a physician. Firstly, the disease progression may be subtle and some of the symptoms may not be easily recognised by patients. Secondly, these patients may have already lost insight throughout the long duration of disease due to lack of appropriate treatment. Thirdly, social pressure from family members may increase the reluctance of patients to visit a physician unless the symptoms worsen. A recent study of the exploration of the pathway to care among a group of patients with FEP indicates that the main reasons for a delay in seeking help from psychiatrists are lack of knowledge about psychosis; belief that a doctor cannot help the patient; changes not considered to be related to mental illness; and lack of knowledge about how to seek help.[13] These reasons may contribute to the long DUP of some patients in the present study. Previous studies have shown an association between long DUP with an insidious onset of symptoms and early onset of poor global functional status.[14] A prospective study by Sipos et al illustrated the risk factors thought to affect admission to hospital, whereby negative symptoms (odds ratio [OR], 0.29; 95% confidence interval [CI], 0.12-0.68) and duration of untreated illness of more than 6 months (OR, 0.32; 95% CI, 0.16-0.63) were associated with a reduced likelihood of rapid admission.[15] This study revealed similar findings, in that a short DUP was related to a higher rate of hospital admission.

In addition, this study examined the effect of DUP on TTR. Sixty nine percent of patients with DUP of 0 to 90 days responded to treatment within the first 60 days, suggesting rapid recovery within the group of patients with short DUP. These results support the findings of others, in that a short DUP has a higher rate of remission.[1] One possible reason for this result is that patients with a short DUP would have incurred less established brain damage during their DUP; therefore, the damage is potentially reversible and recovery would be quicker.

A study by Amminger et al suggested that a long DUP is associated with certain cognitive deterioration in patients with FEP.[16] Areas that were most affected by DUP included visual motor function, processing speed and, most importantly, social cognition. Deterioration in these cognitive functions might affect patients' motivation to cooperate with doctors, delaying their responses to treatment. Another equally plausible explanation may be that the 'type' of psychosis that presents early responds better to treatment than psychosis that presents late. However, the present findings could not provide results to support either explanation. Nevertheless, these preliminary findings do have important implications for future approaches to the treatment of patients with schizophrenia.

In this study, DUP was correlated with treatment adherence, although other studies have shown otherwise. Comparison of DUP in different ranges with treatment adherence indicated that long DUP was correlated with poor treatment adherence. This phenomenon may be explained by the effect of psychosis on the patient at various stages of presentation. Patients with a short DUP tended to present acutely with more severe symptoms, thus encouraging them to actively seek treatment for relief of symptoms. The insidious onset of presentation for those with a long DUP allowed time for patients to adapt to the symptoms. As a result, various factors such as the side effects of medication would outweigh the benefits of taking the antipsychotic drugs in the patients' minds. In addition, the loss of insight and more severe negative symptoms associated with long DUP might reduce compliance with medication. This is consistent with findings of Heydebrand et al,[17] who suggested that the severity of negative symptoms in patients with psychosis is associated with neuropsychological deficits, including executive function. Such deterioration in cognitive function might affect patients' ability to adhere to medication. Early intervention would improve adherence to medication.[18] However, DUP may be only one of many factors that predict the adherent behaviour of patients, as

this may be a multi-factorial phenomenon. Factors such as age, sex, cognitive function, and social behaviour may require further investigation to ascertain their effects on adherence to medication.[1]

Functional outcome, in terms of months in full-time employment, was assessed in this study using a 12-month scale. DUP and academic and occupational functioning were not correlated in this study, although some studies have shown that long DUP may correlate with a poor outcome.[12,] This factor may be explained by numerous factors other than DUP alone, including the severity of illness, age, education level, and economic situation. Moreover, many patients were students and their academic performance was not assessed in this study. Some patients dropped out of school after recovery from FEP. This factor made academic and occupational functioning a less favourable factor in terms of accuracy of determining a patient's functional level. The use of patients' social relations, daily life activities,[2] or the Global Assessment of Functioning Scale[18] may be better tests for determining patient's functional outcome with respect to DUP.

Finally, this study did not find any significant relationship between DUP and the number of relapses of psychosis. This negative finding concurs with a review by Malla et al, which concluded that DUP may be related to ease of reducing psychotic symptoms once treatment begins for FEP, but there was no evidence of a relationship to likelihood of relapse.[10] A study by Carbone et al found that early intervention could prevent relapse only in the phase of active intervention, but not in the following period.[4] Therefore, continuity of care is crucial for the long-term treatment of patients with FEP.

A limitation of this study was the data collection method for the analysis of DUP. Data relating to the factors that determine DUP were estimated retrospectively.

Another limitation was that only the effect of DUP on outcome measures for FEP was studied. Therefore, other confounding variables that would have an impact on the outcome could not be ruled out. However, these results suggest that DUP is an important predictor of certain outcome measures in patients with FEP and highlight the importance of early diagnosis and treatment of schizophrenia.

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