ORIGINAL ARTICLE

# Duration of untreated psychosis and it's effect on the symptomatic recovery in schizophrenia – Preliminary results

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## Abstract

**OBJECTIVES:** A long duration of untreated psychosis (DUP) is known to be associated with a poorer prognosis and with worse symptomatic and functional outcome. The aim of the study was to test the hypothesis that early detection and treatment with antipsychotics in the prodromal phase of the illness improves the outcome; to compare short and long-term outcome in patients with DUP longer than 1 year (group 1) with patients that were treated already in the prodromal phase of the disease (group 0).

**DESIGN AND SETTING:** Eighty-seven patients with schizophrenia were included to the retrospective study, 37 patients to group 0 and 50 patients to group 1. The course and outcome of the disease was studied in the two groups. The severity of schizophrenia was evaluated by measuring several outcome parameters. The symptom severity was evaluated using a check list developed from CAARMS inventory; the average daily dose of antipsychotics was calculated as well as the number and duration of hospital admissions. Groups were compared during the acute psychosis of first episode (t1) and at the conclusion of the study (t2).

**RESULTS:** More symptoms of greater intensity were present during the first and second evaluations in group 1 as compared to group 0 patients. The patients in group 0 needed lower dosages of antipsychotics even several years after treatment had been initiated. This effect persisted until the final evaluation; 11% were without antipsychotics at the conclusion of the study. Patients in group 1 were hospitalized more frequently; they needed more hospitalizations and these were of longer duration. Only 38% of patients in group 0 were treated in the hospital, 27% were hospitalized only once.

**CONCLUSIONS:** Better outcome can be achieved with early antipsychotic treatment. Patients with long DUP differ from patients who were treated already in the prodromal phase in several outcome measures.

**Abbreviations:**
DUP – duration of untreated psychosis
CAARMS – comprehensive assessment of at risk mental states
ICD-10 – International Classification of Diseases – 10th Edition
LPP – Ljubljana prodrome project
cpu – chlorpromazine units

## INTRODUCTION

Schizophrenia is a complex mental disorder that often begins in adolescence or early adulthood and can cause significant changes in behaviour, perception and cognition, with resulting impairments in multiple functional domains.

The illness course is variable. Many predictors of outcome have been identified (Hafner *et al*. 1998, Andreasen & Black, 2001). Delay in treatment, expressed as duration of untreated psychosis (DUP) and assessed as the time of onset of psychotic symptoms to the time of adequate antipsychotic treatment, has been investigated very extensively in studies of first episode psychosis as one of the predictors of illness outcome. Longer DUP is associated with poorer prognosis and with significant psychosocial impairment (Harrigan *et al*. 2003), more frequent and longer hospitalizations (Helgason, 1990), slower and less complete recovery, and more frequent relapses (Crow *et al*. 1986). There is also some suggestion that untreated psychosis may be neurotoxic, and that could be prevented by early treatment (Lieberman & Fenton, 2000). Many studies have examined the relationship of DUP with psychopathology. The most consistent finding is a significant relationship between longer DUP and a higher level of negative and deficit symptoms (McGlashan 1999, Perkins *et al*. 2005). However, there are only few studies that were designed specifically to examine outcome on employment or other functional domains (Malla & Payne 2005).

Our project, known as the 'Ljubljana Prodrome Project' [LPP] has functioned in Slovenia for several years. It practices early detection and treatment with psychotropic medications and psychosocial interventions of patients in the early, or prodromal, phase of psychotic illness. Since many of its patients have been followed up for several years, this service provides a unique opportunity to compare the outcomes in patients who were treated with antipsychotic medication very early in the development of the illness with the outcomes in patients who presented in the usual way, with long durations of untreated psychosis.

The aim of our study was to test the importance of DUP for long-term course and severity of schizophrenia; to test the hypothesis that early treatment in the prodromal phase of the illness with antipsychotics improves the outcome; to compare short and long-term outcome in patients with DUP longer than 1 year (group 1) with patients that were treated already in the prodromal phase of the disease (group 0). In this paper we present our results concerning symptom severity, the average daily dose of prescribed antipsychotics and the number and duration of hospital admissions. Results concerning functional domains of education, employment and marital status will be presented at later time.

## SUBJECTS AND METHODS

Eighty-seven patients with first-episode schizophrenia were included to the retrospective study. 37 patients that comprised group 0 (15 male, 22 female) were all patients who had been identified clinically within the Ljubljana Prodrome Project as having early positive and/or negative psychotic symptoms. Despite antipsychotic treatment during the prodrome, conversion to full psychosis occurred (DUP = 0). They had an average age of 38 years (range 22–56). 50 patients (26 male, 24 female) with DUP longer than 1 year (average DUP 46.5 months, range 14–240 months) comprised group 1 with average age of 41 years (range 26–63 years).

Clinical criteria for schizophrenia were met according to International Classification of Diseases – 10th Edition (ICD-10). Exclusion criteria were neurological diseases, alcohol or other substance dependence and affective disorders. All subjects were treated at University Psychiatric Hospital in Ljubljana, Slovenia.

The course and outcome of the disease were studied in the two groups. The severity of schizophrenia was evaluated by measuring several clinical and paraclinical parameters. The symptom severity was evaluated using a check list developed from CAARMS inventory (Yung *et al*. 2002); the average daily dose of antipsychotics was calculated as well as the number and duration of hospital admissions; sociodemographic parameters evaluated included educational level achieved, employment and marital status.

Groups were compared during the acute psychosis of first psychotic episode (t1) and at the conclusion of the study (t2). All the data was gathered from hospital and outpatients´ clinic records.

Analyses were made with the statistical package SPSS (version 13.0). The applied methods are $\chi 2$ test and Mann-Whitney U test for group comparisons.

The Republic of Slovenia Research and Ethics Committee in Ljubljana approved the research protocol on 15th November 2005 (nr. 82/11/05).

## RESULTS

Results concerning symptom severity, the average daily dose of prescribed antipsychotics and the number and duration of hospital admissions are presented in this paper.

Symptom severity score was higher in group 1 patients as compared to group 0 patients at t1 (first acute psychotic episode) in all clusters of CAARMS inventory except in negative symptoms, physical symptoms and in general psychopathology score (Table 1).

**Table 1. Average symptom severity score at t1**

| | Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | **0** (DUP = 0) N=37 | | | **I** (DUP > 1 year) N=50 | | | |
| | $\bar{x}$ | **st.d.** | **range** | $\bar{x}$ | **st.d.** | **range** | **F / df /** p |
| Non-Bizarre Ideas | 3.86 | 1.88 | 0–8 | 8.04 | 2.30 | 2–12 | 81.15 / 1 / **0.000**** |
| Bizarre ideas | 1.18 | 1.83 | 0–6 | 4.10 | 2.76 | 0–10 | 30.86 / 1 / **0.000**** |
| Perceptual abnormalities | 2.48 | 1.40 | 0–5 | 3.84 | 1.93 | 0–10 | 12.45 / 1 / **0.001**** |
| Disorganised speech | 0.24 | 0.59 | 0–2 | 1.06 | 0.79 | 0–2 | 27.63 / 1 / **0.000**** |
| Cognitive symptoms | 3.13 | 1.94 | 0–7 | 6.54 | 2.36 | 1–10 | 51.01 / 1 / **0.000**** |
| Affect | 1.56 | 1.28 | 0–4 | 3.58 | 1.19 | 1–6 | 56.63 / 1 / **0.000**** |
| Negative symptoms | 1.18 | 1.37 | 0–4 | 1.28 | 1.64 | 0–4 | 0.075 / 1 / 0.785 |
| Behavioural changes | 3.08 | 1.87 | 0–6 | 5.48 | 1.41 | 2–8 | 46.18 / 1 / **0.000**** |
| Physical changes | 1.29 | 0.74 | 0–2 | 1.22 | 0.81 | 0–2 | 0.21 / 1 / 0.651 |
| General psychopathology | 2.75 | 1.38 | 0–6 | 2.84 | 1.58 | 0–7 | 0.06 / 1 / 0.799 |

* p < 0,05; ** p < 0,01;

**Table 2. Average symptom severity score at t2**

| | Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | **0** (DUP = 0) N=37 | | | **I** (DUP > 1 year) N=50 | | | |
| | $\bar{x}$ | **st.d.** | **range** | $\bar{x}$ | **st.d.** | **range** | **F / df / p** |
| Non-Bizarre Ideas | 0.86 | 1.53 | 0–7 | 3.98 | 2.42 | 0–10 | 46.98 / 1 / **0.000**** |
| Bizarre Ideas | 0.37 | 0.92 | 0–4 | 1.12 | 1.75 | 0–8 | 5.46 / 1 / **0.022*** |
| Perceptual abnormalities | 0.54 | 0.93 | 0–4 | 1.68 | 1.58 | 0–6 | 15.23 / 1 / **0.000**** |
| Disorganised speech | 0.05 | 0.22 | 0–1 | 0.20 | 0.45 | 0–2 | 3.24 / 1 / 0.076 |
| Cognitive symptoms | 0.86 | 1.60 | 0–8 | 3.78 | 2.03 | 0–10 | 52.08 / 1 / **0.000**** |
| Affect | 0.32 | 0.58 | 0–2 | 2.96 | 1.69 | 0–6 | 82.59 / 1 / **0.000**** |
| Negative symptoms | 0.43 | 0.76 | 0–2 | 2.10 | 1.65 | 0–4 | 32.30 / 1 / **0.000**** |
| Behavioural changes | 0.89 | 1.35 | 0–6 | 4.34 | 1.91 | 0–7 | 87.79 / 1 / **0.000**** |
| Physical changes | 0.32 | 0.53 | 0–2 | 0.84 | 0.68 | 0–2 | 14.64 / 1 / **0.000**** |
| General psychopathology | 1.40 | 1.09 | 0–5 | 2.64 | 1.63 | 0–7 | 15.79 / 1 / **0.000**** |

* p < 0,05; ** p < 0,01;

At t2 (conclusion of the study) more symptoms of greater intensity were present in group 1 patients with DUP longer than 1 year as compared to group 0 patients who were treated in the prodromal phase. Except for the category of disorganised speech, differences were all statistically significant (Table 2).

Patients in group 0 were treated with antipsychotic drugs very early in the development of psychosis, in the prodrome phase of the illness. 10/37 (27%) patients were treated with typical antipsychotic and 27/37 (73%) with atypical antipsychotic. The average daily dose for prescribed antipsychotics was 118 chlorpromazine units (cpu), st.d. 58.17, range 50–334 cpu.

Patients in group 0 needed lower daily dosages to achieve remission at t1 (first acute psychotic episode) as compared to group 1 patients (Mann-Whitney U = 280,00, z = –3,69, $p$ = 0,000). The average daily dose for prescribed antipsychotics in group 0 was 334 cpu, st.d. 211.89, range 75–750 cpu. The average dose in group 1 was 750 cpu, st.d. 436.56, range 67–2250.

Also at t2 (conclusion of the study) statistically significant difference between the groups was noted concerning average daily dosage of antipsychotic drugs (Mann-Whitney U = 320,00, z = –3,17, $p$ = 0,002). Group 0 patients were prescribed lower dosages of antipsychotic drugs (average daily dose 200 cpu, st.d.149,75, range 0–668 cpu) and 4/37 (11%) were

**Table 3.** Average number of hospital admissions and hospital days

| Time of illness duration (years) | Group | | | | | |
|---|---|---|---|---|---|---|
| | **0** (DUP=0) N=37 | | | **I** (DUP>1 year) N=50 | | |
| | Number of patients | Average number of hospital admissions | Average number of hospital days | Number of patients | Average number of hospital admissions | Average number of hospital days |
| ≤ 5 | 16 | 0.4 | 5.8 | 10 | 1.6 | 85.3 |
| 6–10 | 15 | 1.8 | 37.5 | 13 | 2.6 | 228.7 |
| ≥11 | 6 | 0.3 | 34.8 | 27 | 9.7 | 630.9 |

without any antipsychotic drug as compared to group 1 patients (average daily dose 571, st.d. 306,71, range 50–1667 cpu).

Patients in both groups were divided into three subgroups according to the time of illness duration (less than 5 years, 6–10 years, more than 11 years). Average number of hospital admissions and number of hospital days were calculated (Table 3). Patients in group 1 were hospitalized more frequently (Mann-Whitney U = 165,00, z = –5,26, $p$ = 0,000) as compared to group 0 patients; their hospital stay was also longer (Mann-Whitney U = 125,00, z = –5,73, $p$ = 0,000).

Only 14/37 (38%) patients in group 0 were treated in the hospital, 10/37 (27%) were hospitalized only once. In group 1, 46/50 (92%) patients were treated in the hospital.

## DISCUSSION

The findings of first-episode studies of schizophrenia suggest that the longer psychosis proceeds unchecked before treatment, the poorer the response to antipsychotic medication and the poorer the outcome in terms of symptoms and relapse (Marshall *et al.* 2005). This issue was initially controversial because some researchers failed to find the link, and other asserted on theoretical ground that the relationship between DUP and outcome was confounded by underlying illness severity, which produced both delayed treatment and also worse outcomes (McGorry *et al.* 2007). Controversial results could also arise due to differences in study designs, length of follow-up, inclusion of first episode psychosis other than schizophrenia, sample size, and reporting of treatment experience and other patient characteristics. Studies vary widely in how DUP is defined and measured, since identifying precise points when psychosis emerges and remits is conceptually ambiguous and clinically difficult (Singh, 2007). Social outcomes are underreported compared to measures of psychopathology, particularly in trials of interventions (Tulloch *et al.* 2006).

Our retrospective study is the first study to report on long term outcomes for patients who have been first treated during the prodromal phase of psychotic illness. It is important to say that prodromal symptoms are still non-specific and so far we cannot predict conversion to acute psychosis accurately. Only patients treated with antipsychotics in the prodromal phase that converted to full psychotic illness were included to the study.

In this paper we present data on symptom severity scores, the average daily dose of prescribed antipsychotics and the number and duration of hospital admissions as measures of outcome.

Our findings show that more symptoms of greater intensity were present during both evaluations in group 1 as compared to group 0 patients. Patients with DUP longer than 1 year have worse outcome regarding symptomatic recovery. This finding is in concordance with results of two meta-analyses that found small-to-moderate effect of DUP on a range of outcome variables, including symptomatic recovery (Perkins *et al.* 2005, Marshall *et al.* 2005).

The patients in group 0, who had been treated with antipsychotics in the prodromal phase, needed lower dosages of antipsychotics even several years after treatment had been initiated. This effect persisted until the final evaluation; 11% were without antipsychotics at the conclusion of the study. Patients also received psychosocial interventions. Until recently, treatment with antipsychotic drugs during the prodromal phase raised many questions regarding ethical implications. Introduction of novel antipsychotic drugs with lower side effect profile enabled few study designs that showed positive outcomes when treating early in the course of illness (McGorry *et al.* 2002, Morrison *et al.* 2004, McGlashan *et al.* 2006).

Our results show that patients in group 1 with DUP longer than 1 year had more hospital admissions and these were of longer duration, 92% of them needed hospital treatment. Only 38% of patients in group 0 were treated in the hospital, 27% were hospitalized only once. Longer DUP was associated with more frequent and longer hospitalizations and slower and less complete recovery and more frequent relapses also in some other studies (Chong *et al.* 2004, Ucok *et al.* 2006).

In conclusion, better outcome can be achieved with early antipsychotic treatment. Patients with long DUP differ from patients who were treated already in the prodromal phase in several outcome measures.

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