INFLUENCE OF DURATION OF UNTREATED PSYCHOSIS ON THE SHORT-TERM OUTCOME IN FIRST-EPISODE SCHIZOPHRENIA

BHARATHI K[1], PUGAZHENDHI K[1], BALAMURUGAN K[2], PUNITHAVATHI D[1]*

[1]Department of Psychiatry, Government Villupuram Medical College and Hospital, Villupuram, Tamil Nadu, India. [2]Department of Pediatrics, Government Villupuram Medical College and Hospital, Villupuram, Tamil Nadu, India.
*Corresponding author: Punithavathi D; Email: punithavathidhanasekaran6@gmail.com

ABSTRACT

Objectives: Schizophrenia is a devastating disease and many patients present late for treatment due to difficulty in identifying symptoms by family members. The objective of this study is to find if there is an association between a longer duration of untreated psychosis (DUP) and poor treatment outcome in first-episode Schizophrenics and to find if there is an association between premorbid social adjustment on DUP.

Methods: Anti-psychotic-naïve patients with an international classification of diseases-10 schizophrenia were evaluated 12 weeks after their first in-patient hospitalization. Association between untreated initial psychosis duration (measured from the beginning of first symptom as well as from first hospital admission) was examined by conducting the clinical interview, symptom severity by positive and negative syndrome scale, and clinical global impression scale, pre-morbid social adjustment by premorbid social adjustment (PSA) scale; and symptoms improvement after treatment by CGI-I scale.

Results: Of the 57 patients studied, 57.9% showed improvement after treatment, paranoid type was more common, patients responded better when treated with combined typical and atypical antipsychotics and improvement was better when DUP was <2 years. There was a major negative correlation between positive syndrome scores and DUP. There was no association of DUP with negative syndrome score, psychopathology score and PSA score.

Conclusion: DUP was an independent predictor of treatment outcome and early intervention is necessary for better prognosis.

Keywords: Duration of untreated psychosis, First-episode schizophrenia, Positive syndrome scale.

INTRODUCTION

Schizophrenia is a chronic, debilitating disorder characterized by disordered thinking; psychotic symptoms, and loss of function in specific cognitive functions, such as working and declarative memory [1]. This disease has a devastating effect on the individual's quality of life and prospects for employment, marriage, and parenthood. In addition to personal misfortune, schizophrenia also burdens the public health system due to loss of productivity and lifelong caregiver needs [2]. There is a poor response to treatment when there is a delay in the initiation of treatment of psychosis and an increased level of duration of untreated psychosis (DUP) [3].

Schizophrenia may be biologically toxic and long-term morbidity due to psychosis may be prevented if treatment is initiated as early as possible with anti-psychotics [4]. DUP has been reported as a self-determining marker of prognostic outcome in Schizophrenia [5]. Many individuals experiencing their first episode of psychosis will have no personal or family experience of mental illness and hence do not recognize the symptoms while some lack insight as a result of the mental illness. This results in many patients presenting in crisis to the psychiatrist. It becomes necessary to admit persons with the first episode of Schizophrenia to assess the extent of psychopathology to offer time for educating the patient and his family along with pharmacological and psychological treatment [2].

Many authors have observed a significant relationship between DUP and the prognosis of short-term psychosis: Earlier the treatment better the improvement. This is due to the factors that impede the period

between having a psychotic symptom and seeking treatment for it are the same ones that prevent treatment response [6].

DUP can be assessed by the presence of positive symptoms such as hallucinations, thought disorders, odd beliefs or delusions, the presence of negative symptoms such as depression, loss of energy, anhedonia, or loss of interest and the presence of social withdrawal, poor interpersonal kinship. This study was done to estimate the influence of DUP on the short-term outcome of Schizophrenia and to find if there is an association between premorbid social adjustment (PSA) on DUP.

METHODS

This was a prospective cohort study done at the Institute of Mental Health, Chennai, Tamil Nadu, India between July 2013 and June 2014. Patients of age 18–45 years, diagnosed with first episode and drug-naive schizophrenia, who were admitted as in-patients at the Institute of Mental Health, Chennai, Tamil Nadu, India were included in the study. Patients with other psychiatric disorders, comorbid substance abuse, substance-induced psychotic disorder, and a history of head injury, mental retardation, or epilepsy were excluded from the study. All patients were included after obtaining written informed consent. Patient's sociodemographic data was entered in semi-structured pro forma after a detailed clinical interview. The impact of schizophrenia was done using the positive and negative syndrome scale (PANSS) and improvement in outcome was assessed using the clinical global impression scale (CGI-S) while the premorbid period was done with PSA scale by interviewing the care-giver [7]. Outcome variable on CGI-I was converted into dichotomous data as unimproved (score of ≥4) and

improved (score of <3). Patients were treated by the psychiatrist in charge of the ward, based on symptom severity and he was completely blind to the study sample. Follow-up assessment was done after 12 weeks by administering PANSS and CGI-S, after confirming the drug compliance from care-givers.

Data entry and analysis were done using SPSS software version 22.0 (IBM, New York, USA). Descriptive data were given in summary statistics while statistical analysis was done using the Chi-square test, student t-test for paired samples, and Pearson's r-test for correlation. In measuring DUP, there was more chance of right skew, hence after the initial data analysis; DUP was normalized by taking the log to base 10 to allow the use of parametric tests. $p < 0.05$ was considered statistically significant.

RESULTS

In the present study to find the influence of DUP on first episode Schizophrenia, 60 consecutive patients (n=60) were screened, evaluated and enrolled in the study. Of the 60 patients, two patients were lost for follow-up and one patient was found to be HIV positive, and data of these three patients (n=3) were excluded from assessment. At the end of 12 weeks, follow-up assessment was completed for 57 patients and their caregivers.

In the present study on first episode Schizophrenic patients (n=57), the age of patients had a range between 19 years and 42 years with a mean age of 31.82±6.0 years. The disease was more common in males (75.4%) (n=43/57). About 42.1% of the patients had education up to middle school (n=24/57) followed by education up to secondary school (21.1%) (n=12/57). More than half of the patients were unmarried (54.4%) (n=31/57). Most of the patients (80.7%) were in a joint family system (n=46/57). Half of the patients in the present study were unemployed (50.9 %) (n=29/57).

Family history of Schizophrenia was present only in 26.3% of patients (n=10/57). Age of onset of the first episode in the present study was 28.46±6.0 years with a range between 17 and 38 years. The mean DUP was 3.02±3.0 years with a range between 4 months and 10 years. Almost half of the patients had a DUP of more than 2 years (47.4%) (n=27/57) while 31.6% of them had a DUP between 1 and 2 years (n=18/57). The mean duration of hospitalization was 31.30±23 days with a range between 10 days and 90 days.

The mean score of positive syndromes of PANSS was 18.67±8.0 with a range between 9 and 34. The mean score of negative syndromes of PANSS was 19.74±8.0 with a range between 7 and 39. The mean general psychopathology score was 34.21±10 days with a range between 15 and 68. The mean CGI-S score was 4.39±1.0 (range between 3 and 6) while the mean CGI-I score was 3.26±1.0 (range between 2 and 5). The mean PMSA score was 0.32 (range 0–0.8). While there was a statistically significant negative correlation between PANSS positive syndrome score and DUP (−0.324, p=0.014), there was no correlation between DUP and age at onset of illness, PANSS negative syndrome score, and general psychopathology score.

After ascertaining the baseline characteristics, all patients were admitted, treated for their symptoms, and then evaluated for improvement, again at the end of the treatment period. Of the 57 patients evaluated, 57.9% showed improvement in their symptoms at the end of 12 weeks (n=33/57). There was no difference between patients showing improvement and those not showing improvement gender-wise (p=0.948), education-wise (p=0.417), employment-wise (p=0.236), socioeconomic status-wise (p=0.999), family-type-wise (p=0.802), and family history-wise (p=0.423).

Paranoid schizophrenia was the most common type showing improvement after treatment (72.7%) (n=24/33) while undifferentiated schizophrenia was common in patients not showing improvement (41.7%) (n=10/24). Hebephrenic type did not show improvement. This difference between patients showing improvement and not showing

improvement was statistically significant (Fisher's exact test = 8.330, p=0.020) (Fig. 1).

Among the patients who showed improvement after treatment, many showed improvement within 15 days of hospital stay (42.4%) (n=14/33) while among those who were unimproved, many did not show improvement even after 30 days (33.3%) (n=8/24). However, this difference was not statistically significant (p=0.086). There was no statistically significant difference in premorbid functioning (PSA score) between patients showing improvement and those not showing improvement (t=1.654, p=0.104).

Among patients who showed improvement, most of them showed improvement with use of combined typical and atypical anti-psychotics (84.8%) (n=28/33) while many of the patients who did not show improvement had received only typical anti-psychotics (79.2%) (n=19/24). This improvement with combined anti-psychotics was statistically significant (Pearson Chi-square=82.22, p=0.0001) (Fig. 2). In patients who showed improvement with treatment at 12 weeks, many had a DUP of <2 year (84.84%) (n=28/33) while in the unimproved group, most of them had a DUP of more than 2 years (91.7%) (n=22/24). This difference was statistically significant (Chi-square for Trend=28.28, p=0.001) (Fig. 3).

In the present study comparing DUP with improvement after treatment (n=57), after control of confounding variables such as gender, socioeconomic status, duration of hospitalization, general psychopathology, and premorbid functioning, it was found that DUP was an independent factor in predicting the clinical outcome statistically.

DISCUSSION

The mean DUP in the present study (3.02 years) was comparable with studies by Philip *et al.* (4 years) while it was longer (11 years) in the study by Tirupati *et al.* [8,9]. Nearly half of the patients had a DUP more than 2 years which was similar to the study by Tirupati *et al.* and confirms the finding that patients in developing countries present late for treatment [9]. Even though the present study did not find any association between DUP and gender, Pu *et al.* had found that males were more affected with younger age at onset and longer DUP [10]. There was no correlation between DUP and age at presentation in the present study which was similar to the results by Qin *et al.* [11] The present study did not find any correlation between DUP with educational level, marital status, and employment but the study by Chilale *et al.* and Birnbaum *et al.* have found low level of education and unemployment was associated with long DUP in Schizophrenia [12,13]. Some studies have reported that a longer DUP in Schizophrenic patients was due to the larger extended/joint family, which was able to compensate and cope with the dysfunctional member, concluding that such a family system seemed to be crucial to delay in treatment. In the present study,
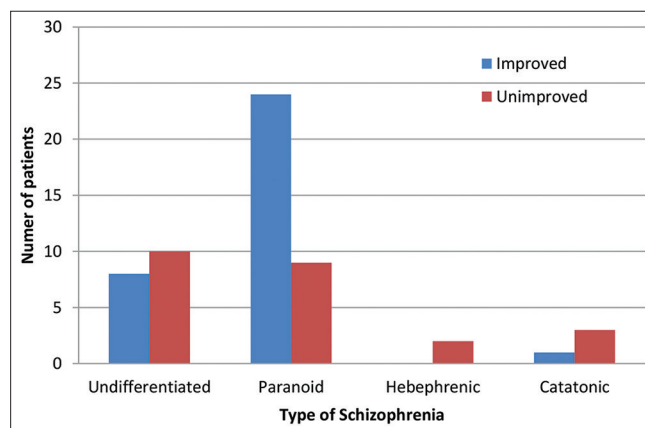

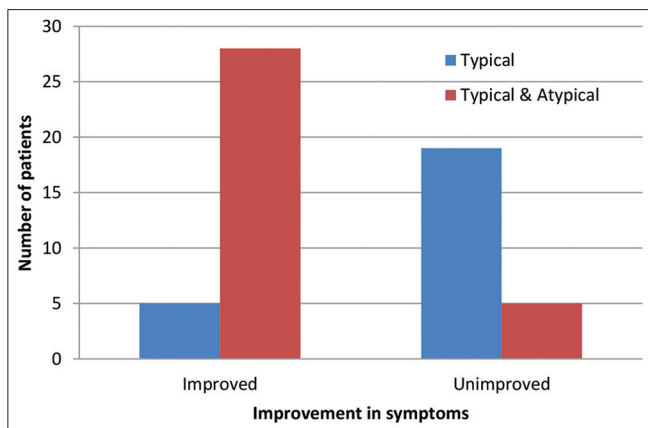**Fig. 1: Types of Schizophrenia and patients showing improvement after treatment**

Fig. 2: Comparison between anti psychotic treatment and clinical improvement in first episode Schizophrenics
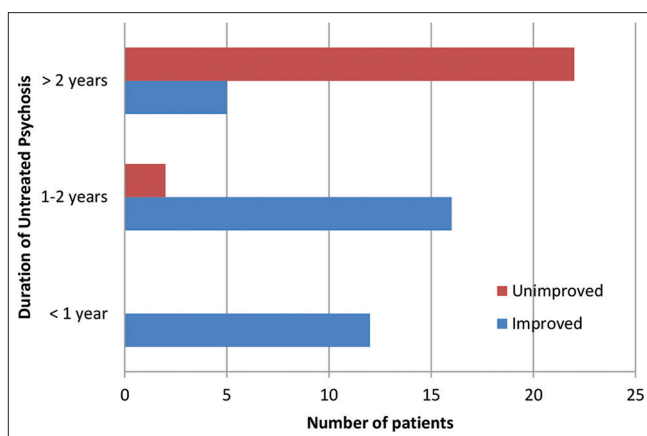

Fig. 3: Comparison between duration of untreated psychosis and treatment outcome after treatment

though 80.7% of patients were in the joint family system, there was no significant correlation of family type with DUP.

Paranoid Schizophrenia was the most common type of Schizophrenia in the present study. The association of Paranoid Schizophrenia with improvement after treatment has been recorded in studies like Birnbaum et al. but in the present study, there was a significant association between patients with undifferentiated Schizophrenia (41.7%) with DUP at baseline assessment [13]. This association was not seen in other studies. In the present study, premorbid functioning (PSA score) did not had a positive correlation with DUP, but the study by Díaz-Caneja et al. showed that poor premorbid functioning was associated with a longer DUP and poor outcome [14]. The correlation of DUP with symptom severity in the present study found a significant negative correlation with positive symptoms which was similar to the study by Birnbaum et al. [13] This implies that Schizophrenic patients with positive symptoms seek treatment earlier and have a shorter DUP. The present study did not find a correlation between negative symptoms and DUP but De Haan et al. had found a considerable correlation between DUP and negative symptoms [15].

In the present study, during post-treatment evaluation of patients, there was a statistically significant difference in mean DUP between the improved and the unimproved groups. This finding was similar to other studies which showed that shorter DUP was associated with good outcome and treatment response than those with longer DUP [11,13,16] The present study did not found any significant difference in the duration of hospital stay among the improved and unimproved group. This was similar to the review study by Penttilä *et al.* [17].

The mode of drug treatment between improved and unimproved groups showed statistically significant differences. The improvement was better with combined treatment of typical and atypical antipsychotics, but this result has to be interpreted with caution as the type of drugs, dosage, and adequacy of dose was not done in the study. In the present study, the correlation found between DUP and treatment outcome was statistically significant, after control of confounding factors such as age at onset of illness, the severity of symptoms in positive and negative domains, general psychopathology, and premorbid functioning.

To conclude, DUP was an independent predictor of treatment outcome and early intervention is necessary for better prognosis. Improving symptoms of initial psychosis may benefit patients and their families not only by improving long-term prognosis by restricting disease progression but also by preserving a person's ability to respond to antipsychotic treatment.

AUTHOR CONTRIBUTIONS

KB conceptualized, designed, and approved the study. KBM collected and analyzed the data. KP analyzed and interpreted data.

CONFLICTS OF INTEREST

None declared.

FUNDING

None.

ETHICAL APPROVAL

Obtained from the Institutional Ethical Committee of Institute of Mental Health, Chennai, Tamil Nadu, India.

REFERENCES

1. Druhin A, Shoukkathaly S, Balachandran S. Sociodemographic profile of schizophrenia with and without obsessive compulsive symptoms. J Evid Based Med Healthc. 2017;4(92):5614-20. doi: 10.18410/jebmh/2017/1124
2. Semple D, Smyth R. Schizophrenia. In: Oxford Handbook of Psychiatry. 4th ed. UK: Oxford University Press; 2019. p. 262-303.
3. Farooq S, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: A systematic review and meta analysis. Schizophr Res. 2009;109(1-3):15-23. doi: 10.1016/j.schres.2009.01.008
4. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull. 1991;17(2):325-51. doi: 10.1093/schbul/17.2.325
5. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. Am J Psychiatry. 2005;162(10):1785-804. doi: 10.1176/appi.ajp.162.10.1785
6. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. Arch Gen Psychiatry. 2005;62(9):975-83. doi: 10.1001/archpsyc.62.9.975
7. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76. doi: 10.1093/schbul/13.2.261, PMID: 3616518
8. Philip M, Gangadhar B, Jagadisha, Velayudhan L, Subbakrishna DK. Influence of duration of untreated psychosis on the short-term outcome of drug-free schizophrenia patients. Indian J Psychiatry. 2003 Jul;45(3):158-60. PMID: 21206847, PMCID: PMC2952161
9. Tirupati NS, Rangaswamy T, Raman P. Duration of untreated psychosis and treatment outcome in schizophrenia patients untreated for many years. Aust N Z J Psychiatry. 2004 May;38(5):339-43. doi: 10.1080/j.1440-1614.2004.01361.x, PMID: 15144511
10. Pu C, Qiu Y, Zhou T, Yang F, Lu Z, Wang C, *et al*. Gender differences of neurocognitive functioning in patients with first-episode schizophrenia in China. Compr Psychiatry. 2019;95:152132. doi: 10.1016/j.comppsych.2019.152132
11. Qin H, Zhang J, Wang Z, Min H, Yan C, Chen F, *et al*. Duration of untreated psychosis and clinical outcomes of first-episode schizophrenia: A 4-year follow-up study. Shanghai Arch Psychiatry.

2014 Feb;26(1):42-8. doi: 10.3969/j.issn.1002-0829.2014.01.006, PMID: 25114480, PMCID: PMC4118001

12. Chilale HK, Banda R, Muyawa J, Kaminga AC. Duration of untreated psychosis and associated factors in first episode psychosis in Mzuzu in Northern Malawi. Afr J Psychiatry. 2014;17:503-7. doi: 10.4172/Psychiatry.1000106

13. Birnbaum ML, Wan CR, Broussard B, Compton MT. Associations between duration of untreated psychosis and domains of positive and negative symptoms. Early Interv Psychiatry. 2017 Oct;11(5): 375-82. doi: 10.1111/eip.12256, PMID: 26177007, PMCID: PMC4713366

14. De Haan L, Linszen DH, Lenior ME, De Win ED, Gorsira R. Duration of untreated psychosis and outcome of schizophrenia: Delay in intensive psychosocial treatment versus delay in treatment

with antipsychotic medication. Schizophr Bull. 2003;29(2):341-8. doi: 10.1093/oxfordjournals.schbul.a007009

15. Díaz-Caneja C, Pina-Camacho L, Rodríguez-Quiroga A, Fraguas D, Parellada M, Arango C, *et al*. Predictors of outcome in early-onset psychosis: A systematic review. NPJ Schizophr. 2015;1:14005. doi: 10.1038/npjschz.2014.5

16. Albert N, Melau M, Jensen H, Hastrup LH, Hjorthøj C, Nordentoft M, *et al*. The effect of duration of untreated psychosis and treatment delay on the outcomes of prolonged early intervention in psychotic disorders. NPJ Schizophr. 2014;3:34. doi: 10.1038/s41537-017-0034-4

17. Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. Br J Psychiatry. 2014;205(2):88-94. doi: 10.1192/bjp.bp.113.127753