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Duration of Untreated Psychosis as a Predictor of Shortterm Outcome in Schizophrenia

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Abstract
Background: *Duration of untreated psychosis (DUP) is one of the few potentially modifiable predictors of outcomes of schizophrenia. It has been postulated that a longer DUP leads to a poorer prognosis and outcome might be improved through earlier detection and treatment*
Aims*: To analyze the associations between DUP and short-term outcome in schizophrenia.*
Methodology: *Consecutive patients fulfilling the International Classification of Diseases-10 criteria for schizophrenia who were never treated before were considered for the study. Socio demographic details were noted and data relating to the onset of psychosis were collated from interviews with the patient and a close relative of the patient. The patients were Scale for the Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative symptoms (SANS), Clinical Global Impression (CGI) and Global Assessment of Functioning Scale (GAF) at the time of admission. Follow up assessment was done after a period of 8 weeks by administering SAPS, SANS and GAF. The outcome was assessed using the Clinical Global Impression-schizophrenia scale and GAF.*
Results: *The mean duration of untreated psychosis was 12.78±3.52 months. Nearly 25% of the patients had DUP greater than 18 months. On assessment of outcome, there was a significant association between duration of hospitalization and outcome. Improved patients have a short duration of untreated psychosis than the unimproved patients and this association was found to be significant even after the confounding factors were controlled.*
Conclusions*: The results show that improved patients have a short duration of untreated psychosis than the unimproved patients and this association was found to be significant even after the confounding factors were controlled.*
Keywords*: Schizophrenia, Duration of Untreated Psychosis (DUP), Outcome.*

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I. Introduction

Schizophrenia is a chronic disabling disorder of variable but profoundly disruptive psychopathology that involves cognition, emotion, perception and other aspects of behavior[1].Onset of schizophrenia typically occurs during adolescence or early adulthood, persists throughout life and affects persons of all social classes[2]. Both patients and families often suffer from poor care and social ostracism because of wide spread ignorance about the disorder[3]. Schizophrenia is usually identified and defined in terms of its clinical presentation, course and outcome. Some of the commonly measured outcomes in schizophrenia are symptom outcomes [4-7], cognitive and neurobiological outcomes[8,9], patient related outcomes[10,11], social outcomes[12], duration of untreated psychoses[13] and economic outcomes.[14,15]More recently, several groups of investigators have proposed that a long duration of untreated initial psychosis may also affect long- term outcome in schizophrenia

In the past two decades, duration of untreated psychoses (DUP) has been an intense focus of clinical and research interest. Norman and his colleagues in a systematic review had found that there is a substantial evidence of DUP being an independent predictor of treatment outcome, particularly remission of positive symptoms, over the first year or so of treatment[16].In a follow up study done by Craig *et al* on first episode schizophrenic patients had stated that duration of untreated psychoses was not significantly associated with 24-month illness course or clinical outcome[17] .Harris *et al* (2005) in a prospective, naturalistic study of 318 first episode psychoses patients found that shorter DUP correlated moderately with decreased severity of positive symptoms, and enhanced social and occupational functioning and quality of life. DUP exceeding 1 year was associated with a poor outcome and there was no association with DUP and negative symptoms[18]. In a

systematic review of 26 first-episode studies, Marshall *et al* in 2005 found that a longer DUP was not associated with worse symptoms or poorer functioning at first presentation, at 06- and 12-months following treatment. Longer DUP was associated with more severe overall symptoms and with worse overall functioning. Patients with long DUP were also less likely to experience remission at 6, 12, and 24 months[19]. In a study done by Tirthali *et al*[20]on 119 schizophrenic patients had stated that there is a delay in accessing treatment for schizophrenia in india, a low- middle income country and longer DUP is associated with poorer psychopathological and functional outcomes. Shrivatsava *et al*[21] in a 10yr follow up study on 200 schizophrenia patients had found that duration of untreated psychosis is not significantly associated with long term clinical and social outcomes.

However, despite the knowledge of such factors, the prediction of outcome in schizophrenia has remained a challenging task and is generally poor. One of the well-established facts and consistent finding about outcome of schizophrenia is that patients from developing countries including India have better outcomes than those from the developed countries[22].Though there is no definitive evidence as to whether reduction of DUP will alter the course of schizophrenia for better, this issue has considerable public health importance. Given the low psychiatrist to population ratio and difficulties in reaching a psychiatrist, it is unlikely that patients from developing countries have shorter DUP than those from the developed countries.

With this back ground we have addressed these issues by following up a representative, sample of individuals with a first episode of psychosis, and assessing whether the duration of untreated psychosis is independently associated with the outcome of schizophrenia.

II. Aims And Objectives

1. To assess the duration of untreated psychosis of the study sample.
2. To assess the relationship between short term outcome in schizophrenia with reference to sociodemographic variables and clinical variables.
3. To assess the influence of duration of untreated psychosis on the short-term outcome in schizophrenia.

III. Materials And Methods

This is a cross sectional hospital based follow up study. The study was conducted in the Department of Psychiatry, of a tertiary care hospital for a period of one year i.e., from 1st November 2019 to 30th October 2020.The study sample was collected from patients admitted for schizophrenia who were never treated before. Patients were selected consecutively.

INCLUSION AND EXCLUSION CRITERIA

Drug naive patients with a diagnosis of schizophrenia as per ICD-10 criteria from 18-60 years of age were included.

Patients with medical condition that might influence the current state of psychiatric presentation current substance use disorder or history of substance dependence Patients who did not give consent for the study, without reliable informant were excluded.

IV. Methodology

Consecutive patients fulfilling the ICD-10 criteria for schizophrenia, admitted as inpatients in tertiary care hospital from November 2019 to October 2020 were evaluated. Those satisfying the inclusion and exclusion criteria were taken into the study. Data relating to the onset of psychosis were collated from interviews with the patient and a close relative of the patient. After explaining psychosis in clear language, we asked when the patient first experienced or when the family members first noticed psychotic symptoms. In line with the previous studies[21,22], onset of psychosis is defined as presence for 1 week or more of the following psychotic symptoms: delusions; hallucinations; marked thought disorder; marked psychomotor disorder; and bizarre, grossly inappropriate and/or disorganized behavior with a marked deterioration in function and the end point was considered as admission to the hospital.

The patients were administered the Semi-structured proforma, SAPS[23], SANS)[24], Clinical Global Impression-Schizophrenia Scale[25] and (GAF) [26] at the time of admission. Follow up assessment was done after a period of 8 weeks by administering SAPS, SANS and GAF. All those who completed 8 weeks of follow-up were enquired from their caregivers about compliance to medication. The outcome was assessed using the Clinical Global Impression-schizophrenia scale and GAF. The data collected thus were tabulated and Statistical analysis was done using SPSS-16.

V. Result

Table 1: Duration Of Untreated Psychosis Of Total Sample

DUP IN MONTHS	<6	7-12	13-18	>18	MEAN DURATION 12.78±3.52
TOTAL NUMBER OF PATIENTS(76)	44(57.9)	8(10.5)	5(6.6)	19(25%)	

Table 2 : Correlation Of Clinical Variables With Reference To Dup

Variable	**Correlation**	**P value**
Age at presentation	0.072	**0.02**
Age at onset	-0.100	0.17
Psychotic domain	-0.025	**0.048**
Disorganization domain	0.385	**0.04**
Negative domain	0.22	**0.002**

Table 3: Relationship Of Variables And Outcome

Variable	**Improved**	**Unimproved**	**P value**
Duration of hospitalization			
<7days	22(64.7)	8(40%)	**0.01**
8-14days	2(5.9%)	7(35%)	
>15days	10(29.4%)	5(25%)	
Symptoms			
Psychoticism	2.03± 0.904	4.25± 2.023	**0.0001**
Disorganization	1.47± 0.861	5.95± 1.669	**0.0002**
Negative	1.59± 1.6	7.60± 4.43	**0.002**

Table 4: Dup And Outcome

Variable	**Improved**	**Unimproved**	**P value**
DUP(mean)	6.72±2.13 months	23.1±2.5 months	**0.0001**

Table 5: Dup And Outcome without confounding factor

IMPROVEMENT	**CORRELATION COEFFICIENT**	**P-VALUE**
DUP	-0.761	**0.0002**

VI. Discussion

Initially 81 patients were considered for the study of them 3 patients did not give consent for the study and 2 patients were excluded because of co morbid substance use, thus making the final study sample to 76. The mean duration of untreated psychosis of the total sample was 12.78±3.52 months which is shorter than that reported in earlier studies in India by Gangadhar BN *et al*[27] (98.8 weeks) and Murthy GV *et al*[28] (85.8 weeks). Of the total sample, 57.9% of the patients had duration of untreated psychosis less than 6 months and nearly 25% of the patients had duration of untreated psychosis greater than 18 months with 2 patients having DUP greater than 3 years (table 1).

Table 2 shows the correlation between DUP with reference to variables. In our study we found that there is a positive correlation between age at presentation to the clinician and duration of untreated psychosis and this difference was found to be statistically significant (p=0.02). This could be due to delay in identification of the illness leading to later presentation to the psychiatric services.[29] When relationship between age at onset of illness was assessed with reference to DUP, there was a negative correlation between age at onset of illness and DUP. Similar findings were reported by Padmavathi *et al*[30] who in her study stated that early onset of illness would lead to prolonged duration of untreated psychosis if unidentified, and thus influencing the outcome. Psychopathology at the baseline showed a strong positive correlation in disorganization and negative domains. There is also a weak negative correlation between psychotic domain and the duration of untreated psychosis. This was found to be statistically significant. This indicates that as duration of untreated psychosis increases there will be increase in the incidence of negative symptoms leading to increased severity of illness which may lead to poorer outcomes. Our findings were in accordance with Thirthalli *et al*[31] who in his study had found a significant correlation between baseline psychopathology and DUP.

The patients were assessed for their outcome by the CGI and GAF scale in the subsequent follow-ups. Table 3 shows the correlation of outcome with duration of hospitalization and symptoms. In relation to duration of the hospital stay, among the improved group 64.7% were hospitalised less than a week, in the unimproved group 40% of the patients were hospitalized less than a week, 35% of patients were hospitalised between 8-14 days and 25% of the patients were hospitalised more than 2 weeks. This difference was found to be statistically significant (p=0.01) as longer duration of hospital stay in patients with longer DUP could be because of more severe baseline symptomatology which will have poorer response to treatment thus increasing the length of the hospital stay. This finding of ours was in contrast to that of Haas[33]*et al* who in his study has reported that there is no significant difference in terms of duration of hospitalization between the long and short DUP groups. The mean score on psychotic symptom domain was 2.03 ±0.904 for the improved group and 4.25±2.023 for the unimproved group, the mean score on disorganization domain was 1.47 ±0.861 for the improved group and 5.95 ±1.66 for the unimproved group. In the improved group the mean score on negative symptom domain was 1.59 ±1.6 and 7.6±4.43 for the unimproved group and the difference between the two groups in all the symptom domains was found to be statistically significant. This indicates that there was a significant improvement in psychopathology of patients belonging to improved group after 8 weeks of treatment. However, our findings are in contrast with that of Philip [34]M *et al* who in their study had proposed that there is no significant difference between improved and unimproved groups with reference to psychopathology after 6-8 weeks of neuroleptic treatment in drug naïve schizophrenic patients. The mean DUP among the patients belonging to improved group is 6.72±2.13 months and in the unimproved group the mean DUP is 23.1±2.50 months (table 4) This difference between the two groups was found to be statistically significant ($p<0.01$). In order to find out the relationship of confounding factors on DUP and outcome, a partial correlation was done after controlling the confounding factors such as age, age at onset of illness, symptom domains of psychotic, disorganized and negativism. It was found that there was a negative correlation (r= -0.76) between DUP and outcome and this relationship was found to be statistically significant ($p<0.01$) Table 5. This finding of ours is similar to other studies that shorter DUP is associated with good outcome and treatment response than those with a longer DUP.In a study done by Philip *et al* [34]on drug naïve schizophrenic patients had reported that patients with a short DUP have shown improvement at the end of 6 weeks following treatment. Harrigan *et al*[35]in their study had proposed that duration of untreated psychosis is an independent predictor in the outcome of schizophrenia after controlling the confounding factors like chronological age, age at illness onset and socio demographic variables. The largest experimental study TIPS project aimed at reducing the impact of reducing DUP had demonstrated that reducing DUP (from a median of 1.5 to 0.5 years) led to markedly improved clinical presentations and improved medium and long term outcomes[36].However, when the intervention was interrupted, resulted in measurable increase in DUP followed by attendant worsening in symptoms, thus validating the causal relationship between DUP and the outcome in schizophrenia.[10]

VII. Conclusions

The mean duration of untreated psychosis was 12.78±3.52 months. Nearly 25% of the patients had DUP greater than 18 months. Longer duration of untreated psychosis is associated with increased age at presentation and higher baseline psychopathology. The results show that improved patients have a short duration of untreated psychosis than the unimproved patients and this association was found to be significant even after the confounding factors were controlled. This concludes that duration of untreated psychosis was found to be an independent factor that significantly influences the outcome in schizophrenia.

LIMITATIONS

1. The study is time bound and therefore contributed to limited sample size.
2. The study was done on a sample taken from the teaching hospital-based population; it may not be representative of the general population.
3. Assessment of duration of untreated psychosis involves retrospective recall of time of onset of psychosis, which has the usual recall bias from the patient.
4. Variables related to duration of untreated psychosis such as pathways to care, mode of onset, premorbid social adjustment, substance use were not included.

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