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First Episode Is the Best Episode: Lessons and Limitations in Duration of Untreated Psychosis (DUP) and Outcome in Schizophrenia

Amresh Srivastava
University of Western Ontario, amresh.srivastava@sjhc.london.on.ca

Larry Stitt
University of Western Ontario, larry.stitt@schulich.uwo.ca

Meghana Thakar
Mental Health Foundation of India

Gurusamy Chinnasamy
University of Western Ontario

Nilesh Shah
University of Mumbai

First episode is the best episode: Lessons and limitations in duration of untreated psychosis (DUP) and outcome in schizophrenia

Amresh Srivastava[1*],
Larry Stitt[2],
Meghana Thakar[3],
Gurusamy Chinnasamy[4]
Nilesh Shah[5]

- Mental Health Foundation of India (PRERANA Charitable Trust) and Silver Mind Hospital, 209 Shivkripa Complex, Gokhale Road, Thane, Mumbai, Maharashtra, India 400 602 (Present Address: Regional Mental Health Care, 467 Sunset Drive, St. Thomas, Ontario, Canada N5H 3V9; Department of Psychiatry, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada; and Lawson Health Research Institute, London, Ontario, Canada)
- 2Department of Epidemiology & Biostatistics, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada N6A 5C1
- 3Mental Health Foundation of India (PRERANA Charitable Trust) and Silver Mind Hospital, 209 Shivkripa Complex, Gokhale Road, Thane, Mumbai, Maharashtra, India 400 602

- 4. Research Office, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada N6A 5C1 (Present Address: novaNAIT - Centre for Applied Research and Technology Transfer, The Northern Alberta Institute of Technology, 10504 Princess Elizabeth Avenue, Edmonton, Alberta, Canada T5G 3K4)
- 5 LTMG Hospital, University of Mumbai, Sion, Mumbai, Maharashtra, India 400 022
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- *Corresponding author. Tel.: +1-519-; fax: +1-519-. E-mail address: dr.amresh@gmail.com (A. Srivastava)

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Abbreviations

- AIMS = Abnormal Involuntary Movement Scale
- BG = Bender-Gestalt test
- CGIS = Clinical Global Impression Scale
- DOSMED = Determinants of Outcome of Severe Mental Disorder
- DSM-IV = Diagnostic and Statistical Manual IV
- GAF = Global Assessment of Functioning
- GP = General psychopathology
- HDRS = Hamilton Depression Rating Scale
- PANSS = Positive and Negative Syndrome Scale
- QOL = Quality of Life
- WMS = Wechsler's Memory Scale

ABSTRACT

- Background: Early intervention in psychosis is an opportunity. Research ahs shown that if any thing community members can do to prevent psychosis is to report early. This has opened newer vistas for understanding the complexity of brain and behaviour in schizophrenia. At the same time it has raised the bar of expectations regarding its correlation to outcome. It finally narrows down to meaningful public campaign for awareness, which will decide success of research to clinics in schizophrenia management. Duration of untreated psychosis (DUP) has emerged as a reliable predictor of outcome and provides credence to development of early intervention services. It is not quite clear if DUP works in isolation and what other factors along with DUP would determine outcome long-term outcome of schizophrenia is multifactorial in nature. The present study examines effect of DUP on outcome of schizophrenia
- Method: we conducted a ten years follow up study of first episode hospitalized DSM III-R schizophrenia and correlated multiple outcome criteria with DUP at Mumbai. We carefully determined onset of psychosis using criteria for appearance of positive symptoms, negative symptoms or significant social decline. Data was analyzed using SAS.
- Results: we analyzed 101 patients available at ten years. We found that mean DUP was higher for group, which showed Clinical recovery on GCIS [14.0(SD=8.0) months for recovered & 10.8 (SD=5.7) months in nonrecovered group p=0.091]. There is a significant difference in favour of DUP≤6 months in terms of subscales of PANSS; However DUP was not found to be significantly associated with the end point parameters of good clinical or social outcome.
- Conclusion: We find that DUP is just one factor in determinants of outcome. Several other psychopathological & phenomenological factors collectively play a role in determining outcome. Future research needs to be directed towards combination of determinants of outcome in early intervention of psychosis

Introduction

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- There has been intense interest in DUP because of the proposal that psychosis is some how neurologically toxic 1. If this is true then delay in treating people with psychosis could impair prognosis, while reducing delay could improve it 7. However despite the blossoming of early intervention services, there is continuing disagreement over whether there is a real association between DUP and outcome. Several conflicting evidence have been reported 2,3,4 .
- Though DUP has been reported as an independent marker of outcome, measurement errors and variability in DUP in terms of heterogeneity have also been reported and caution advised 5,6,. The strength of association between DUP and outcome has been found to be only 'moderately strong' based upon the available data, accounting for approximately 13% of variance or 1 in 3 to 1 in 4 of those who did not achieve remission 7. Until now, very few long-term studies have examined this association. Long-term outcome of schizophrenia is multifactorial in nature. It not clearly known if short DUP is a strong determinant of long-term outcome. 8. The present study examines effects of DUP on clinical and social outcome in ten year's long-term follow up in a cohort of first episode psychosis.

Methods

- Design
- This study is a naturalistic, prospective, longitudinal follow-up study conducted at Mumbai, India. Assessments were conducted at the baseline and at the end of ten years follow up by trained and experienced clinical research staff. Inter-rater reliability was established for quantification of outcome.
- Sample and settings
- Two hundred patients admitted with first episode psychosis were recruited as per inclusion criteria, and 101 were available at the end point. Wherever necessary patients were traced, contacted and assessed.
- Inclusion criteria:
- At base
- Hospitalized
- Availability of key relatives;
- Confirmed diagnosis of psychotic disorder- non-affective as per DSM-III-R;
- Age range of 18-45 years
- Informed consent for participation in the study.
- At end point
- Reconfirmed diagnosis of schizophrenia as per DSM IV –TR 9 at the follow up of ten tears;
- Informed consent
- Available objective data from key relative

Criteria

- Exclusion criteria: we excluded cases of primary organic psychotic disorder intellectual disability, drug and substance induced psychosis, any change in diagnosis from baseline to endpoint and epilepsy. comorbid alcoholism and substance abuse.
- The study was carried out in a non-governmental, psychiatric hospital certified as a psychiatric facility by the State Government as per Indian Mental Health Act 1983 from a period of 1993 to 2007. Independent Ethics Commission, Mumbai, approved the study.
- Informed consent: All patients and their relatives were explained the nature and purpose of study and an informed consent was obtained at the beginning of the study as well as at the end of the follow up for repeat assessment.
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Assessment of DUP

- The assessment of duration of untreated psychosis was done clinically by a detailed interview with the patient and the key relatives. . We carefully assessed known prodromal signs and tried to elicit the time of first-distressing symptoms either positive or negative symptom to decode the onset of illness
- Positive symptoms (hallucinations, delusions, and odd beliefs thought disorder)
- Negative symptoms (depression, dysphoria, apathy, anergia, apathy, and amotivation)
- Social decline (withdrawn behavior, poor interpersonal relationship, social avoidance, and lack of interest in education or work)
- Assessment tools

- We used Clinical and social outcome criteria based upon Meltzer's outcome 10 criteria recommendations. We operational zed the definition on a scale of 1-to-5 where one represented poorest and 5 the best outcome for some of the parameters. This scale was developed for the local conditions and used in other studies 11 Clinical Outcome was measured by 1] Clinical Global impression scale (CGIS) 12 2] Psychopathology (positive symptoms, negative symptoms and disorganization) using Positive and Negative syndrome scale [PANSS]) 13 l., 1987), 3] Depressive symptoms using Hamilton Depression Rating Scale (HDRS) 14, 4] Factors of Compliance, 5] EPS, using Abnormal Involuntary Movement Scale(AIMS) 15 6] Aggression, 7] Hospitalization, and 8] Suicidality. Social outcome was measured using 1] Quality of life 16, 2] Global Functioning using GAF, 17. 18 3] Independent living, 4] Family burden, and 5] Social burden measured operationalized criteria. Raters in this study were not blinded.

Outcome criteria

- We used GCIS for measuring severity as well as improvement by CGIS-S & CGIS-I respectively. Primary criteria - a score of 2 or less i.e. scoring ‘improved and much improved’ rating were considered ‘good outcome’ on CGIS
- Secondary outcome criteria: clinical improvement as defined by
- Being not hospitalized for minimum 2 preceding years,
- GAF >80,
- QOL >80,
- >3 on scales of social functions, independent living, education, and social burden.
- The statistical analysis was performed using SAS, version 9.1. Probability values less than 0.05 were considered to be statistically significant.

RESULTS

- Mean duration of untreated psychosis was observed as 12.7 months (SD =7.3). The majority of patients (73%) had duration of untreated psychosis ranging between 6 months to 24 months (Table 1).
- There were no differences between short and long DUP in terms of age at intake and gender (Table 2, p=. 148 and p=. 799, respectively).
- No statistically significant differences were observed between the two groups on parameters of clinical and social recovery

TABLE 1

Duration of untreated psychoses on differential time line.

Parameter	Value (SD)
Mean (SD)	12.7 (7.3)
Median (Minimum, Maximum)	11.0 (3, 35)
≤6 months	20 (19.8%)
6-11 months	34 (33.7%)
12-24 months	40 (39.6%)
>24 months	7 (6.9%)

TABLE 2

Differences in gender and age at intake between subjects with short and long DUP (<12 months vs ≥ months)

Outcome	<12 Months DUP (n=54)	≥12 Months DUP (n=47)	Test Statistic	P V
Age at Intake	27.7 (7.4)	30.1 (9.0)	$t_{98}=1.46$	.14
Male gender	39 (72.2%)	35 (74.5%)	$X_1^2=0.06$	.79

TABLE 3

Difference in effect of duration of untreated psychoses on follow-up outcomes on multiple clinical and social parameters using 12 months cut-off for short and long DUP.

Outcome	<12 Months DUP (n=54)	≥12 Months DUP (n=47)	Test Statistic	P V
PANNS	52.4 (9.4)	50.6 (8.3)	t_{99}=0.99	.32
Positive Symptoms	9.1 (4.1)	8.2 (3.7)	t_{99}=1.17	.24
Negative Symptoms	12.8 (8.0)	11.5 (6.7)	t_{99}=0.91	.36
General Psychopathology	27.9 (11.5)	30.6 (12.2)	t_{99}=1.11	.27
HDRS	13.1 (5.2)	13.2 (5.3)	t_{95}=0.18	.86
GAF	77.6 (13.1)	80.5 (9.6)	t_{94}=1.22	.22
QOL	65.9 (14.1)	69.3 (15.2)	t_{98}=1.16	.24
Disorganization Abnormal (>3)	25 (46.3%)	19 (40.4%)	X_1^2=0.35	.55
>1 Hospitalization in past 10 years	34 (64.2%)	27 (58.7%)	X_1^2=0.31	.57
IP Social Abnormal (≤3)	37 (68.5%)	36 (76.6%)	X_1^2=0.82	.36
Work Abnormal (≤3)	44 (81.5%)	31 (67.4%)	X_1^2=2.63	.10
EPS Abnormal (>2)	18 (34.6%)	17 (36.2%)	X_1^2=0.03	.87
Independent Living Abnormal (≤3)	26 (49.1%)	25 (54.4%)	X_1^2=0.28	.59
Aggression Abnormal (>2)	20 (37.0%)	19 (41.3%)	X_1^2=0.19	.66
Family Burden Abnormal (>3)	33 (63.5%)	21 (47.7%)	X_1^2=2.40	.12
Suicidality Abnormal (2-5)	28 (53.9%)	23 (52.3%)	X_1^2=0.02	.87
Recovered (CGI –I <3)	29 (53.7%)	32 (68.1%)	X_1^2=2.17	.14

Discussion

- There is a well-established association between DUP, critical period and early intervention. This association is independent of confounding factors, including premorbid functioning, gender, diagnosis and age of onset of symptoms variance in functional recovery has been reported 19.
- The finding of 48 weeks DUP in the present study is not surprising from a developing country where stigma is rampant, awareness is poor, accessibility of care is limited and resources for mental health are less than sufficient. A DUP as much as 796 weeks has been reported from India which is primarily because of lack of availability and accessibility of mental health services rather than the psychosis remaining 'unidentified' 20,21.
- Mental illness remains untreated despite recognition. There are several cultural, social, religious, economic and personal factors which determine approach to mental health care which obliviously leads to longer DUP. 22. Long DUP has also been reported in western literature e.g. a Canadian study observed duration of untreated psychosis as 84 weeks 23.

- In the present study in a multivariate analysis, results did not show any statistically significant correlation between various categories of duration of untreated psychosis and outcome parameters.
- The significant findings were the lack of correlation with symptom remission and level of social functions measured by several psychosocial parameters.
- We compared patients with less than 12 months of DUP and more than 12 months of DUP and found that no clinical or social parameters at ten years outcome correlated DUP below 12 months or more than 12 months.
- This lack of association may arise from the followings possibilities:

Complexity in assessment of DUP.

- Nature of treatment being inadequate because of limited resources
- The long-term outcome in schizophrenia is not influenced by DUP because most of neuronal changes takes place early in the course or even preceding the onset and therefore an intervention as late as 12 months does not contribute to long term outcome24
- DUP remains relevant only for short period of follow up and once the psychosis has persisted long enough, enough toxic damage has been caused to change any thing in the outcome.
- The finding also indicates that longer the DUP worse the outcome but a shorter DUP does not necessarily mean a good outcome.
- Further, in our study out of 13 outcome parameters of clinical and social relevance none of the parameter showed any correlation. All the parameters most importantly, social function, global function, quality of life and independent living show no correlation.
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- It is likely that DUP correlates with outcome measures in conjunction with several other factors. It further suggests that the benefit of early intervention in long term is gradually lost, no matter when the intervention is done due to several factors such as, poor treatment, lack of follow up, inconsistencies in management, poor adherence, poor psychosocial intervention & frequent relapses. The assumption that delay in treating people with psychosis could impair psychosis while reducing delay would improve it, is not as straight forward as often stated. [25] There has been continuing disagreement over whether there is a real association between DUP and outcome. [3, 26]

- We need more studies comparing ultra short DUP, short DUP and long DUP to understand more clearly about its association with outcome. Further studies also need to examine how powerful predictor DUP is? [27].
- Success of this concept depends upon public campaign and resources for treatments. Research of DUP has given a new responsibility for community awareness programs for early identification, which remains a daunting, task everywhere [28, 29] .

SUMMARY AND CONCLUSIONS

- Our study finds that DUP alone does not determine long term outcome status in first episode schizophrenia. Long DUP leads to poor outcome and the short DUP does not necessarily lead to good outcome due to psychopathological heterogeneity in early phase. [30,31,32] ... There is a missing link in association of DUP and outcome.

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CONFLICT OF INTEREST

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