Int J Med. Public Health. 2019; 9(3):81-86.
A Multifaceted Peer Reviewed Journal in the field of Medicine and Public Health
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Original Article

A Study on the Characteristics of Patients Who do not Recover in the Long-term Treatment of First Episode Schizophrenia

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ABSTRACT

Background: Despite revolutionary advances in treatment of Schizophrenia, about 30-40% patient do not achieve a state of recovery. This limited outcome interferes achieving a positive outcome and wellness. Long term outcome in schizophrenia has been poorly studied. There is a dearth of longitudinal studies that determine factors affecting outcome in patients with first episode of schizophrenia. While short term studies have yielded some findings, long term studies in this domain are rare. The present study looks at the characteristics and factors that affect non recovery in patients with first episode schizophrenia over a ten year duration. **Methodology:** 101 patients attending a non government private psychiatric hospital were followed up over a 10 year period and assessed for recovery and outcome parameters using the Clinical Global Impression Scale (CGIS ≤ 2), the Positive and Negative Symptoms Scale for Schizophrenia (PANSS) based on RSWG criteria, Hamilton Depression Rating Scale (HDRS), Quality of Life Scale (QOLS), Global Assessment of Functioning (GAF) and the Abnormal Involuntary Movement Scale (AIMS) for extrapyramidal symptoms. Independent living and family burden were studied on a 1 to 5 point likert scale with 1 being worst and 5 being good. Non recovery was defined as Good outcome was defined as a score of 2 or less on CGIS. The results were analyzed statistically and presented. **Results:** When non recovered subjects were assessed on various parameters, significant reductions in total PANSS scores, positive and negative symptom scores, depression scores on the HDRS (p<0.0001 in all cases). The non recovered group had significantly greater number of hospitalizations (p<0.0001), more disorganized behavior (p<0.0002), greater interpersonal issues (p=0.0013) and poor outcome on independent living (p<0.0001). Assessment of the baseline characteristics of both groups revealed that age at the time of entry into the study was lower in the non-recovery group (p<0.0001) while greater negative symptom scores (p<0.0001), greater depression scores (p<0.0001) and greater aggression was present. **Conclusion:** The present study shows that early age of onset of psychosis and presence of severe negative symptoms are significantly related to future non-response in long term outcome of first episode schizophrenia. It is also important mentioning that symptom reduction alone is insufficient when looked as an outcome measure in schizophrenia.

Key words: Outcome, Schizophrenia, Recovery, Non-recovery, Positive symptoms, Negative symptoms, HDRS, PANSS, CGI-S, Hospitalizations.

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History
- Submission Date: 22-01-2019
- Revised Date: 19-05-2019
- Accepted Date: 31-10-2019

DOI : 10.5530/ijmedph.2019.3.20

Article Available online
http://www.ijmedph.org/v9/i3

INTRODUCTION

Schizophrenia is a complex and debilitating brain disorder that typically emerges in late adolescence and early adulthood.[1] Schizophrenia afflicts approximately 1% of the population worldwide incurringsubstantial individual, family and societal burden[2] along with shortened life span.[3] There is a dearth of studies that have measured outcome in schizophrenia.[4] A review that looked at outcomes in schizophrenia over the past century observed that the outcome in terms of complete recovery and resolution of symptoms has never been more than 25-40%.[5] It has been argued by many researchers that outcome of schizophrenia needs to be measured on clinical and psychosocial parameters.[6] Lack of uniformity and clarity in measuring outcome has been the main cause for confusion in understanding outcome in schizophrenia.[7] However even when social and clinical outcomes are considered, it does not show an encouraging trend[8] and some authors have even posited questions as to whether patients that suffer from schizophrenia ever recover.[9]

An analysis of outcome literature reveals that better outcomes have been reported from Asian and other developing countries.[10] In the International Pilot Study on Schizophrenia, Indian researchers have reported a good outcome for schizophrenia with the trend being favorable as in > 60% recover over a 15 year period.[11] The Madras longitudinal study has also shown good outcome in range of 65-75% for schizophrenia in India.[12] Short term outcomes particularly in first episode psychosis has been encouraging as seen in studies.[13] The response rate measured shows <30% relapses in first episode psychosis and good response in about 82% cases in short term as-

Cite this article : Shrivastava A, Karia S, Shah N, Sousa AD. A Study on the Characteristics of Patients Who do not Recover in the Long-term Treatment of First Episode Schizophrenia. Int J Med Public Health. 2019;9(3):81-6.

sessments.[14,15] The main challenge in treatment has been to sustain the outcome for longer periods in these patients. There is evidence that good outcome sustains up to 2 years but it may decline in the long term management of schizophrenia.[16] Despite revolutionary treatment advances in schizophrenia a number of patients still fail to show a complete recovery from the disorder.[17]

Antipsychotic drugs form the mainstream of treatment in schizophrenia. It is not clearly known what role antipsychotics may play in the treatment and maintenance of treatment or remission in schizophrenia in the long term course.[18] Identification of the subjects, who are not likely to respond, is important not only from a clinical perspective but also from an economic and public health point of view.[19] Significant work has been done regarding the determinants of course and outcome in schizophrenia but early identification of non-responders would be important to assist and plan the comprehensive management of the patient. The present research examines factors for non-response in first episode schizophrenia patients who has been treated for a period of ten years.

Despite revolutionary advances in treatment of schizophrenia, about 30-40% patient do not achieve a state of recovery. This limited outcome interferes achieving a positive outcome and wellness. Wellness as outcome criteria for schizophrenia is currently under extensive investigation. Studies suggest that a true outcome in schizophrenia is recovery with includes personal and positive state of health which is return to a state of wellness. It is recognised that there are number of barriers to achieve the state of wellness which are personal, social, environmental, illness, treatment related and other factors. In this paper we try to examine the long term outcome of first episode schizophrenia. We believe that these factors may be responsible for the limited and poor state of outcome in some cases.

MATERIALS AND METHODS

This study was carried out in a non-governmental psychiatric hospital certified as a psychiatric facility by the State Government as per the Indian Mental Health Act 1983 in Mumbai; India. The study period spanned from January 1992 to January 2005. An Independent Ethics Commission approved the study. Patients who were available at the end of ten years from a cohort of first episode schizophrenia (patients experiencing their first episode of psychotic symptoms and seeking treatment) were assessed for clinical recovery. The scales used in the assessment were the Clinical Global Impression Scale (CGI-S),[20] the Positive and Negative Symptoms Scale for Schizophrenia (PANSS),[21] Hamilton Depression Rating Scale (HDRS),[22] Quality of Life Scale (QOLS),[23] Global Assessment of Functioning (GAF),[24] Abnormal Involuntary Movement Scale (AIMS) for extrapyramidal symptoms.[25] Independent living and family burden were studied on a 1 to 5 point liker scale with 1 being worst and 5 being good. Good outcome was defined as a score of 2 or less on CGIS.

On using the PANSS, the RSWG criteria[26] based on ratings at 8 focal symptoms in positive, negative and general psychopathology subscales of PANSS (P1, P2, P3, N1, N4, N6, G5, G9) were applied for clinical remission; patients were judged to be in clinical remission according to a severity criterion (scores obtained at each of these items had to be ≤ 3 points, indicating mild severity of symptoms).

Descriptive statistics for demographic characteristics and patient scores at baseline and after ten years of follow-up were calculated. To test the degree of change between baseline and final follow-up assessments, paired *t*-tests were used for continuous variables and McNamara's chi-square tests were used for dichotomous variables. Logistic regression was used to evaluate invariable associations between baseline characteristics and recovery as defined by the CGI-S. Lack of fit was evaluated using the Hosmer-Lemeshow goodness of fit statistic. The seven clinical parameters included negative symptoms, positive symptoms, disorganization, hospitalization in the past two years, suicidality, extra pyramidal function and aggression at the ten year follow-up.

RESULTS

There are two main findings in this study that were evaluated first were the clinical features of patients who did not show improvement at the end of ten years, despite consistent treatment and clinical features at the very beginning which tended to indicate candidates vulnerable for non-response.

A total of 101 subjects made up the study population and this further divided into recovered (n=61) and non recovered subjects (n=40). When non recovered subjects were assessed on various parameters (Table 1), significant reductions in total PANSS scores, positive and negative symptom scores, depression scores on the HDRS and improvement on GAF were noted (p<0.0001 in all cases). Larger number of patients had shown aggressive and violent behavior and disorganized behavior at the baseline. Medications had no effect on recovery of the subjects except Aripiprazole which was used by larger number of patients in the non recovered group (p=0.0203) (Table 2).

When recovered and non recovered subjects were compared after a 10 year period, the subjects with non recover had significantly greater scores on the PANSS (p<0.002), greater positive symptom scores (p=0.0241), greater negative symptom scores (p=0.0003) and lower quality of life scores (p<0.0001). Both groups did not differ on GAF scores (Table 3). The non recovered group had significantly greater number of hospitalizations (p<0.0001), more disorganized behavior (p<0.0002), greater interpersonal issues (p=0.0013) and poor outcome on independent living (p<0.0001) (Table 3).

When the baseline characteristics of both groups were compared at the start of the study, age was lower in the non recovery group (p<0.0001) while greater negative symptom scores (p<0.0001), greater depression scores (p<0.0001) and greater aggression was present (Table 4). It is worthwhile noting that positive symptom scores, duration of illness at the start of the study, total PANSS scores, CGI scores and gender played no role in recovery (Table 4).

DISCUSSION

As pointed out by some researchers, the issue of what the actual rates and correlates of recovery are is an empirical question.[27] Researchers have recently examined five elements of recovery for 130 participants from the United States with co-occurring substance abuse and schizophrenia spectrum disorders. Over a 10-year period they reported that 63% had achieved symptom remission as defined as having mean BPRS scale scores of "3" or less, 62% were in a later phase of substance abuse treatment and at the time abstinent from substances and 57% were living independently. Beyond that, 41.4% of participants had worked in a competitive job in the past year, 49% had regular healthy social contacts and 58% reported acceptable satisfaction with their overall circumstances. Importantly, the attainment of one element of recovery was often not linked to the attainment of others.[28]

Indian studies have linked duration of untreated psychosis as a factor in the long term outcome of schizophrenia.[29] Long term outcome is directly related negatively to delays in seeking treatment. A longitudinal 10 year study in first episode schizophrenia patients demonstrated that treatments received, social support, compliance and delay in treatment all affect outcome in schizophrenia.[30] A review on Indian research in schizophrenia has also emphasized that elucidating factors affecting recovery and non recovery in schizophrenia shall help in the primary prevention of the problem itself.[31] Women in India has been shown to often have

Table 1: Characteristics of non-recovery patients with schizophrenia at baseline and 10 years.

Outcome Parameter	Baseline Mean (SD)	Ten Year Follow-up	Difference	95% Confidence Interval	Statistical analysis
PANNS	102.1 (12.5)	54.9 (9.0)	47.2 (10.4)	43.8 - 50.5	t=22.65, $p<0.0001$*[a]
Positive Symptoms	26.4 (4.2)	9.8 (3.8)	16.5 (5.8)	14.7 - 18.4	t=24.99, $p<0.0001$*[a]
Negative Symptoms	27.5 (5.7)	15.4 (6.0)	12.1 (9.1)	9.1 - 15.0	t=19.639, $p<0.0001$*[a]
Global Psychopath	49.6 (15.6)	26.3 (10.0)	23.3 (15.3)	18.3 - 28.2	t=9.4462, $p<0.0001$*[a]
HDRS	20.6 (5.6)	14.1 (4.9)	6.5 (7.8)	4.0 - 9.0	t=7.3410, $p<0.0001$*[a]
GAF	48.7 (11.3)	79.9 (10.7)	-31.2 (12.2)	-35.3 - -27.1	t=18.223, $p<0.0001$*[a]
Outcome Parameter		**Baseline N (%)**		**At 10 years**	**Statistical analysis**
score>21 Positive Symptoms		34 (85%)		0 (0.0%)	$p<0.0001$*[b]
score>21 Negative Symptoms		35 (87.5%)		5 (12.5%)	$X^2=42.5$, $p<0.0001$*[c]
Disorganization score >3		36 (90.0%)		27 (67.5%)	$X^2=4.781$, $p=0.0289$*[c]
EPS ≤2		38 (95.0%)		25 (62.5%)	$p=0.0007$*[b]
Disturbed Independent Living		40 (100.0%)		35 (87.5%)	$p=0.0547$ NS[b]
Aggression		33 (82.5%)		17 (42.5%)	$X^2=12$, $p=0.0005$*[c]
Family Burden		2 (5.6%)		22 (61.1%)	$p<0.0001$*[b]
Suicidality - Occasional or Occasional with plan		27 (75.0%)		20 (55.6%)	$X^2=1.857$, $p=0.173$ NS[c]
GAF≤80		36 (90%)		20 (55.6%)	$p=0.0002$*[b]

*significant ($p<0.05$), NS-not significant, [a]Paired t test used in the calculation, [b]Fisher's test used in the calculation due to small cell sizes, [c]Chi square test used in the analysis.

Table 2: Medications used in the patients (recovered and non recovered groups).

Medication	Recovered		Statistical Analysis
	No (*n*=40)	Yes (*n*=61)	
Clozapine	6 (15.0%)	4 (6.6%)	$p=0.1882$*[a]
Risperidone	10 (25.0%)	17 (27.9%)	$X^2=0.008$, $p=0.9293$ NS[b]
Olanzapine	8 (20.0%)	12 (19.7%)	$X^2=0.002$, $p=0.9677$ NS[b]
Quetiapine	9 (22.5%)	12 (19.7%)	$X^2=0.008$, $p=0.9293$ NS[b]
Aripiprazole	11 (27.5%)	5 (8.2%)	$X^2=5.382$, $p=0.0203$*[b]
Ziprasidone	3 (7.5%)	3 (4.9%)	$p=0.6788$ NS[a]

*significant ($p<0.05$), NS-not significant

Comparisons made using Chi-square test except for Clozapine and Ziprasidone for which Fisher's Exact two-tailed test was used due to small expected cell sizes.

better outcomes in schizophrenia than men while delay in seeking treatment is often longer in the case of women.[32]

Several authors have suggested that the earliest phases of recovery may involve seeing oneself as a person whose story is worthy of being told, whereas the later stages of recovery involve achieving mastery in the process of constructing and negotiating meaning around the course of the events of one's life.[33]

Most clinicians measure outcome in schizophrenia depending upon their own judgment. In this sample of 101 patients 40 patients did not show clinical response at the end of ten years treatment. The patients who did not respond also showed significant reduction in psychopathology (PANSS total, positive and negative symptom and HDRS scores) and increase in functioning though the level of recovery was short of qualifying as improved on CGIS. More than 60% subjects who did not respond were free from active positive negative and affective symptoms. This suggests that a decrease in symptoms or absence of symptoms alone is not good enough improvement in majority of the patients. Improved outcome perhaps is much more than mere reduction in psychopathology.[34] These patients also show presence of more negative symptoms and more re-hospitalization. Baseline characteristics of subjects who did not respond was typically early age of onset, severe psychopathology and significant burden on the families.It has been consistently reported since the historical times that early onset schizophrenia has poor prognosis.[35] Biological advancements in schizophrenia clearly show that the illness starts much earlier and pathogenesis of the disorder may be rooted in early development.[36] Contrarily increased duration of untreated psychosis leads to more pronounced neurobiological changes[37] and it is therefore clear that younger age of onset of symptoms is an indicator of poorer response.

Our main finding, the presence of severe negative symptoms seen amongst non-responders in the early stage is consistent with reported literature.[38] Negative symptoms have been long recognized as a symptom domain of schizophrenia and it has been consistently reported that negative symptoms are more resistant to treatment and account for most part of dysfunction caused in schizophrenia possibly due to its close association with cognitive dysfunction.[39] Negative symptoms represent a subgroup of schizophrenia which is shown to have specific neurobiological cognitive, imaging and neurophysiological changes.In this background our findings are consistent with reported literature that presence of negative symptoms indicates non-response.

Table 3: Differences between recovered and non recovered subjects at 10 years.

Outcome Parameter	Non Recovered (*n*=40)	Recovered (*n*=61)	Difference	95% Confidence Interval	Statistical analysis
		Mean (SD)			
Age at 10 years	33.4 (7.2)	41.8 (7.3)	-6.5 (7.3)	-9.4 - -3.5	t=5.6863[a], *p*<0.0001*
PANNS	54.9 (9.0)	49.4 (8.2)	5.5 (8.5)	2.1 - 9.0	t=3.1714[a], *p*=0.0002*
Positive Symptoms	9.8 (3.8)	8.0 (3.9)	1.9 (3.8)	0.3 - 3.4	t=2.2915[a], *p*=0.0241*
Negative Symptoms	15.4 (6.0)	10.1 (7.5)	5.4 (6.9)	2.6 - 8.2	t=3.7494[a], *p*=0.0003*
GAF	79.9 (10.7)	78.3 (12.2)	1.6 (11.7)	-3.3 - 6.5	t=0.6761[a], *p*=0.5006 NS
QOL	54.5 (7.5)	76.2 (11.5)	-21.7 (10.1)	-25.8--17.6	*p*<0.0001*[b]
Outcome Parameter		**Non Recovered (*n*=40)**	**Recovered (*n*=61)**		**Statistical analysis**
		N (%)			
>1 Hospitalization		37 (92.5%)	24 (40.7%)		*p*<0.0001*[c]
Disorganization score > 3		27 (67.5%)	17 (27.9%)		X^2=13.82, *p*<0.0002*[d]
IP Social score < 3		36 (90%)	37 (60.7%)		*p*=0.0013*[c]
Work score < 3		39 (97.5%)	36 (60%)		*P*<0.0001*[c]
Disturbed Independent Living		35 (87.5%)	16 (27.1%)		X^2=33.87, *p*<0.0001*[d]
Aggression		17 (42.5%)	22 (36.7%)		X^2=0.194, *p*=0.6595NS[d]
Family Burden		22 (55%)	32 (53.3%)		X^2=0.002, *p*=0.9293 NS[d]
GAF ≤ 80		20 (50%)	35 (58.3%)		X^2=0.274, *p*=0.6004NS[c]
QOL ≤80		40 (100%)	32 (53.3%)		*P*<0.0001*[c]

*significant (*p*<0.05), NS-not significant, [a]Unpaired t test used in the calculation, [b]Wilcoxon sum of the ranks used as data was not normal in distribution. [c]Fisher exact test used in the calculation due to small cell sizes, [d]Chi square test used in the analysis.

Table 4: Differences between recovered and non-recovered subjects at baseline.

Outcome Parameter	Non Recovered (n=40)	Recovered (n=61)	Statistical analysis
	Mean (SD)		
Durn. of symptoms	10.8 (5.7)	14.0 (8.0)	t=2.1898[a], *p*<0.0309*
Age at baseline	24.4 (7.1)	31.8 (7.6)	t=4.9104[a], *p*<0.0001*
PANNS	102.1 (12.5)	108.5 (14.2)	t=2.3205[a], *p*=0.0224*
Positive Symptoms	26.4 (4.2)	29.6 (5.2)	t=2.8203[a], *p*=0.0058*
Negative Symptoms	27.5 (5.7)	20.9 (6.4)	t=5.2887[a], *p*<0.0001*
Global Psychopath.	49.6 (15.6)	57.4 (17.0)	t=2.3288[a], *p*=0.0219*
HDRS	20.6 (5.6)	15.4 (5.6)	t=4.5640[a], *p*<0.0001*
GAF	48.7 (11.3)	48.0 (10.9)	t=0.3111[a], *p*=0.7564 NS
CGI-S	5.5 (0.9)	5.6 (1.0)	t=0.511[a], *p*=0.6105 NS
Outcome Parameter	**N(%)**		**Statistical Analysis**
Male gender	31 (77.5)	43 (70.5)	X^2=0.301, *p*=0.5834 NS[b]
Disorganization > 3	36 (90)	52 (86.7)	*p*=0.5574 NS[c]
EPS ≤ 2	38 (95)	57 (95)	*p*=0.9899 NS[c]
Aggression > 2	33 (82.5)	31 (51.7)	X^2=9.125, *p*=0.0025*[b]
Family Burden > 3	2 (5.6)	2 (3.3)	*p*=0.6474 NS[c]

*significant (*p*<0.05), NS-not significant.

[a]Unpaired t test used in the assessment, [b]Chi square test used in the assessment, [c]Fisher's exact test used in the assessment due to small cell sizes.

Another finding in this study is presence of severe psychopathology for non responsive patients as indicated by presence of positive, negative and affective symptoms as features of non response. This is in line of reported data in literature.[40] Severe illness is also related to more social dysfunction and cognitive dysfunction. Besides, severity of illness leads to frequent and increased duration of hospitalization, longerneuroleptic exposure, greater isolation from one's community and family.[41] There appears to be a direct link between severe psychopathology at the onset and poorer outcome in long run.[42]

Non recovered patients had significantly more severe depressive symptoms at the baseline. Most of the studies report that affective symptoms are common across the course of schizophrenia, more common in acute episode and in general show better response to treatment.[43] In the present study however sever depressive symptoms are seen at baseline among non-responders, which shows significant decrease at the ten years, suggesting response to treatment. At the beginning severe depressive symptoms are seen existing together with negative symptoms. Research data indicates a significant overlap in genetic susceptibility categories of psychotic disorders and affective disorders.[44] Depressive symptoms in schizophrenia may arise as primary or secondary to negative symptoms.[45] Severe depression at the beginning is possibly reflective of depression secondary to negative symptoms and primary depressive symptoms might have responded well. Thus if severe depression is present in acute phase along with severe negative symptoms, then it may be predictive of treatment non response.[46] Our findings are consistent with research available.

Though with poor reliability, the study also shows that type of antipsychotic drug is not related with treatment response or non response in long term. Antipsychotic drugs have limited role in determining outcome of schizophrenia per se.[47] While good response to antipsychotic in early phase and first episode in short term is well established, its response in chronic schizophrenia is limited[48] and in this study all patients were on atypical antipsychotics. Since a number of the patients were on two or three antipsychotic, this finding cannot be interpreted with certainty.

Over all the subjects who did not recover were more severely ill causing significant impact on their families in early stages of the illness though they do show reduction in symptoms over 10 years duration? The present study shows that early age of onset of psychosis and presence of severe negative symptoms are significantly related to future non-response in long term outcome of first episode schizophrenia. Further prospective longitudinal studies in larger populations are needed to establish firmly the findings obtained from this study. It is clear from our study that despite early intervention, adequate social and pharmacological treatment with good compliance, outcome is limited all three, social, clinical as well as functional dimension. This poses few challenges for the treatment. Would there be further deterioration in the patient and how do we go about achieving wellness.

Studies also suggest that neuroplasticity and neuronal regeneration is an important feature in recovering phase of treatment. The patient may need a new care plan at this state of evaluation and strategies of treatment can be modified which may include early identification of treatment resistance, early identification of modifiable factors in the illness, re-evaluation the 'person' who has schizophrenia, patient-centric rehabilitation programs, specific psychosocial interventions, smoking cessation treatments in schizophrenia, management of physical disorder and side effects of medication, re-assessment of pharmacotherapy, improvement in social milieu, lifestyle treatment – diet, weight management, exercise, yoga, cognitive behavior therapies and focus on spirituality.

CONCLUSION

There is a need to enhance hope with better care and further research in schizophrenia.[49,50] It is important that these be incorporated in the long term.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Cite this article : Shrivastava A, Karia S, Shah N, Sousa AD. A Study on the Characteristics of Patients Who do not Recover in the Long-term Treatment of First Episode Schizophrenia. Int J Med Public Health. 2019;9(3):81-6.