Full Length Research Paper

Multiple outcome parameters: A 10 year follow-up study of first-episode schizophrenia

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Schizophrenia is a disease with multiple dimensions, thus its treatment also results in differential outcomes. A number of clinically recovered patients do not recover in several other parameters of social functions which are necessary to lead a socially integrated and functional life, for example, the ability to work or live independently. Until recently, the outcome of schizophrenia has been measured primarily in terms of clinical symptoms. Although there have been revolutionary advances, it is undetermined, the extent to which these patients recover on both clinical and social parameters. This paper examines the status of comprehensive recovery on clinical and social parameters in hospitalized first-episode patients of schizophrenia in a long-term follow-up. 116 patients with first-episode schizophrenia in Mumbai, India, were followed for 10 years. Patients were assessed using clinical and psychopathological dimensions to determine levels of clinical and social recovery. Good outcomes on clinical parameter were seen in 61% of patients, while 46.7% obtained good quality of life, and 72.9% out of the total 116 patients were able to live independently; however, a significant number of these patients were still living with distressing residual symptoms, such as aggression, suicidality, and negative symptoms. The findings show that patient's exhibit differential outcome on multiple parameters, and a significant number continue to live with distressing symptoms, despite continued treatment for long periods. More research is required in outcome measures of response to treatment in schizophrenia, which can represent the real-life situation of these patients.

Key words: Long-term outcome, clinical recovery, social recovery, multidimensional outcome, schizophrenia.

INTRODUCTION

Schizophrenia is a severe mental disorder most commonly affecting young adults, typically in their twenties (Hegarty et al., 1994). Unfortunately, outcomes of schizophrenia continue to be unfavorable, as very few treatments are effective on all dimensions of the illness.

Existing studies suggest that despite revolutionary advances, good clinical outcome (for example, improvement in symptoms) of schizophrenia remains limited (Harrow et al., 2005; Abdel-Baki et al., 2011), while far fewer patients improve in social functions (for example, employment, independent living). A number of patients do not fully improve even after receiving treatment, and many patients live with residual or persisting symptoms as a result (Emsley et al., 2011; Shrivastava et

al., 2010; Andreason et al., 2005).

'Favorable' and 'unfavorable' outcomes depend upon the definitions of the outcome measures; therefore, it remains a matter of considerable debate on what outcome parameters of schizophrenia need to be measured (Ho et al., 2001; Karow et al., 2012; Hofer et al., 2011) which can reflect a real-life comprehensive outcome. A recent study from India showed that, half of the patients who 'recovered' were still exhibiting persistent residual symptoms, suggesting that patients may not recover equally in symptom remission and functionality despite responding to medication (Karow et al., 2012). As such, some patients may respond to all aspects of clinical, social and functional recovery; however, others may only recover in one of these aspects (Bromley and Brekke, 2010; Andreason et al., 2011; Meltzer, 1995).

Many patients shift from remission to relapse during the periods between follow ups. A study by Wunderink et al. (2009) examined the validity of remission in a large community. It was observed that patients fulfilling symptomatic remission criteria subsequently moved out of functional remission, nevertheless, those that did not fulfill functional remission criteria moved into the symptomatic remission category over a period of follow-ups. This demonstrates a significant overlap between remitted and unremitted subjects (Albert et al., 2011). It is therefore evident that remission is not a clinically stable state but rather much more variable than previously assumed.

Outcome research continues to be re-examined and re-defined, and recovery on social parameters is an important consideration (Emsley et al., 2011). The present study examines three indicators of social recovery: work ability (employment), independent living and family burden. Considering these social parameters, along with outcome on clinical parameters, these two measures represent comprehensive recovery. Employment is frequently stated as a goal of people diagnosed with schizophrenia (Schennach et al., 2012). There are wide variations in reported employment rates of schizophrenia patients among different countries. Most recently, European estimates of employment rates within the schizophrenic population range from 8 to 35%, while the rates in the United States are less clear (Marwaha and Johnson, 2004).

In a large community based study from China, (393 people with schizophrenia, 112 of which were never treated) it was reported that rural and urban residents had similar impairments due to symptoms, yet rural residents were three times more likely to be employed (adjusted relative risk 3.27, 95% CI: 2.11 to 5.07, $p <$ 0.001) (Yang et al., 2012). Previous studies have shown that overall employment of persons with schizophrenia seems to be impeded by clinical problems, namely positive and negative symptomologies and poor neurocognitive functioning which have also been

documented as predictive factors for employment status (Schennach et al., 2012).

Independent living has consistently been shown to be a marker of successful outcomes (Warner, 2009). In a 15 year follow-up study by Brown and Birtwistle (1998), it was found that only 19% of schizophrenia patients lived alone, suggesting poor independent living, while 55% were still living with families. Independent living involves dealing with complex personal and social issues and is one of the parameters representing high levels of self-care and the ability to undertake responsibility (Nadine and Medalia, 2004).

In addition to the ability to live independently, family burden is another parameter on which outcome has been measured (Perlick et al., 2006). Living with family, with the exception of living with a partner, is associated with an increased likelihood of recovery (Grandon et al., 2008). This may reflect better social support, which enables better social recovery. In spite of these benefits to the patients, caregivers often experience despair, anger, stress, and reduced quality of life. In a recent study, regarding burden and coping strategies of caregivers, findings revealed that 31.3% caregivers felt distress and 33.3% found stigma upsetting (Tan et al., 2012). Only 14.7% sought help from healthcare workers and 49.3% were interested to know more. Nevertheless, 24.7% verbalized sufficient social support.

As the burden of care giving intensifies, there is an increased propensity for the patient to experience relapse. Therefore, reducing family burden is an important prospective indicator of recovery, and also as an indicator of recovery itself, as it signals the ability and skills of the patient to live more independently with less reliance on family members.

The numbers of patients who recover clinically do not attain significant social and functional recovery, contrarily, socially recovered and functional patients also remain with residual symptoms, suggesting limited clinical recovery. If that is the case, fewer numbers of patients are likely to recover on comprehensive multidimensional parameter. We hypothesize that a far fewer number of patients will attain both social and clinical recovery. Further, fewer numbers of patients will recover when outcome is measured on multiple parameters. This paper examines the comprehensive recovery in a long-term, 10 year follow-up of hospitalized first episode schizophrenic patients.

MATERIALS AND METHODS

This is a cross-sectional study of outcome measurement as per defined criteria on clinical and social parameters of patients who were available at the end of ten years follow up of a cohort of first episode schizophrenia. The study is a part of longitudinal long-term follow-ups study of schizophrenia. Base-line data of patients, who entered this study, was utilized for comparison between baseline and current assessment.

Setting

This study was carried out in Silver-Mind Hospital which is a non-governmental hospital, certified as a psychiatric facility by the State Government, as per the Indian Mental Health Act, 1983. The study started in 1992 and was completed in 2005. The study was approved by the Independent Ethics Commission of Mumbai.

Participants

Participants were hospitalized first-episode patients with schizophrenia. These patients were followed up for a period of ten years. Consenting patients were screened and recruited based on a confirmed diagnosis of schizophrenia as per Diagnostic and statistical manual of mental disorders- fourth edition (DSM-IV) (American Psychiatric Association, 2000), and demonstrated more than 80% compliance with treatment as per patients self-reports, and relatives' statements. These patients were primarily treated with antipsychotic medications, mostly the second generation antipsychotic drugs. They received social treatment in terms of individual family support. There was no structured case management or psychotherapies, except in the first two years of treatment. These patients were subsequently assessed on parameters of psychopathology and social functioning. The mean age of participants was 28.8 years (standard deviation (SD) = 8.2) and the mean illness duration was 12.7 months (SD = 7.3). Patient's characteristics are available in Table 2. The results revealed that 61 of the 101 patients showed 'improvement' on Clinical global impression scale (CGIS) at the end of ten years. During the course of the illness amongst the 101 patients, 36% of patients were never re-hospitalized after initial hospitalization.

Clinical and social assessment parameters and outcome criteria

Clinical outcome was measured using CGIS (Guy, 1976). The clinical outcome measures or clinically good outcomes were indicated by a score of two or less on the CGIS, which meant they were showing "improvement" or "much improvement" on the CGIS between baseline and follow-up. Psychopathology was measured as follows: positive symptoms, negative symptoms and cognitive disorganization, which were assessed using the Positive and negative syndromes scale (PANSS) (Kay et al., 1987). Similarly, the general psychopathology (GP) subscale of PANSS was also used; depressive symptoms were assessed using the Hamilton depression rating scale (HDRS) (Hamilton, 1960); aggression, hospitalization, and suicidality were measured on a scale of 1 to 5 (1 being minimal functioning and 5 being high functioning), and global functioning was assessed by Quality of life (QOL) (WHO-BREF, 1993), as well as the Global assessment of functioning (GAF) (Guy, 1976).

We considered improved functioning as a score of less than 80 on the GAF and greater than 80 on the QOL scale at the end of the ten years. Of particular importance were the three psychopathological and social parameters namely, work ability, independent living and family burden (Table 3). Disturbed independent living (DIL), interpersonal/social functioning (IP), family burden and work ability were assessed using a scale of 1 to 5 (1 being minimal functioning and 5 being high functioning), this was locally tested in earlier studies (Shrivastava and Gopa, 2000).

Statistical analysis

Descriptive statistics (paired t-tests) for characteristics of patient's scores were calculated at baseline and again after the ten year follow-up. Logistic regression and stepwise logistic models were used to evaluate invariable associations between baseline characteristics and recovery as defined by the CGIS (≤ 2).

RESULTS

Overall outcome

Clinically good outcomes, as determined by CGIS scores of two or less, were seen in 61% of patients. Significant improvement in GAF was seen over the 10 years, with 61.7% of patients having scores less than 80. Additionally, 46.7% of patients had achieved good QOL at the end of the 10 year follow-up (scores greater than 80). On the other hand, 39% of patients continued to experience symptoms of aggression, and 53.1% had incidences of suicidality. With respect to symptomologies, there were significant decreases in the total PANSS score (106.0 to 51.6, $p < 0.001$), positive symptoms scores (28.3 to 8.7, $p < 0.001$), negative symptoms score (23.5 to 12.2, $p < 0.001$), scores on the general psychopathology parameter of PANSS (54.3 to 29.1, $p < 0.001$), and scores on HDRS (17.5 to 13.1, $p < 0.001$). These can be seen in Table 1. GAF also showed significant improvement (48.3 to 78.9, $p < 0.001$). In addition to this, 48.5% were able to live independently, 40% were re-employed, and the number of patients who were a burden on family members had significantly decreased (96 to 46%, $p < 0.001$).

Clinical outcome

In a comparison of patients who were classified as recovered based on CGIS scores versus non-recovered on CGIS scores at follow-up, those who recovered were more likely to have quality of life scores greater than or equal to 80, indicative of improved quality of life, compared to those who did not recover (Table 2). Additionally, those in the CGIS non-recovered group were much more likely to display symptoms of suicidality at the endpoint than those in the CGIS recovered group. There were no other significant differences between the two groups on clinical symptoms.

When looking at the number of clinical parameters on which patients were considered recovered, those classified as recovered on the CGIS did tend to have a higher number of recovered parameters; only 13.1% were not recovered on any parameters versus 27.5% of the CGIS non-recovered group; although this was not a significant difference. Both non-recovered and recovered CGIS patients exhibited equivalent recovery on at least 1 parameter (55 and 45.9%, respectively), yet recovered CGIS patients tended to have greater improvement when considering 2 (31.2% for recovered, 15% for non-recovered)

Table 1. Comparison of outcomes between baseline and follow-up.

Outcome	Baseline	Follow-up	P value
	M (SD)	M (SD)	
PANSS	106.0 (13.9)	51.6 (8.9)	<0.001
Positive symptoms	28.3(5.1)	8.7 (3.9)	<0.001
Negative symptoms	23.5 (6.9)	12.2 (7.4)	<0.001
GP	54.3 (16.8)	29.1 (11.9)	<0.001
HDRS	17.5 (6.1)	13.1 (5.2)	<0.001
GAF	48.3 (11.0)	78.9 (11.7)	<0.001
	n	n	
Work ≤ 3	74	75	0.842
DIL ≤ 3	89	48	<0.001
Aggression>2	64	39	<0.001
Family burden>3	4	54	<0.001
Suicidality>1	73	51	<0.001

M = mean, SD = standard deviation. PANSS - Positive and negative syndrome scale; GP - General psychopathology subscale of PANSS; HDRS - Hamilton depression rating scale; GAF - Global assessment of functioning; IP Social - Interpersonal/Social; DIL = Disturbed independent living.

Table 2. Comparison of clinical parameters between recovered and non-recovered patients.

10 year outcome	Clinical recovery (CGIS) (%)		
	Not recovered (n=40)	Recovered (n=61)	P Value
GAF≥80	22 (61.1)	37 (61.7)	0.957
QOL≥80	0 (0.0)	28 (46.7)	<0.001
Positive symptoms>21	0 (0.0)	0 (0.0)	-
Negative symptoms>21	5 (12.5)	7 (11.5)	>0.999 (Fisher's exact)
HDRS>17	10 (25.0)	12 (21.1)	0.648
Suicidality>1	36 (90.0)	15 (24.6)	<0.001
Clinical parameters showing recovery (%)			
None	11 (27.5)	8 (13.1)	0.111
1	22 (55.0)	28 (45.9)	0.564
2	6 (15.0)	19 (31.2)	0.103
3	1 (2.5)	6 (9.8)	0.165
4	0 (0.0)	0 (0.0)	

recovered) or three (9.8% for recovered, 2.5% for non-recovered) parameters, but again these differences were not significant. Neither groups demonstrated recovery on four or more parameters (Table 2).

Social outcomes

In terms of work ability and employment, there was a significant difference in skills necessary for employment in those patients who had recovered (40%), compared to those who were not recovered (25%). In a comparison of patients who were classified as recovered based on CGIS scores versus non-recovered on CGIS scores, those who recovered were more likely to have an independent living score higher than 3 (72.9%) compared to those who were not recovered (12.5%) (Table 3). The CGIS recovered and CGIS non-recovered groups did not differ significantly on family burden scores (46.7% for recovered versus 38.9% for non-recovered).

When looking at the number of social parameters on which patients were considered recovered, almost half (45.0%) of the CGIS non-recovered group did not show recovery on any of the social parameters, which differed

Table 3. Comparison on social parameters between recovered and non-recovered patients.

10 year outcome	Not recovered (%) (n=40)	Recovered (%) (n=61)	P value
Independent>3	5 (12.5)	43 (72.9)	<.001
Work>3	1 (2.5)	24 (40.0)	<0.001
Family burden≤3	14 (38.9)	28 (46.7)	0.457
Number of social parameters showing recovery (%)			
None	18 (45.0)	3 (4.9)	<0.001
1	20 (50.0)	26 (42.6)	0.630
2	2 (5.0)	26 (42.6)	<0.001
3	0 (0.0)	6 (9.8)	0.046

significantly from 4.9% of the CGIS recovered group (p < 0.001) (Table 3). There was no significant difference between both CGIS recovered and CGIS non-recovered groups on one outcome parameter (42.6 and 50%, respectively, p = 0.630). While 42.6% of CGIS recovered patients showed recovery on two parameters, 5% of CGIS non-recovered patients recovered on two para-meters (p < 0.001). Additionally, 10% of CGIS recovered patients had improvement on all three social parameters classifying them as fully recovered, while none of the CGIS non-recovered group showed recovery level scores on all three social parameters (p = 0.046) (Table 3).

Multidimensional outcome

As anticipated, recovery was associated with an increasing number of these three parameters showing recovery (p < 0.001). Of the 101 subjects, there were 18 (17.8%) who did not recover clinically and did function satisfactorily in these three social parameters (see non-recovered column of Table 3). On the other hand, there were 32 (52.4%) of the subjects who recovered clinically and functioned satisfactorily on two or three of these social parameters. Only two of the clinically non-recovered patients functioned satisfactorily on two social criteria.

DISCUSSION

We found that 61% of patients showed improvement over the course of the ten years with respect to clinical para-meters. Of particular importance was that participants improved greatly in suicidality and QOL, yet the majority of participants tended to recover on only one clinical parameter, and none recovered on more than three parameters. Many long-term outcome studies from India have reported similar favorable outcomes results, ranging from 22 to 75% (Susser et al., 1998; Varma et al., 1997).

The Madras longitudinal study (Thara, 2004) from India reported good outcomes as high as 75%, which were accompanied by significant numbers of patients finding employment 10 to 15 years later. This rate of remission is parallel to rates reported from urban and rural Chandigarh as part of the Determinants of outcome of severe mental disorders (DOSMeD) project (Craig et al., 1997); nonetheless, these numbers are lower than the 69% remission rate recorded in Vellore, in the Study of Factors affecting the course and outcome of schizophrenia (SOFACOS) in the early 1980s (Verghese et al., 1989). This is consistent with the favorable outcome hypothesis in low and middle-income countries found in previous literature (Kulhara, 1994; Malhotra et al., 1998; Varma et al., 1996; Susser et al., 1995).

A significant proportion of first-episode schizophrenia pa-tients achieve a moderate to long-term outcome, which results in stability of global functioning rather than dete-rioration, as shown in most industrialized countries (Wallace et al., 2000). There is a growing interest in identifying and surmounting barriers to employment for people with schizophrenia. Our finding of good outcomes in 61% of patients after ten years is consistent with what has been previously reported.

In the present study, among those who recovered on the CGIS, we found that 72.9% were living indepen-dently. Independent living has consistently been shown to be a marker of successful outcomes, as it involves abilities of self-care, undertaking responsibilities, and dealing with complex personal and social issues (Wallace et al., 2000). In a 15 year follow-up study by Brown and Birtwistle (1998), it was found that only 19% of patients lived alone, suggesting poor independent living, while 55% were still living with families. Thus, our results show much higher levels on independent living than seen in previous studies. Perhaps the inclusion criteria of good compliance with treatment in the present study led to this finding, or there may be other cultural or contextual factors that predispose some groups of patients to higher rates of independent living.

In contrast to previous findings by Srinivasan and Thara (1997) who demonstrated robust employment rates from India in which they report an increase in employment rate to 53% in a long-term study, there were no improvements in work or employability skills in our total sample. However, when considering those who were clinically recovered, there were significant differences in employment, with 40% of recovered patients employed.

Multidimensional outcome

We sought out to examine the number of patients who recovered on each of these three criteria alone (work ability, independent living and family burden), as well as on possible combinations of these three parameters. We found that when we combined clinical criteria with two or three other areas of social criteria, the recovery rate dropped to about 10 to 43% (see recovered column in Table 3). This study showed that approximately two thirds of patients recover on clinical aspects only, and by about one third on both parameters. In this study, 46% of patients showed a score of less than 80 on QOL in the recovered group. We then looked at how many patients showed improvement in symptoms, QOL, and level of functioning combined in the recovered group. We found that 45% of patients recovered on two parameters, and 31% recovered on three parameters (QOL and GAF) when taken together. Thus, a comprehensive social recovery occurred in a range of 31 to 45% of patients (Table 2).

Sartorius et al. (1996) found similar results of poor outcomes in chronic schizophrenic patients when followed up for an average of six years. They reported that depending upon the criteria applied, symptomatic remission at follow-up was observed in only 37 to 59% of the cohort. In addition to this, social-vocational recovery was observed in 31% of the cohort. Approximately a quarter of the patients achieved both symptomatic remission and social-vocational recovery; 78% of patients had a relapse during the period of follow-up, with only 3% rated as having a good outcome on the Global assessment scale (GAS).

Liberman and Kopelowicz (2005) compared remitted and unremitted patients and reported that a significantly better level of functioning was measured for remitted versus non-remitted patients, though these remitted patients still showed areas with an inadequate level of functioning. Functional deficits were most often seen in social relations (40%), work (29%) and daily life activities (17%). These findings are in line with the present study being that, at the end of ten years of reasonably continuous treatment, 40% of the patients still exhibited depressive symptoms, 24% presented with negative symptoms and 51% showed symptoms suggestive of suicide behavior, intent or occasional crisis. Moreover,

amongst the subjects who showed clinical recovery, 21.1% showed depressive symptoms, 11.5% showed negative features and 24% showed symptoms of suicidality.

Conclusion

This study has shown that when clinical and social parameters of outcome are combined, outcome rates drop significantly. Though there is significant overlap between these aspects, all subjects achieving symptomatic remission do not necessarily gain social recovery as well. A significant number of patients, despite recovery, still live with persisting symptoms of aggression, depression and a range of suicidal tendencies. Since patients achieve different level of outcome on different parameters, clinical recovery only cannot be sufficient enough to represent a correct state of outcome. It is therefore important that outcome should be measured on multiple parameters, most importantly of clinical and social parameters. Further research is required in this area to decide on what parameters of outcome of schizophrenia should be measured.

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