Negative Symptoms in the Remission Phase of Bipolar Disorder

Shahul Ameen and Daya Ram

Department of Psychiatry, Central Institute of Psychiatry, Ranchi, India

Corresponding author: Daya Ram, Professor of Psychiatry, Central Institute of Psychiatry, Ranchi, India.
E-mail: editor@psyplexus.com

Abstract

Objectives: Though negative symptoms (NS) are major contributors to sociooccupational dysfunction in schizophrenia, NS in remitted bipolar disorder (BPD) are little studied. We evaluated the prevalence and correlates of NS and their contribution to sociooccupational dysfunction in remitted BPD. Methods: Ninety remitted BPD patients, receiving only mood stabilizers, were evaluated with the Scale for Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS) and Social and Occupational Functioning Assessment Scale. Forty-five normal controls matched for age, sex and total years of education were assessed with SANS. Results: NS were present in 26.67% of the patients. The patients had more severe affective flattening, alogia, anhedonia-asociality and avolition-apathy. Primary NS were associated with history of obstetric complications, family history of schizophrenia, earlier age of illness onset, history of mood incongruent psychotic features (MIPF), poor premorbid and current sociooccupational functioning and a greater decline in functioning after illness onset. Factor analysis revealed three factors which explained 62.08% of the variance - secondary negative and subaffective symptoms, primary NS, and anxiety symptoms. Conclusions: As NS are prevalent in remitted BPD and contribute to the patients' sociooccupational dysfunction, they require prompt detection and management (German J Psychiatry 2007;10: 1-7).

Key words: bipolar disorder, negative symptoms

Introduction

Bipolar disorder (BPD) is the sixth leading cause of disability in the world (Murray and Lopez 1996). Following initial optimistic estimations about the outcome of the disorder, now it is clear that substantial morbidity, like functional deficits and poor quality of life, remain in remitted BPD patients (Fagioloni et al., 2005; Sierra et al., 2005). Psychosocial dysfunction is present in 30-60% of BPD patients (MacQueen et al., 2001), and this could be due to cognitive deficits, subsyndromal depression, treatment side effects, or comorbid conditions (Zubieta et al., 2001; Altshuler et al., 2002; Kocsis et al., 1993; van Gorp et al., 1998). Assessment and management of factors contributing to the poor functioning in remitted BPD patients is necessary to ameliorate one of the biggest disabilities in the world.

Although negative symptoms (NS) have been consistently associated with socio-occupational dysfunction (Trumbetta and Mueser 2001) and treatment of NS has been found to improve sociooccupational functioning (Corrigan et al., 2003) in schizophrenia, few studies have assessed NS in remitted BPD (Pearlson et al., 1984, 1985; Reddy et al., 1992; Husted et al., 1995; Maziade et al., 1995; Atre-Vaidya et al., 1998). Reddy et al. (1992) reported mild affective flattening (17%), mild alogia (7%), and attentional impairment (mild in 40%, prominent in 17%) in remitted manic patients with chronic functional impairment. NS in remitted BPD patients have been associated with poorer sociooccupational functioning (Pearlson et al., 1984, 1985; Atre-Vaidya et al., 1998). However, all the previous studies in the area had limited samples, and many had methodological limitations like inclusion of patients taking antipsychotic medications (Reddy et al., 1992; Husted et al., 1995), use of only some subscales of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1982) to rate NS (Reddy et al., 1992), or use of only a subgroup of remitted BPD patients, like those with

chronic impairment of functioning (Reddy et al., 1992) or a history of psychotic symptoms (Pearlson et al., 1984, 1985). No study had distinguished between primary and secondary NS (Carpenter et al., 1988), though this distinction is important from the therapeutic perspective. Furthermore, none of the previous studies had attempted to find the relation of NS to subaffective symptoms through factor analysis, probably due to their small samples. A recent review of psychosocial outcomes in BPD concluded that it remains unclear whether a subset of patients with BPD develops a syndrome analogous to the deficit syndrome of schizophrenia (MacQueen et al., 2001).

In view of the rarity and methodological limitations of existing research in the area, we attempted to comprehensively investigate NS in a large sample of remitted BPD patients. The specific objectives that we pursued were 1) to identify the prevalence of NS, 2) to determine the correlates of primary and secondary NS, 3) to check the relationship of negative and subaffective symptoms, and 4) to assess the relative contribution of NS to the patients' sociooccupational dysfunction.

Materials and methods

Subjects

We carried out this study at the Mood Clinic of Central Institute of Psychiatry, Ranchi, India. This was a cross-sectional, hospital-based study that used purposive sampling technique. The study was approved by the Ethical Committee of Central Institute of Psychiatry and all subjects gave their informed consent. The sample consisted of 90 outpatients and 45 normal controls matched for age, sex and total years of education. The patient group had a discharge diagnosis of bipolar affective disorder based on ICD-10 criteria (World Health Organization 1992). The diagnoses were made during the patient's acute episodes by experienced psychiatrists and were reviewed during the subsequent visits. We included patients who were currently in remission (F 31.7) and were receiving regular prophylactic treatment with one or more mood stabilizers. We excluded patients receiving any other psychotropic medications, had received oral antipsychotics within previous one month or depot antipsychotics within previous three months, had extrapyramidal symptoms as assessed using the Simpson and Angus Extrapyramidal Rating Scale (Simpson and Angus 1970), had significant adverse effects of the mood stabilizer(s) as assessed using the checklists devised by Kutcher (1997), or suffered from comorbid psychiatric disorders, substance abuse (except harmful use of nicotine) or serious medical illness. The normal controls were recruited from the local population. Inclusion criterion for controls was a score <1 in General Health Questionnaire - 5 (Shamsunder et al., 1986), while the exclusion criteria were history of any psychiatric or serious physical disorder and history of psychotic illness in first degree relatives.

Clinical Assessment

Patients were interviewed in detail to ensure remission and to exclude clinically significant depression. NS were assessed using SANS (Andreasen 1982). The scale contains five symptom complexes: affective flattening, alogia, anhedonia-asociality, avolition-apathy and attentional impairment. Carpenter et al. (1988) have divided NS to primary NS, which are enduring, and secondary NS, which are more transient and occur secondary to other factors (e.g., anxiety, suspiciousness, and depression). Affective flattening, alogia and attentional impairment are considered to be the primary NS, while avolition-apathy and anhedonia are the secondary NS. The SANS score for each patient may be calculated as either SANS composite score (the sum of scores for 32 individual items) or SANS summary score (the sum of scores for five global ratings). The summary score is regarded a more sensitive index of the NS syndrome (Andreasen 1982). The presence of NS has been defined as a summary score greater than two (Möller et al., 2002).

Subaffective and residual symptoms were assessed using Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962). To measure the subaffective symptoms, the items were grouped into categories following the classification used by Tarell and Schultz (1987). The items grandiosity, uncooperativeness and excitement were categorized as Mania, and the item anxiety and tension was categorized as Anxiety. Though the category Depression in the original classification contains the items depressed mood, guilt feelings, somatic concern, emotional withdrawal, blunted affect and motor retardation, we removed the last three items from the category so that they do not confound a correlation with NS. The patients' premorbid and current sociooccupational functioning were measured with Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992).

The first author (SA) obtained the sociodemographic and clinical variables through direct interview and from the Case Record File. Except for diagnosis and the current medications, the interviewer (SA) was blind to the clinical and sociodemographic characteristics of the patients at the time of assessment with BPRS, SANS and SOFAS.

Statistical Analyses

The data were analyzed with Statistical Package for Social Science for windows, version 10.0 (SPSS 10.0). We used descriptive analyses, Mann-Whitney U test, chi-square test with Yates correction, and Pearson correlation coefficient To investigate the multivariate relationship between functional impairment and negative and subaffective symptoms, we fitted multiple linear regression models with SOFAS score as the dependent variable, and the SANS scores for primary and secondary NS, and BPRS scores for manic, depressive and anxiety symptoms as independent variables. We controlled for the possible effects of age, premorbid functioning, duration of illness, and the number of past episodes by including these as independent variables as well.

The symptom interrelationships were studied by principal components factor analysis using a correlation matrix and a VARIMAX rotation. Only those factors with Eigen value >1 were retained. Statistical significance required two-tailed p < 0.05.

Results

Demographic characteristics

The mean age of the patient group was 32.29 ± 9.36 years (range 18-69) and 73 (81.1%) of them were male. Mean total years of education was 9.92 ± 4.49 (range 0-18). Thirty seven patients (41.1 %) had a family history of BPD, and six (6.7 %) had a family history of schizophrenia. Nine (10%) patients had a history of obstetric complications (OCs). Information about OCs was missing in 44 patients (48.9%). The mean age at illness onset was 23.26 ± 8.66 years (range 10-57), the mean duration of illness at the time of assessment was 9.78 ± 6.35 years (range 2-34), and mean number of past episodes was 3.75 ± 1.84 (range 2-10). Nine (10%) and seven (7.8%) patients had a history of mood incongruent psychotic features (MIPF) and mixed episodes respectively. Fifty eight (64.4%) patients were treated with lithium carbonate, 17 (18.9%) with carbamazepine, 11 (12.2%) with sodium valproate, and four (4.4%) with a combination of two of these agents. Mean SOFAS scores for premorbid and current sociooccupational functioning were 86.44 ± 3.11 (range 80-90) and 82.70 ± 6.90 (range 60-95) respectively, and the mean decline in functioning after illness onset was 3.80 ± 6.62 (range -10-25). Mean total BPRS score was 20.56 ± 2.32 (range 18-28).

The mean age of the control group was 32.64 ± 8.61 years (range 19-60) and 37 (82.2%) of them were male. Mean total years of education was 11.82 ± 6.44 (range 0-21). The groups were matched for age, sex and total years of education.

Prevalence of NS

The SANS scores obtained by the two groups are compared in Table 1. The patient group secured significantly higher scores in the SANS items unchanging facial expression, affective nonresponsivity, poverty of speech, poverty of content of speech, grooming and hygiene, impersistence at work or school, physical anergia, recreational interests and activities, sexual interest and activity, ability to feel intimacy and closeness and relationships with friends and peers. The patient group had significantly high global ratings in all the SANS subscales except attention, and significantly high scores in SANS composite and summary scores. Considering a SANS summary score of > 2 as the presence of NS (22), NS were found to be present in 24 (26.67%) patients. Of these, six patients had a SANS summary score of three, five scored four, three scored five, four scored six, three scored seven, one scored eight and two scored nine.

Table 1. Comparison of remitted bipolar disorder patients (n = 90) and normal controls (n = 45) on SANS scores (SANS = Scale for Assessment of Negative Symptoms; ns = not statistically significant)

SANS Item	Patients	Controls	p
Unchanging facial expression	0.88 ± 1.01	0.04 ± 0.21	< .0005
Decreased spontaneous movements	0.41 ± 0.86	0.13 ± 0.34	ns
Paucity of expressive gestures	0.30 ± 0.71	0.16 ± 0.37	ns
Poor eye contact	0.94 ± 1.21	0.76 ± 0.91	ns
Affective nonresponsivity	0.39 ± 0.86	0.00 ± 0.00	< .01
Lack of vocal inflections	0.06 ± 0.27	0.00 ± 0.00	ns
Global score in affective flattening	0.61 ± 0.92	0.02 ± 0.15	< .0005
Poverty of speech	0.26 ± 0.66	0.02 ± 0.15	< .05
Poverty of content of speech	0.23 ± 0.67	0.00 ± 0.00	< .05
Blocking	0.00	0.00	ns
Increased latency of response	0.11 ± 0.48	0.02 ± 0.15	ns
Global score in alogia	0.18 ± 0.46	0.00 ± 0.00	< .01
Grooming and hygiene	0.22 ± 0.58	0.02 ± 0.15	< .05
Impersistence at work or school	0.43 ± 0.87	0.02 ± 0.21	< .01
Physical anergia	0.54 ± 1.12	0.02 ± 0.36	< .05
Global score in avolition - apathy	0.44 ± 0.85	0.00 ± 0.00	< .0005
Recreational interests and activities	0.54 ± 1.05	0.02 ± 0.15	< .01
Sexual interest and activity	0.27 ± 0.82	0.00 ± 0.00	< .05
Ability to feel intimacy and closeness	0.31 ± 0.84	0.00 ± 0.00	< .01
Relationships with friends and peers	0.46 ± 1.02	0.00 ± 0.00	< .01
Global score in anhedonia - asociality	0.41 ± 0.82	0.00 ± 0.00	< .0005
Social inattentiveness	0.13 ± 0.43	0.02 ± 0.15	ns
Attentiveness during mental status testing	0.53 ± 0.72	0.60 ± 0.84	ns
Global score in attention	0.20 ± 0.45	0.02 ± 0.29	ns
SANS composite score	7.02 ± 7.18	1.89 ± 1.61	< .0005
SANS summary score	1.84 ± 2.34	0.11 ± 0.32	< .0005

Table 2. Association of primary and secondary negative symptoms with demographic and clinical variables (BPD = Bipolar disorder; SZ = Schizophrenia; OCs = Obstetric complications; MIPF = Mood-incongruent psychotic features; ns = not statistically significant)

Variables		Primary NS		Secondary NS	
		r	p	r	p
Age		-0.19	ns	-0.07	ns
Premorbid functioning		-0.28	<.01	-0.17	ns
Age of illness onset		-0.27	<.05	-0.07	ns
Total no. of past episodes		0.10	ns	-0.08	ns
Current functioning		-0.35	<.01	-0.75	<.0005
Decline in functioning		0.24	<.05	0.71	<.0005
Anxiety		0.17	ns	0.21	< .05
Depression		0.20	ns	0.51	<.0005
Mania		-0.16	ns	-0.07	ns

		Mean ± S.D.	Z	p	Mean ± S.D.	Z	p
Sex	Male	0.85 ±1.28	1.01	ns	0.86 ± 1.56	0.36	ns
	Female	0.53 ± 1.07			0.82 ± 1.13		
Family history of BPD	Present	0.70 ± 1.15	0.54	ns	1.14 ± 1.81	0.65	ns
	Absent	0.85 ± 1.31			0.66 ± 1.18		
Family history of SZ	Present	2.67 ± 1.97	2.91	<0.01	1.50 ± 2.07	0.86	ns
	Absent	0.65 ± 1.07			0.81 ± 1.44		
History of OCs	Present	2.44 ± 1.33	3.80	<.0005	2.00 ± 2.00	2.01	ns
	Absent	0.54 ± 0.93			0.81 ± 1.47		
History of MIPF during episodes	Present	1.44 ± 1.33	2.00	<.05	2.00 ± 2.45	2.07	<.05
	Absent	0.72 ± 1.22			0.73 ± 1.29		
History of mixed episodes	Present	1.14 ± 0.90	1.60	ns	1.57 ± 1.40	2.00	<.05
	Absent	0.76 ± 1.26			0.80 ± 1.48		

Correlates of NS

Table 2 shows how different sociodemographic and clinical variables are related to the severity of primary and secondary NS. Primary NS scores were computed by adding the summary scores for affective flattening and alogia. Attentional impairment, a primary NS, was excluded from the analysis as there was no significant group difference for this item. Secondary NS scores were computed by adding the summary scores for avolition-apathy and anhedonia. Primary NS were significantly associated with history of OCs, family history of schizophrenia, younger age at illness onset, history of MIPF in past episodes, poorer premorbid and current sociooccupational functioning and a greater decline in functioning after illness onset. Secondary NS showed significant associations with history of MIPF in past episodes, history of mixed episodes, poorer sociooccupational functioning, a greater decline in functioning after illness onset, and the severity of subaffective depressive and anxiety symptoms.

Contribution of NS to sociooccupational dysfunction

Regressing SOFAS score on primary and secondary NS, and controlling for age, duration of illness, total number of past episodes, level of premorbid functioning, and the severity of subsyndromal anxiety, manic, and depressive symptoms, we observed a highly significant effect (negative) of secondary NS (t = -8.52, df = 79, p <0.0001) and a significant effect of premorbid functioning (t = 3.11, df = 79, p <0.01) on level of current sociooccupational functioning (Table 3).

Factor analysis of negative and subaffective symptoms

To get a more comprehensive picture of the the patients' symptoms and to see how the NS are related to the subaffective symptoms, a factor analysis was conducted on the SANS subscales and the subaffective symptoms (Table 4). Those items that showed a correlation of >0.30 are reported. Three clearly interpretable and clinically relevant factors were identified, and these explained 62.08% of the variance. The first and strongest factor represented secondary negative and subaffective symptoms, with strong positive loadings for avolition – apathy, anhedonia- asociality, anxiety, and depression. The second factor represented primary NS, with strong positive loadings affective flattening, alogia and attention. These two factors accounted for 48% of the variance. The third factor represented anxiety symptoms, with strong positive loadings for anxiety and strong negative loadings for attention and mania.

Table 3. Regression analysis to compare contributions of primary and secondary negative symptoms and other variables to score in SOFAS (SOFAS = Social and Occupational Functioning Assessment Scale; ns = not statistically significant)

	B	SE	Beta	t-statistic	p
(Constant)	31.16	17.16		1.82	ns
Age	0.11	0.06	0.14	1.74	ns
Duration of illness	0.04	0.10	0.04	0.45	ns
Total no. of past episodes	-0.46	0.29	-0.12	-1.61	0.11
Premorbid functioning	0.53	0.17	0.24	3.11	<0.01
Anxiety	-0.69	0.65	-0.08	-1.06	ns
Mania	2.19	1.37	0.12	1.61	ns
Depression	0.04	0.44	0.01	0.10	ns
Primary negative symptoms	0.07	0.44	0.01	0.15	ns
Secondary negative symptoms	-0.33	0.38	-0.70	-8.52	<0.0001

Model fit F= 16.39, df=9,79, p <0.0001; R^2=0.65

Table 4. Factor analysis of the SANS subscales and subaffective symptoms (SANS = Scale for Assessment of negative symptoms)

	1	2	3
Affective flattening		0.75	
Alogia		0.82	
Avolition - apathy	0.82		
Anhedonia- asociality	0.81		
Attention		0.62	-0.31
Anxiety	0.30		0.53
Mania			-0.86
Depression	0.76		
% of variance explained	26.08	20.69	15.31
Cumulative % for the set	26.08	46.77	62.08

Discussion

Methodological considerations

We obtained obstetric history by direct interview with elder family members and through letters mailed by the patients after consulting their mothers. A high degree of concordance between maternal reports and birth records has been previously found (Brent et al., 1982; O'Callaghan et al., 1990).

Since features of NS have been known to occur in relatives of patients with psychotic disorders (Tsuang et al., 1990), persons who had a first degree relative with psychotic disorders were excluded from being normal controls.

There are also some methodological limitations to this study. First, the study was conducted in a tertiary level referral centre and was restricted to patients who were compliant to treatment. Second, the subjects were predominantly male. These factors might limit the generalisability of our findings. Finally, information about OCs was not available for nearly 50% of the patients.

Prevalence of NS

Our observed prevalence of NS, at 26.67%, accords quite well with value of 28.13% reported by Möller et al. (2002) in patients with affective psychoses 15 years after discharge using the same definition for presence of NS.

Our patient group had significantly high scores (p <.0005) in all the SANS subscales except attention. The absence of a higher score in attention was unexpected, as Reddy et al. (1992) had found prominent attentional impairment in 17% of BPD patients. However, all their patients had chronic impairment of functioning. Also, concerns have been raised about validity of the SANS attention subscale (Walker and Harvey 1986).

Correlates of NS

In our sample, primary NS were associated with history of OCs. Pearlson et al. (1984, 1985) had also found association between OCs and presence of NS in BPD. This finding has one important practical implication: since OCs contribute to NS and subsequent sociooccupational dysfunction in patients with BPD, improved obstetric care for females from families loaded with BPD may be an economically promising approach to the primary prevention of this disability.

Primary NS were associated with a younger age of onset of BPD in our sample. Attentional impairment, a primary NS, has been previously associated with an earlier age of onset of BPD (Reddy et al., 1992). NS are also associated with earlier age of onset in schizophrenia (Bellino et al., 2004).

We found that both primary and secondary NS are associated with a history of MIPF in past episodes. This is a replication of the findings of Miklowitz (1992) who reported that patients suffering from mania with MIPF had more severe NS after nine months of presentation.

Sex was not associated with the severity of NS in this study. This is in contrast to the findings in schizophrenia, where several authors (For e.g., Carpenter et al., 1988) have detected more severe NS in males. There might be a true ab-

sence of such a relationship in BPD, or this finding could be a type II error due to overrepresentation of males (81.1 %) in our sample.

One interesting observation is that while no associations were detected between the severity of primary NS and specific BPD-related variables like number of past episodes and family history of BPD; significant associations were found with variables more related to schizophrenia, like family history of schizophrenia and history of MIPF, and factors which are correlated with NS in schizophrenia, like history of OCs, level of premorbid functioning and younger age at illness onset. These findings support the concept of unitary psychosis which proposes that BPD and schizophrenia are distributed along a continuum of the same complex of genetic and environmental causes (Crow, 1987).

Sociooccupational dysfunction and NS

Our study found that the severity of primary and secondary NS are inversely correlated to the patients' current sociooccupational functioning, and that the severity of secondary NS is the best predictor of the patients' current sociooccupational functioning. The association between severity of NS and the level of sociooccupational functioning in BPD has also been reported by other authors (Atre-Vaidya et al., 1998; Pearlson et al., 1984, 1985; Reddy et al., 1992). However, the previous studies have not considered the contribution of the depressive symptoms to the psychosocial dysfunction. We found that, after controlling for previously identified correlates of sociooccupational dysfunction like age of onset (Carlson et al., 2002) and severity of depressive and anxiety symptoms (Altshuler et al., 2002; Ozer et al., 2002; Kuschizophrenianir et al., 2000), the level of premorbid functioning and the severity of secondary NS are significant predictors of the level of patients' current functioning. A recent review had reported that high premorbid social or functional status is amongst the best predictors of psychosocial recovery in BPD (MacQueen et al., 2001).

The clinical implications of these findings are immense. As BPD is the sixth leading cause of disability in the world, and as NS are the major contributors of sociooccupational dysfunction in remitted BPD, timely recognition of the subgroup of patients who have primary or secondary NS and implementation of appropriate pharmacological and psychosocial interventions may help in the amelioration of one of the biggest disabilities of the world.

Factor analysis of negative and subaffective symptoms

To the best of our knowledge, this is the first study to report the factor analysis of NS in remitted BPD. Negative factor have been related to depressive syndrome in a principal component analysis which included patients with affective and nonaffective psychoses (Peralta et al., 1997).

Our findings suggest that there are two groups of remitted BPD patients with NS - one with subaffective symptoms and secondary NS, and another with primary NS. The former group may benefit from pharmacological or psychosocial interventions aimed at management of their subaffective and secondary NS, while the other group may require more specific interventions for their primary NS.

Conclusions

NS are prevalent in remitted BPD, and contribute to the patients' sociooccupational dysfunction. Identification of primary and secondary NS in remitted BPD patients, especially those who have risk factors like history of OCs, family history of schizophrenia, earlier age of illness onset, poor premorbid functioning and history of history of MIPF or mixed episodes, and implementation of appropriate psychosocial and pharmacological interventions are necessary to improve the disability caused by BPD.

References

Literatur... Altshuler LL, Gitlin MJ, Mintz J, Leight KL, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002; 63: 807-811

Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. Arch Gen Psychiatry 1982; 39: 784-788

Atre-Vaidya N, Taylor MA, Seidenberg M et al. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 3, 120-126

Bellino S, Rocca P, Patria L et al. Relationships of age at onset with clinical features and cognitive functions in a sample of schizophrenia patients. J Clin Psychiatry 2004; 65: 908-914

Brent GH, Marcenko-Bourer I, Smiley D. Paranatal complications are not associated with affective disorder in the offspring of bipolar manic-depressives. Neuropsychobiology 1982; 8: 1-9

Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE. Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. Am J Psychiatry 2002; 159: 307-309

Carpenter WT Jr, Heinricks DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988; 145: 578-583

Corrigan PW, Reinke RR, Landsberger SA, Charate A, Toombs GA. The effects of atypical antipsychotic medications on psychosocial outcomes. Schizophr Res 2003; 63: 97-101

Crow TJ. Psychosis as a continuum and the virogene concept. Br Med Bull 1987; 43: 754-767

Fagiolini A, Kupfer DJ, Masalehdan A et al. Functional impairment in remission phase of bipolar disorder. Bipolar Disord 2005; 7: 281-285

Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM IV: A review of measures of social functioning. Am J Psychiatry 1992; 149: 1148-1156

Husted JA, Beiser M, Iacono WG. Negative symptoms in the course of first-episode affective psychosis. Psychiatr Res 1995; 56: 145-154

Kocsis JH, Shaw ED, Stokes PE et al. Neuropsychologic effects of lithium discontinuation. J Clin Psychopharmacol 1993; 13: 268-275

Kuschizophrenianir A, Cooke RG, Young LT. The correlates of community functioning in patients with bipolar disorder. J Affect Disord 2000; 61: 81-85

Kutcher SP. Child and Adolescent Psychopharmacology. Philadelphia: W. B. Saunders 1997

MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr Scand 2001; 103: 163-170

Maziade M, Roy MA, Martinez M et al. Negative, psychoticism, and disorganized dimensions in patients with familial schizophrenia or bipolar disorder: continuity and discontinuity between the major psychoses. Am J Psychiatry 1995; 152: 1458-1463

Miklowitz DJ. Longitudinal outcome and medication noncompliance among manic patients with and without mood-incongruent psychotic features. J Nerv Ment Dis 1992; 180: 703-711

Möller HJ, Bottlender R, Grob A et al. The Kraepelinian dichotomy: preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. Schizophr Res 2002; 56: 87-94

Murray CJL, Lopez AD. The Global Burden of Disease and Health Statistics. Boston: Harvard University Press 1996

O'Callaghan E, Larkin C, Waddington JL. Obstetric complications in schizophrenia and the validity of maternal recall. Psychol Med 1990; 20: 89-94

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10: 799-812

Ozer S, Ulusahin A, Batur S, Kabakci E, Saka MC. Outcome measures of interepisode bipolar patients in a Turkish sample. Soc Psychiatry. Psychiatr Epidemiol 2002; 37: 31-37

Pearlson GD, Garbacz DJ, Breakey WR, Ahn HS, De Paulo JR. Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. Psychiatr Res 1984; 12: 1-9

Pearlson GD, Garbacz DJ, Moberg PJ, Ahn, HS, DePaulo JR. Symptomatic, familial, perinatal, and social correlates of computerized axial tomography CAT changes in schizophrenics and bipolars. J Nerv Ment Dis 1985; 173: 42-50

Peralta V, Cuesta MJ, Farre C. Factor structure of symptoms in functional psychoses. Biol Psychiatry 1997; 42: 806-815

Reddy R, Mukherjee S, Schnur D. Comparison of negative symptoms in schizophrenic and poor outcome bipolar patients. Psychol Med 1992; 22: 361-365

Shamsunder C, Sriram TG, Muraliraj SG, Shanmughan V. Validity of a short 5-items version of the General Health Questionnaire. Indian Journal of Psychiatry 1986; 28: 217-219

Sierra P, Livianos L, Rojo L. Quality of life for patients with bipolar disorder: relationship with clinical and demographic variables. Bipolar Disord 2005; 7: 159-165

Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970; 212: 11-19

Tarell JD, Schultz SC. Nursing assessment using the BPRS: A structured interview. Psychopharmacol Bull 1988; 24: 105-111

Trumbetta SL, Mueser KT. Social functioning and its relationship to cognitive deficits over the course of schizophrenia. In: Keefe RSE, McEvoy JP (eds) Negative symptom and cognitive deficit treatment response in schizophrenia. Washington, DC: American Psychiatric Press; 2001: 33-67

Tsuang MT, Lyons MJ, Faraone SV. Heterogeneity of schizophrenia: conceptual models and analytic strategies. Br J Psychiatry 1990; 156: 17-26

van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. Arch Gen Psychiatry 1998; 55: 41-46

Walker E, Harvey P. Positive and negative symptoms in schizophrenia: attentional performance correlates. Psychopathology 1986; 19: 294-302

World Health Organization. ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization 1992

Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. Psychiatry Res 2001; 102: 9-20