

MOOD SYMPTOMS IN STABILIZED PATIENTS WITH SCHIZOPHRENIA: A BIPOLAR TYPE WITH PREDOMINANT PSYCHOTIC FEATURES?

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SUMMARY

Background: Schizophrenia (SZ) and bipolar disorder (BD) are traditionally distinguished on the basis of progressive deterioration and long-term outcome, but a more dimensional approach is warranted. There are limited data on the occurrence of manic symptoms in patients with schizophrenia. The aim of the current study was to search for patterns in the clinical symptomatology, which may suggest the presence of one or several mood disorders under the label of schizophrenia.

Subjects and methods: Hundred-seventy-five patients diagnosed with schizophrenia according to DSM-5 were included in the study. The psychometric assessment included the Positive and Negative Syndrome Scale, Young Mania Rating Scale, The Montgomery-Åsberg Depression Rating Scale and the Calgary Depression Scale. The statistical analysis included MANOVA, Pearson Correlation coefficient and principal components analysis.

Results: Significant subthreshold manic symptoms were present in 25.14% of patients. Mood symptoms correlated with positive symptoms. The PCA revealed a complex structure with 15 factors (one positive, negative, somatic, anxiety, neurocognitive, disorganization and manic, five depressive and three psychomotor/excitement/hostility/violence).

Conclusion: Psychotic mood disorders are often phenotypically indistinguishable from schizophrenia, so it is likely that psychotic affective patients have been misdiagnosed with schizophrenia. The current study suggests that there seem to be patients with mania misdiagnosed as 'schizophrenics' because of the presence of psychotic features, a condition better described as 'schizophreniform bipolar disorder'.

Key words: bipolar disorder - psychotic symptoms - psychosis

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INTRODUCTION

The core concepts of schizophrenia and manic depression developed by Emil Kraepelin were based on supposed progressive deterioration in schizophrenia and a better long-term outcome in bipolar disorder. However, even Kraepelin reported that his clinical experience included a 'displeasing' (Angst 1986) number of patients with features of both disorders. The existence of these cases can be conceived as a strong argument in favor of the 'unitary psychosis theory' (Einheitspsychose), as conceived in the 1800s (Moller 2008, Angst 2002, Berrios & Beer 1994, Lake & Hurwitz 2006). A different idea was presented already in 1905 when Specht argued that all psychoses derived from mood abnormalities. In addition, some UK authors have

associated paranoia with depression and delusional guilt (Specht 1905, Doran et al. 1986). If psychotic mood disorders explain many paranoid presentations, questions arise about the distinction between schizophrenia and psychotic mood disorders (Lake & Hurwitz 2006, Pope & Lipinski 1978, Abrams et al. 1974, Maier et al. 2006).

Kasanin was the first to coin the term schizoaffective psychosis in 1933 (Kasanin 1933) when he described a group of psychotic mood patients according to contemporary classification systems. In 1937, Langfeldt described the so-called 'schizophreniform psychoses' characterized by many affective clinical elements and favorable outcome (Langfeldt 1937), while Kant in 1940 described 'recovered schizophrenics' as having a higher number of affective psychoses among their

relatives in comparison to schizophrenic patients (Kant 1940). Valuable contributions in the nosology were made by Kurt Schneider (1887-1967) who also described for the first time a 'concurrent' and a 'sequential' form of schizoaffective psychosis (Huber 2002, Marneros 2003, Marneros 1983).

Recent studies suggest that many patients with schizophrenia are likely to experience depressive symptomatology. While reported cross-sectional prevalence of depression in schizophrenia is less than 10%, lifetime prevalence is as high as 75%, although fewer patients experience the fullblown depression (Zisook et al. 2006, Buckley et al. 2009, Conley et al. 2007). Traditionally, there has been a focus on post-psychotic depression which is considered to be a result of demoralization and increasing insight following the resolution of the psychotic episode (Conley et al. 2007, Birchwood et al. 2005).

However, limited data exists on the occurrence of mania in patients with schizophrenia, at least partially because the presence of mania changes the diagnosis. By definition no patient with schizophrenia ever experiences a manic or hypomanic episode.

The aim of the current study was to investigate the presence of depressive and manic symptoms in stabilized patients diagnosed with schizophrenia. The secondary aim was to search for patterns in the clinical symptomatology, which would indicate the presence of one or more mood disorders under the label of schizophrenia.

SUBJECTS AND METHODS

Study population

The study included a total of 175 patients diagnosed with schizophrenia according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013). All were inpatients or outpatients of private psychiatric facilities in Thessaloniki, Greece. At the time of assessment all participants were stabilized and able to follow the study protocol. 'Stabilization' was defined as being treated at stable medication dosage without further improvement expected in the foreseeable future according to the treating psychiatrist. Patients affected with any major physical or neurological condition were excluded.

All participants signed for informed consent and the study protocol was approved by the Ethics Committee of the Aristotle University Medical School, Thessaloniki, Greece.

Clinical assessment and diagnosis

The diagnosis of schizophrenia was made according to DSM-5 criteria on the basis of a semi-structured

interview based on the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN v 2.0) (Wing et al. 1990) by a licensed psychiatrist (KF) and a psychologist (MS). Computerized medical records were used to assess the type and dose of antipsychotics taken by the patient. Antipsychotics doses were translated to chlorpromazine equivalents (Gardner et al. 2010).

Psychometric assessment

The psychometric assessment included the Positive and Negative Symptoms Scale (PANSS) (Kay & Fiszbein 1987), the Young Mania Rating Scale (YMRS) (Young et al. 1978), the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg 1979, Williams & Kobak 2008), and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al. 1993). Drugs side-effects were measured by UKU Side-effects rating scale (Lingjaerde et al. 1987) and Simpson-Angus scales (S-A) (Janno et al. 2005).

Grouping according to mood symptoms

A cut-off score of ≥ 7 on the CDSS was used to identify patients with clinically significant depression (cut-off specificity is 91%, sensitivity is 85%) (Addington et al. 1993).

The cut-off of 12 for the YMRS is considered to be the cut-off for remission (therefore the cut-off for the diagnosis of mania) while the score of 4 is considered the level of complete remission (Berk et al. 2008). A cut-off of 6/7 was used as the arbitrary level for subthreshold manic symptoms.

Statistical analysis

The primary aim inter-group differences were determined by Multiple Analysis of Variance (MANOVA) with gender and diagnostic group (according to YMRS or CDSS score) as grouping variables and age and education as the covariates. The dependent variables were BMI, chlorpromazine equivalent antipsychotic dosage, PANSS subscales, YMRS, MADRS, UKU and Simpson Angus scale (S-A). The t-test was used as the post hoc test. Since 22 post hoc tests were performed, according to Bonferroni correction the p-value was set to $0.05/22=0.0022$. The secondary aim of the analysis was to calculate the correlation between the variables representing mood rating and the rest of clinical variables and for this reason the Pearson Correlation coefficient was used. The third aim was to search for patterns in the clinical picture. For this reason principal components analysis (PCA) with varimax normalized rotation was performed. At a second step the same method was applied with the use of factor scores for each patient as variables.

RESULTS

One hundred seventy-five patients satisfied the inclusion criteria. Sixty-one (34.85%) were females, aged 34.89±12.12 and 114 (65.15%) were males, mean age 36.82±12.69 years (Table 1). Forty four patients (44/175; 25.14%), of whom 12 were females (12/61; 19.67%) and 32 males (32/114; 28.07%), presented subthreshold manic symptoms (YMRS≥7). Approximately 5% of the study sample had elated mood, 10% presented irritability, 7% increased motor activity and energy, 8% pressured speech and 15% manic-like thought content. Lack of insight, appearance and thought disorder were the most frequently elevated YMRS items.

Patients with YMRS≥7 had significantly higher scores in 4 items (conceptual disorganization, excitement, grandiosity and hostility) and a tendency for higher

scores in other 2 (totally in 6) out of the 7 items of the PANSS positive subscale. Only the prevalence of delusions was similar in the two groups. Concerning the negative subscale, the YMRS≥7 group manifested with higher scores only in difficulties in abstract thinking and stereotyped thinking. On general psychopathology scale, again this group had higher scores in a number of items. Overall, the higher YMRS group scored higher in several PANSS items, and presented higher scores in all YMRS items, suggestive of the presence of a mood disorder. In this patient group (YMRS≥7), the CDSS and the MADRS items suggested the presence of guilt and difficulties in concentration, while the UKU was suggestive of less emotional indifference, more tremor, reduced salivation and less decreased sexual desire. The Simpson Angus scale was suggestive of more shoulder shaking, more tremor and rigidity and abnormal glabella tap.

Table 1. Descriptive statistics of patients with YMRS<7 compared with those with YMRS≥7.

	YMRS<7 (N=131)		YMRS≥7 (N=44)		p-value ^a
	Mean	SD	Mean	SD	
Age (years)	34.26	12.08	41.77	12.13	<i>0.000</i>
BMI (Kg)	25.62	4.67	26.15	4.01	0.507
CPZ equivalent (mg)	414.59	528.66	1344.73	1118.29	<i>0.000</i>
PANSS-Positive	14.78	5.43	18.39	4.71	<i>0.000</i>
PANSS-Negative	18.54	7.02	19.59	6.40	0.382
PANSS-General	24.99	6.02	31.16	7.50	<i>0.000</i>
PANSS-EC	6.73	2.48	8.91	4.26	<i>0.000</i>
CDSS	1.28	3.01	2.00	3.12	0.176
MADRS	5.47	7.81	7.11	6.37	0.208
YMRS	0.80	1.64	12.80	3.92	<i>0.000</i>
UKU	7.31	5.39	7.25	4.42	0.949
S-A	0.80	2.21	2.20	2.43	<i>0.000</i>

^a p-values correspond to uncorrected t-test, Significant values are in italic (p<0.05)

CPZ: chlorpromazine; BMI: Body mass index; PANSS: Positive and Negative Symptoms Scale; EC: Excitement component; CDSS: Calgary Depression Scale for Schizophrenia; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; UKU: side effect rating scale; S-A: Simpson-Angus scale

Table 2. Descriptive statistics of patients with CDSS scores<7 compared to those with CDSS scores ≥7.

	CDSS<7 (N=167)		CDSS≥7 (N=8)		p-value ^a
	Mean	SD	Mean	SD	
Age (years)	36.16	12.67	35.88	8.49	0.950
BMI (Kg)	25.62	4.46	28.54	4.82	0.073
CPZ equivalent (mg)	640.21	798.37	820.64	1338.80	0.547
PANSS-Positive	15.57	5.50	18.13	4.64	0.198
PANSS-Negative	18.73	6.86	20.38	7.23	0.510
PANSS-General	26.19	6.75	33.88	7.40	<i>0.002</i>
PANSS-EC	7.23	3.16	8.25	3.15	0.376
CDSS	0.95	1.77	12.25	4.03	<i>0.000</i>
MADRS	4.98	6.06	24.75	9.87	<i>0.000</i>
YMRS	3.80	5.77	4.13	5.54	0.877
UKU	6.92	4.68	15.13	8.06	<i>0.000</i>
S-A	1.18	2.39	0.63	0.74	0.514

^a p-values correspond to uncorrected t-test, Significant values are in italic (p<0.05)

CPZ: chlorpromazine; BMI: Body mass index; PANSS: Positive and Negative Symptoms Scale; EC: Excitement component; CDSS: Calgary Depression Scale for Schizophrenia; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; UKU: side effect rating scale; S-A: Simpson-Angus scale

The analysis of the CDSS and the MADRS suggested that more than up to 25% of patients report some kind of depressive feelings, and a similar percentage has some kind of depressive thought content. Approximately 10% presented suicidal ideation.

Patients with CDSS \geq 7 (n=7) had similar PANSS scores to the rest, but significantly different scores in several items of the general psychopathology scale. They also had similar YMRS item scores. Whatsoever, this group presented higher UKU scores in the items reflecting concentration difficulties, memory, tension, reduced sleep, reduced salivation, diarrhea, constipation, micturition disturbances, palpitations/tachycardia and weight loss. There were no differences in the S-A scale item scores.

Three patients (1.71%) had both CDSS and YMRS above the cut-off scores (37.5% of 'depressed' and 6.81% of 'manic' patients).

Two MANOVA analyses showed a main effect for mood both in the case of 'manic' vs. 'non manic' (Wilks=0.196, F=58.04, effect df=11, error df=156; p<0.001) and in the case of 'depression' vs. 'no depression' (Wilks=0.399, F=21.31, effect df=11, error df=156; p<0.001). In the analysis concerning 'mania' a main effect for gender was also found (Wilks=0.869, F=2.12, effect df=11, error df=156; p=0.021). In the 'depression' MANOVA there was no significant effect for gender. Interaction of mood-by-gender was not significant in either analysis, but in both analyses age had a significant effect. The results of the post-hoc t-tests are shown in Tables 1 and 2.

From psychopharmacological point of view, patients with YMRS scores \geq 7 were treated with higher dosages of neuroleptics and subsequently presented higher S-A scores, more positive symptoms, general psychopathology and excitement (Table 1). Patients with CDSS \geq 7 presented more general psychopathological symptoms, depression and side effects according to UKU (Table 2).

Table 3. Correlation matrix between the PANSS subscales and the UKU and Simpson-Angus scores and mood scales (Pearson correlation coefficients)

	CDSS	MADRS	YMRS
PANSS-Positive	<i>0.16</i>	<i>0.19</i>	<i>0.32</i>
PANSS-Negative	0.11	<i>0.31</i>	0.03
PANSS-General	<i>0.34</i>	<i>0.42</i>	<i>0.40</i>
PANSS-Excitement component	0.11	0.11	<i>0.34</i>
UKU	<i>0.42</i>	<i>0.61</i>	-0.03
S-A	0.01	0.08	<i>0.23</i>

*Significant values are in italic (p<0.05)

PANSS: Positive and Negative Symptoms Scale;

CDSS: Calgary Depression Scale for Schizophrenia;

YMRS: Young Mania Rating Scale;

MADRS: Montgomery-Åsberg Depression Rating Scale;

UKU: side effect rating scale; S-A: Simpson-Angus scale

Males were receiving higher dosages of neuroleptics (799.36 \pm 920.14 vs. 366.42 \pm 507.95 in chlorpromazine

equivalents; p<0.001) and had higher S-A scores (1.45 \pm 2.65 vs. 0.59 \pm 1.34; p=0.02).

The correlation matrix suggested that positive symptoms were correlated with all mood scale scores, and negative symptoms only with MADRS. General psychopathology correlated with all mood scales. The excitement component, as well as the Simpson Angus score, correlated only with the YMRS. The UKU correlated only with depressive scales (Table 3).

Finally, the PCA revealed the presence of 15 factors reflecting the following: (1) depression (psychotic melancholia according to CDSS) (2) Excitement-hostility-irritability; (3) negative symptoms; (4) positive symptoms; (5) neurocognitive impairment; (6) sleep and somatic concerns; (7) non-melancholic depression (according to MADRS); (8) disorganization; (9) core manic symptoms; (10) non-psychotic melancholic aspect of depression; (11) an aspect of psychomotor retardation; (12) feeling of guilt; (13) psychomotor acceleration; (14) anxiety; (15) depression without lassitude.

Factors (1)-(5) and factor (7) explained more than 5% of symptomatology variance.

These factors explain 72% of observed variance.

DISCUSSION

There is an ongoing debate whether psychotic disorders should be seen under categorical or dimensional approach. Subsequently the boundaries of categorical diagnostic entities remain obscure, and apart from spectrum approach, many authors argue that schizophrenia is an umbrella label which includes several distinct disorders (Weiser et al. 2005).

The current study showed that a large proportion of stabilized patients with schizophrenia experienced significant manic (25.14%) or depressive (4.57%) symptoms. Our results showed similar depression rates to those seen in the general population; only the gender ratio was 1:1 suggesting a lower than expected depression rate in females and a higher in males. However, only 1.71% of patients had simultaneously mixed manic and depressive symptoms, a much lower rate than seen in bipolar disorders (Bauer et al. 2005, Perugi et al. 2015, Popovic et al. 2015). Manic, but not depressive symptoms, were related to gender, higher overall psychopathology, treatment with higher antipsychotic doses and more extrapyramidal side effects. It is noteworthy that the present results regard 'stabilized' patients, that is, patients treated with antipsychotics and in at least partial remission. As antipsychotics also have an anti-manic action (Popovic et al. 2012), it is likely that a higher number of patients diagnosed with schizophrenia manifested more severe manic symptoms during the acute psychotic episode.

All mood symptoms correlated with positive symptoms and general psychopathology but only manic symptoms correlated with excitement and extrapyramidal side effects. The latter is probably secondary to

the need for higher doses of antipsychotics to treat the condition. On the other hand, depressive symptoms correlated with negative symptoms and general adverse events. This may be supported by a recent study on schizophrenia patients, which showed a beneficial effect of adjunctive antidepressants on depressive and negative symptoms (Helfer et al. 2015), with a relatively low risk of exacerbation of psychosis and adverse effects (Helfer et al. 2015; Mosheva et al. 2016).

Inclusively, our model included 15 factors: one positive, one negative, one somatic, one manic, five depressive and one anxiety, three psychomotor/excitement/hostility/violence, one neurocognitive impairment and one disorganization factor.

The model in the current paper identified five depressive factors plus one anxiety factor, while previous research has identified three dimensions of depression (retardation, depressive core symptoms, and accessory depressive symptoms) (Müller et al. 1999). The model also identified a core manic factor plus a psychomotor acceleration factor.

The presence of mood symptoms is suggested to be predictive of a better outcome but, on the contrary, 'schizophrenic' symptoms were not predictive of a worse outcome (Pope & Lipinski 1978, Holmboe et al. 1968, Noreik et al. 1967). Clinically, schizophrenia differs in the presence of manic symptoms and cognitive impairment from bipolar disorder (Kaymaz & Van Os 2009). Notably, some studies disputed the predictive value of mood symptoms (Welner et al. 1977, Möller et al. 1982, Gift et al. 1980). In the present study, mood symptoms correlated positively with psychotic symptoms. This may indicate that mood symptoms characterize patients with worse response and more residual psychotic symptoms, or perhaps that these patients were treated suboptimally for an underlying affective disorder.

Overall it seems that the data propose the presence of a continuum, with non-psychotic mood disorders at the one end and predominantly psychotic disorders with non-congruent psychotic features at the opposite end (Coryell & Tsuang 1982; Loch et al. 2011; Van Os et al. 2000; Smith et al. 2009).

It is important to bear in mind that the psychometric tools, even more than the clinical picture, define whether a particular cluster of symptoms will be detected or not (Peralta & Cuesta 2001). Manic symptoms have been identified only in a minority of reports studying the factor structure of clinical symptoms of schizophrenia in samples (Lorr et al. 1962; Kitamura et al. 1995; Peralta & Cuesta 1999) or in recent-onset cases (van Os et al. 1996; McGorry et al. 1998) but rarely in follow-up studies (Willem Van der Does et al. 1995; Salokangas 1997). This is most likely due to the fact that most schizophrenia studies use only 'classic' schizophrenia scales like the PANSS, SANS etc., and do not routinely include scales which assess mood

symptoms, such as YMRS. In fact, one of the main strengths of the present study is that a large number of psychometric tools were used, which assessed not only psychotic but also affective symptoms. Other strengths of the present paper include the high inter-rater reliability (all patients were assessed by the same psychologist and psychiatrist, with expertise in mood disorders) and factor analysis.

First limitation of this paper is that, due to the limited sample size, both type I and type II errors are possible. Secondly, due to its cross sectional design and the fact that the study was performed in stabilized patients, the incidence of acute psychotic and mood symptoms may be underestimated.

CONCLUSIONS

The results of the present study point out that there seems to be a portion of patients with genuine mania who were diagnosed as 'schizophrenics' probably because of the predominance of psychotic features at interview. Furthermore, manic symptoms were found to correlate with positive symptoms. Taken together, these findings suggest that there is a significant number of patients diagnosed with schizophrenia who actually suffer from a type of bipolar disorder with psychotic symptoms, which could be defined as 'schizophreniform bipolar disorder'.

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Contribution of individual authors:

Konstantinos N. Fountoulakis & Xenia Gonda: conceptualized and designed the study;

Katerina Moutou: statistical analysis;

Konstantinos N. Fountoulakis, Dina Popovic, Mariela Mosheva & Xenia Gonda: manuscript Drafting;

Konstantinos N. Fountoulakis, Dina Popovic, Mariela Mosheva, Melina Siamouli, Katerina Moutou & Xenia Gonda: critically reviewed the manuscript as submitted.

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