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Manic symptoms in schizophrenia spectrum disorders

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This study investigated the presence of manic symptoms in stable patients diagnosed with schizophrenia spectrum disorders (SSDs) aiming to identify their association with clinical symptoms. A total of 75 out-patients, 41.3% female [47.81 (±10.521) year-old] were assessed using the Young Mania Rating Scale (YMRS), Positive and Negative Syndrome Scale (PANSS), Generalized Anxiety Disorder-7 scale (GAD-7), and Risk Assessment of Suicidality Scale (RASS). Participants were divided into two groups based on YMRS scores: Group 1, without or with minimal symptoms of mania (YMRS ≤ 10) and Group 2, with distinct manic symptoms (YMRS > 10). We performed statistical analysis using the IBM SPSS version 29.0. Our analysis revealed a positive significant correlation between YMRS total score and PANSS total score ($r^2 = 0.516$, $p = 2.15 \times 10^{-6}$), PANSS-Positive subscore ($r^2 = 0.600$, $p = 1.31 \times 10^{-8}$) and PANSS-General Psychopathology subscore ($r^2 = 0.444$, $p = 6.646 \times 10^{-5}$), Bonferroni corrected at $p = 0.0004$. Moreover, positive symptoms as assessed by the PANSS-Positive subscale score differed significantly between the two YMRS groups [$t(73) = 3.982$, $p = 0.00016$, $d = 1.040$]. Linear regression analysis showed that the severity of positive symptoms predicted the occurrence of manic symptoms. This study could serve as a pilot study, observing manic symptoms in SSDs and as recruitment goes on, it is expected to yield more robust evidence of their prevalence in SSDs and their associations with clinical symptoms forming the phenotypic characterization basis for further dimensional research in the psychopathology and etiopathogenesis of SSDs.

Keywords: Global functionality, mania, manic symptoms, neurocognitive functions, PANSS, schizophrenia spectrum disorders, suicidality, YMRS.

Introduction

Schizophrenia is a severe mental disorder characterized by significant alterations in thought, perception, emotion, and behavior. Often regarded as a single mental disorder, it appears to reflect considerable heterogeneity. Schizophrenia symptoms are typically grouped into positive, negative, and disorganized symptoms, but no single symptom cluster is pathognomonic of schizophrenia (1). While mania is generally easy to recognize (2), severe cases with psychotic features can be misdiagnosed as schizophrenia, and milder cases may be mistaken for personality disorders (3). Furthermore, it is critical to distinguish between mania and manic symptoms. Whereas a manic episode significantly impacts various domains of functioning, may include psychotic symptoms, and usually requires hospitalization (4), manic symptoms do not necessarily meet the criteria for a full-blown manic episode.

Manic symptoms can appear within a range of psychiatric diagnoses, and do not exclusively form part of manic episodes. The relationship between schizophrenia and manic symptoms remains an area of limited research. Evidence, however, indicates the presence of manic symptoms across various diagnostic categories, including schizophrenia and schizoaffective disorder (5). Moreover, van Os and Kapur (2009) proposed changing the categorical dichotomy of schizophrenia and bipolar disorder (BD) to a dimensional conceptualization (6). Diagnosis of schizoaffective disorder requires meeting criteria for a major mood episode for most of the lifetime of the illness as well as psychotic symptoms without overt mood symptoms within a 2-week period (7). Manic symptoms are often part of schizoaffective disorder, but no consensus currently exists as to whether this disorder lies within the schizophrenia spectrum disorders (SSDs), the mood disorders or both (8–11).

Manic symptoms can significantly impact the clinical course and prognosis of schizophrenia (12) and as such, their assessment has been included in the mania domain of the Clinical-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) scale proposed by DSM-5 for assessing the severity of psychotic symptoms in schizophrenia (13). A Korean study examining the psychometric properties of the Young Mania Rating Scale (YMRS) in SSDs, using a receiver operating characteristic analysis, found the optimal cut-off score for distinguishing schizophrenia patients with manic symptoms from those without to be 10, with a sensitivity of 88.3% and a specificity of 75.6% (14). This is in contrast to the cut-off point of 12 taken to be the threshold for diagnosing mania in mood disorders (15). They concluded that a YMRS score of 10 indicates mild mania severity on the Clinical Global Impression (CGI) scale, making it a reasonable threshold for identifying manic symptoms in patients with SSD.

Overlooking mania could result in missed opportunities to use pharmacological treatments and may lead clinicians to make excessively pessimistic prognoses (16). Individuals with schizophrenia often experience a more severe course of illness and have worse prognoses than those with schizoaffective disorder. Further research is necessary to categorize better the various clinical phenomena that fall under the umbrella of manic syndromes and SSDs. This study aims to investigate the presence of mania in stable patients diagnosed with SSDs. We hypothesized that in patients with SSD, manic symptoms are associated with clinical psychopathology.

Results

A total of 75, 44 male (58.7%) patients with SSD [mean age 43.55 (±11.800) years] and 31 female (41.3%) patients with SSD [mean age 47.81 (±10.521) years] met the inclusion criteria. The mean YMRS score for the total sample was 6.36 (±5.753). We dichotomized our group according to the severity of YMRS scoring and used the YMRS cut-off score of 10, suggested to be appropriate for the detection of mania in SSDs (Kim *et al*., 2018). The total sample was dichotomized into two groups: Group 1, without or with minimal symptoms of mania (YMRS ≤ 10) and Group 2, with distinct manic symptoms (YMRS ≥ 10). Group 1 ($N = 55$) had a mean YMRS total score of 3.42 (±3.004) and Group 2 ($N = 20$) had a mean YMRS total score of 14.45 (±3.052). The two groups differed significantly in terms of total mean YMRS scoring [$M = 11.032$ [95% confidence interval (CI): 9.462 to 12.602], t (73) = 14.005, $p = 2.252 \times 10^{-22}$, $d = 3.657$], as expected. As Levene's test for equality of variances was non-significant ($p = 0.807$), we could safely assume that the data were normally distributed. A *post-hoc* power calculation for independent t-tests at $\alpha = 0.05$ found the statistical power to be equal to 1.000.

Descriptive statistics were used to provide a comprehensive summary of the mean YMRS individual item and total score for the total sample (Table 1). Table 2 summarizes the demographic characteristics of the participants without or with minimal manic symptoms and mania. Sex distribution and family history of mental illness did not differ significantly

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Table 1. YMRS total score and YMRS individual items' mean (SD) scores and 95% CI of the means for $N = 75$ patients with SSD

YMRS Items	Min	Max	Mean ($N = 75$)	95% CI of Mean		Standard Deviation (SD)
				Upper	Lower	
1. Elevated Mood	0	3	0.56	0.39	0.73	0.758
2. Increased Motor Activity/Energy	0	3	0.31	0.16	0.45	0.636
3. Sexual Interest	0	2	0.12	0.02	0.22	0.434
4. Sleep	0	3	0.20	0.05	0.35	0.637
5. Irritability	0	4	0.61	0.39	0.84	0.971
6. Speech (Rate and Amount)	0	6	0.89	0.55	1.24	1.512
7. Language/Thought Disorder	0	3	0.64	0.46	0.82	0.765
8. Thought Content	0	8	1.03	0.65	1.41	1.652
9. Disruptive/Aggressive Behavior	0	3	0.37	0.22	0.52	0.653
10. Appearance	0	4	0.67	0.46	0.87	0.890
11. Insight	0	4	0.96	0.63	1.29	1.418
Total YMRS Score	**0**	**22**	**6.36**	**5.04**	**7.68**	**5.753**

Table 2. Demographics of the total sample ($N = 75$) dichotomized according to YMRS score

YMRS Total Score [*N*, Mean (SD)]	Group 1 (≤10)	Group 2 (>10)
Age (years)	45.35 (11.409), $N = 55$	45.20 (11.719), $N = 20$
Body Mass Index (BMI, kg/m^2)	27.55 (4.879), $N = 50$	26.29 (7.459), $N = 17$
Antipsychotic Dose (in Olanzapine Equivalents, mg)	19.96 (17.416), $N = 48$	22.17 (18.183), $N = 18$
Antidepressant Dose (in Fluoxetine Equivalents, mg)	43.10 (37.24), $N = 19$	33.03 (18.86), $N = 7$
Benzodiazepine Dose (in Diazepam Equivalents, mg)	15.51 (8.434), $N = 10$	20.00 (7.071), $N = 4$
Total Number of Episodes	2.41 (1.643), $N = 54$	1.95 (1.268), $N = 19$
Total Number of Hospitalizations	1.20 (1.592), $N = 55$	0.90 (1.483), $N = 20$
Age (years) at First Episode Psychosis	28.40 (10.399), $N = 55$	27.70 (10.854), $N = 20$
Total Number of Suicidal Attempts	1.85 (2.430), $N = 55$	1.75 (2.291), $N = 20$
Total Illness Duration (years)	17.15 (12.002), $N = 55$	17.50 (11.199), $N = 20$
Sex (*N*, %)		
Male	35 (63.6)	9 (45.0)
Female	20 (36.4)	11 (55.0)
Marital Status (*N*, %)		
Single	35 (66.0)	12 (60.0)
Married	9 (17.0)	5 (25.0)
Separated	1 (1.9)	0 (0.0)
Divorced	6 (11.3)	1 (5.0)
Lives with Other	1 (1.9)	1 (5.0)
Widow/Widower	1 (1.9)	1 (5.0)
Employment (*N*, %)		
Used to Work, but Now Unemployed	35 (64.8)	9 (45.0)
Never Worked, Nor Working Now	6 (11.1)	4 (20.0)
Employee (Private or Public Sector)	6 (11.1)	3 (15.0)
Freelancer (Salesman/Skilled Worker)	1 (1.9)	0 (0.0)
Doctor/Lawyer/Engineer/Priest/Teacher	3 (5.6)	1 (5.0)
University Student	1 (1.9)	1 (5.0)
Manual Worker/Builder/Farmer/Etc.	2 (3.7)	2 (10.0)
Family History of Mental Illness		
no	20 (36.4)	7 (35.0)
yes	35 (63.6)	13 (65.0)
Drug Use in the Past		
no	33 (60.0)	12 (63.2)
mild	15 (27.3)	3 (15.8)
severe	7 (12.7)	4 (21.1)
Drug Use at Present		
no	52 (94.5)	16 (84.2)
mild	3 (5.5)	2 (10.5)
severe	0 (0.0)	1 (5.3)

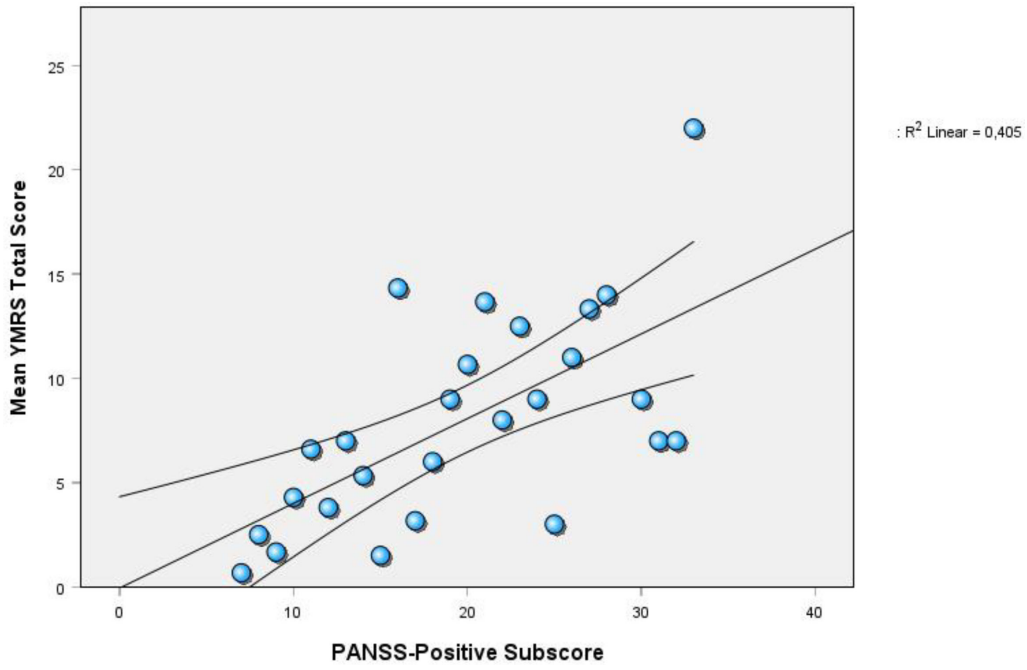

Figure 1. Simple scatter plot of PANSS-Positive subscore versus mean YMRS total score.

between the two groups (*Fisher's exact test* = 0.147 and *Fisher's exact test* = 1.000, respectively). For both, a *post-hoc* power calculation for chi-square tests with $df = 1$ at $\alpha = 0.05$ and for a medium effect size of 0.33, found the statistical power to be equal to 0.820.

Interestingly, we found a positive significant correlation between YMRS total score and the Positive and Negative Syndrome Scale (PANSS) total score ($r^2 = 0.516$, $p = 2.147 \times 10^{-6}$), the PANSS-Positive subscore ($r^2 = 0.600$, $p = 1.310 \times 10^{-8}$; Figure 1), and the PANSS-General Psychopathology subscore ($r^2 = 0.444$, $p = 6.646 \times 10^{-5}$), but the correlation between YMRS total score and PANSS-Negative subscore failed to reach significance (Table 3). Furthermore, independent-samples *t*-tests were performed to explore mean differences in PANSS total and subtest, Generalized Anxiety Disorder -7 scale (GAD-7), and Risk Assessment of Suicidality Scale (RASS) scores between participants without or with minimal symptoms of mania, and in those with manic symptoms. Positive symptoms scoring, as assessed by the PANSS-Positive subscale, was the only psychopathology measure that stood the stringent criterion of the Bonferroni multiple correction and showed a statistically significant difference between the two YMRS groups [PANSS-Positive subscore *mean diff* = 6.841 (95% CI: 3.417to 10.265), $t(73) = 3.982$, $p = 0.00016$, $d = 1.040$] (Table 4). A *post-hoc* power calculation based on data from this independent *t*-test comparison, for $d = 1.040$ and $\alpha = 0.05$, found the statistical power to be over 0.999, a more than adequate value for detecting an effect. More specifically, analyzing correlations between individual YMRS items and the PANSS total and subscale scores (Table 5), PANSS-Positive subscore was positively correlated with YMRS item 7 on language and thought disorder ($r^2 = 0.449$, $p = 5.239 \times 10^{-5}$) and YMRS item 11 on insight ($r^2 = 0.522$, $p = 1.593 \times 10^{-6}$) at a *post-hoc* calculated power of 0.990 and 0.999, respectively, given $\alpha = 0.05$.

Finally, linear regression established that the PANSS-Positive subscale score could significantly predict the YMRS total score [$F(1,73) = 36.851$, $p = 5.214 \times 10^{-8}$]. The YMRS total score accounted for 32.6% of the explained variability in PANSS-Positive score.

Discussion

In this study, we found an increased number of manic symptoms denoting the presence of mania in just over one in four (26.7%) stable participants with SSDs. An earlier epidemiological study from Canada found that the prevalence of an episode of mania in patients with schizophrenia in the community was 17.7 % (17), and a more recent study showed significant subthreshold manic symptoms (YMRS score > 7) to be present in 25.1% of patients (18).

In this group of patients with SSD, we showed that positive symptoms were associated with mania. Interestingly, the severity of positive symptoms was found to predict the presence of manic symptoms, such that, the higher the PANSS-Positive score, the more likely the presence of

Table 3. Spearman (r^2) correlation matrix for YMRS Total score versus PANSS total score and subscores with exact *p* values

	1	2	3	4
1. YMRS Total Score				
2. PANSS-Positive Subscore	0.600 $p = 1.310 \times 10^{-8}$			
3. PANSS-Negative Subscore	0.310 $p = 0.007$	0.463 $p = 2.829 \times 10^{-5}$		
4. PANSS-General Subscore	0.444 $p = 6.646 \times 10^{-5}$	0.783 $p = 1.079 \times 10^{-16}$	0.695 $p = 4.498 \times 10^{-12}$	
5. PANSS Total Score	0.516 $p = 2.147 \times 10^{-6}$	0.851 $p = 4.241 \times 10^{-22}$	0.805 $p = 3.023 \times 10^{-18}$	0.952 $p = 3.822 \times 10^{-39}$

Table 4. Comparison of total scores and subscores for PANSS, GAD-7, and RASS scales between the two groups according to YMRS scoring

YMRS Total Score ($N = 75$)	Group 1 (YMRS ≤10), $N = 55$	Group 2 (YMRS >10), $N = 20$
PANSS-Positive Subscore, Mean (SD)	*mean diff* = 6.841 (95% CI: 3.417 to 10.265), $t(73) = 3.982$, $p = 0.00016$, $d = 1.040$	
	14.25 (6.743)	20.95 (6.452)
PANSS-Negative Subscore, Mean (SD)	*mean diff* = 2.282 (95% CI: −1.690 to 6.254), $t(73) = 1.145$, $p = 0.256$, $d = 0.299$	
	18.86 (8.000)	21.10 (6.851)
PANSS-General Subscore, Mean (SD)	*mean diff* = 6.777 (95% CI: 1.197 to 12.358), $t(73) = 2.420$, $p = 0.018$, $d = 0.632$	
	33.98 (11.270)	40.65 (9.494)
PANSS Total Score, Mean (SD)	*mean diff* = 15.900 (95% CI: 4.672 to 27.128), $t(73) = 2.822$, $p = 0.006$, $d = 0.737$	
	67.10 (22.794)	82.70 (18.991)
GAD-7 Total Score	*mean diff* = 4.430 (95% CI: 0.455 to 8.404), *Mann-Whitney U* = 370.50, $Z = -2.07$, $p = 0.038$	
[Median (IQR), min-max and Mean (SD)]	4.00 (1–8), min 0 – max 27	9.80 (7.978)
RASS Total Score, Mean (SD)	*mean diff* = 50.750 (95% CI: −104.762 to 206.262), $t(73) = 0.651$, $p = 0.517$, $d = 0.172$	
	320.00 (284.617)	370.75 (22.267)

CI: Confidence Intervals, GAD – 7: Generalized Anxiety Disorder Assessment −7, IQR: Interquartile Range, M: mean, max: maximum, min: minimum, PANSS: Positive and Negative Syndrome Scale, RASS: Risk Assessment Suicidality Scale, YMRS: Young Mania Rating Scale.

manic symptoms. Our findings replicate results from a previous study on 175 patients with schizophrenia aiming to search for patterns in clinical symptomatology suggestive of the presence of mood disorders under the label of schizophrenia, also showing that mood symptoms correlate with positive symptoms (18).

Furthermore, to ascertain whether metabolic variability is associated with the clinical features of schizophrenia, Malaspina *et al*. (2021) examined the association of *N*-acetylaspartate (NAA) and choline (Cho) levels with clinical symptoms in patients with schizophrenia. They found a positive correlation between manic symptoms, as assessed by the YMRS, and whole-hippocampus multivoxel average choline millimolar concentration of Cho, denoting that both manic symptoms and positive symptoms reflect demyelination. On the contrary, negative symptoms were correlated with decreased NAA hippocampal levels reflecting a different pathophysiologic process, consistent with microgliosis/astrogliosis and/or lower vitality (19).

Table 5. Spearman's (r^2) correlation matrix for PANSS-Positive subscore versus individual YMRS item scores with exact *p* values

	1	2	3	4	5	6	7	8	9	10	11
1. PANSS-Positive Subscore											
2. Elevated Mood [YMRS1]	–										
3. Increased Motor Activity [YMRS2]	–	0.545 $p = 4.305 \times 10^{-7}$									
4. Sexual Interest [YMRS3]	–	–	–								
5. Sleep [YMRS4]	–	–	–	–							
6. Irritability [YMRS5]	–	–	–	–	–						
7. Speech [YMRS6]	–	0.473 $p = 1.812 \times 10^{-5}$	–	–	–	–					
8. Language/ Thought Disorder [YMRS7]	0.449 $p = 5.239 \times 10^{-5}$	0.444 $p = 6.614 \times 10^{-5}$	0.516 $p = 2.105 \times 10^{-6}$	–	–	0.468 $p = 2.258 \times 10^{-5}$	0.515 $p = 2.258 \times 10^{-6}$				
9. Thought Content [YMRS8]	–	–	–	–	–	–	–	0.685 $p = 1.196 \times 10^{-11}$			
10. Disruptive/ Aggressive Behavior [YMRS9]	–	–	–	–	–	0.446 $p = 6.185 \times 10^{-5}$	–	0.434 $p = 9.822 \times 10^{-5}$	–		
11. Appearance [YMRS10]	–	–	–	–	–	–	–	–	–	–	
12. Insight [YMRS11]	0.522 $p = 1.593 \times 10^{-6}$	–	–	–	–	–	–	–	–	–	–

Significant progress has been made in understanding the genetics of schizophrenia over the last 15 years, shedding light on the close relationship between SSDs and other conditions, particularly BD and childhood neurodevelopmental disorders. A clearer picture is emerging, suggesting that clinical heterogeneity partly reflects etiological heterogeneity. For example, several etiological pathways are influenced by the catechol-O-methyltransferase gene (*COMT*), including prefrontal cognition or emotional processing in the amygdala and the prefrontal cortex, in addition to other insults to the brain such as adolescent cannabis use. This means that the individual clinical phenotype may result from a combination of distinct symptom dimensions and their associated genetic risk factors (20).

COMT is an enzyme catalyzing the breakdown of dopamine and norepinephrine, thought to be involved in the pathophysiology of BD and schizophrenia. COMT striatal activity, but not the rs4680 (*COMT Val/Met*) functional polymorphism, may be a biomarker for manic symptoms (21), and research has suggested that the effect of this variant may be associated with comorbid manic symptoms in schizophrenia (22). Using the OPCRIT criteria (23), an Irish study showed significant overtransmission of the *Val* allele for mania in patients with schizophrenia (24).

Interestingly, it has been suggested that second-generation antipsychotics, with the exception of clozapine, may induce states of agitation often resembling manic states, possibly via their antidepressant actions on serotonergic and noradrenergic neurotransmission (25).

In the era of promoting health economics through screening (26), we suggest that administering the YMRS, a relatively easy-to-use and cost-effective tool, to screen readily for mania in SSDs may prove a valuable strategy for the busy clinician. YMRS could help identify mania in SSDs, as early intervention may lower the costs of treating poorly responding revolving-door patients (27) and improve patient outcomes (28), thus decreasing costs for the patient and the mental health and welfare systems. Adding mood stabilizers (29) and engaging the patient in psychoeducation (30) may prevent frequent relapses associated with high expenditure for the patient and society.

It is crucial, however, to interpret our findings by considering the various limitations of this study. First, the subjective nature of YMRS introduces inter-rater variability, which could affect the reliability and validity of the assessments. It has recently been suggested that implementing flags and mitigation strategies during trials may enhance the value of YMRS data, direct emphasis toward rater training, and bolster the reliability and validity of trial outcomes (31). Therefore, future YMRS assessments will have to be undertaken by the same trained rater for all patients. This study could serve as a pilot study, as a more representative and larger sample size is required in future studies to enhance data reliability. In the future, genotyping either for known genetic polymorphisms or within a genome-wide association study (GWAS) protocol, without an *a priori* hypothesis, holds promise for disentangling the dimensional etiology of SSDs, part of which seems to stem from the presence of manic symptoms. Another strategy for furthering our understanding of manic symptoms in SSDs may be to focus on patients with drug-naïve first-episode SSD, to eliminate any drug-induced agitation.

Nevertheless, this study highlights that by addressing manic symptoms contributing to and associated with positive psychotic psychopathology in individuals with SSDs, we could improve the management of acute SSD episodes and promote remission, especially in poorly responding patients with undetected, hence suboptimally treated manic symptoms.

Conclusions

This study explored the presence of manic symptoms in patients with SSDs. We showed the severity of positive symptoms to correlate with an increased number of manic symptoms, as assessed by the YMRS. In this group of patients, positive symptoms also predicted the presence of manic symptoms. It, therefore, appears that in SSDs, YMRS could be used as a friendly and reliable screening tool promoting individualized and precision management, increasing the cost-effectiveness of interventions. Further, beyond cross-sectional studies, the high degree of phenomenological pleiotropy within SSDs points to the need for extensive transdiagnostic research to delineate biologically distinct entities incorporating carefully collected phenotypical data from diverse global communities, with the application of new and emerging technologies.

Materials and Methods

Participants

All patients attending the out-patient clinic of the 3rd Psychiatric Department of the Aristotle University of Thessaloniki, aged 18 to 66 years, with an SSD diagnosis, according to DSM-5, were invited to participate. Further inclusion criteria were stable medication for at least 1 month and the absence of any somatic disorder. Recruitment took place between June 2023 and June 2024. All participants signed written informed consent, following approval by the Research and Ethics Committee of the Aristotle University of Thessaloniki (Prot. No. 166/2023, dated 6/6/2023). This study is ongoing as it is part of an international research project involving centers from 22 countries worldwide.

Assessment Tools

We used the YMRS (32), which evaluates the severity of manic symptoms in acute mania and is widely used in clinical trials (33, 34). The scale consists of 11 items based on the patient's subjective reports over the previous 48 h and the examiner's observations during the interview. The selection of each item was based on the published accounts of the key manic symptoms in bipolar affective disorder (35). In this instrument, the irritability, speech, thought content and disruptive/aggressive behavior items are scored from 0 to 8 as they carry greater weight and compensate for poor cooperation in severe cases. The rest are rated from 0 to 4.

In addition, psychopathology was assessed with the PANSS (36, 37). Participants were also required to complete the self-report GAD-7 (38), and the RASS (39). Sociodemographic information for each patient and illness-related factors including current medication, illness duration, age at first episode psychosis, number of attempted suicides, family history of mental illness, total number of episodes, and total number of hospitalizations, were also recorded following interviews with patients and carers and further consultation of medical records, if required.

Study Design/Procedures

Assessment was performed during three sessions on separate days within 1 month. The first session was physician-led and included a thorough medical and psychiatric history taking. The second session, usually no later than a week after the second session, was psychologist-led under the supervision of a psychiatrist. It comprised the clinical interview for assessing psychopathology, including completion of the YMRS, by one of four clinical psychology research assistants. Self-report scales were completed during the third and final session (Figure 2).

Statistical Analyses

All analyses were run using the IBM Statistical Package for Social Sciences (IBM SPSS version 29.0). Descriptive statistics for the whole group were summarized as mean and standard deviation (SD) for YMRS total and individual item scores. We then dichotomized our sample according to YMRS total score setting the cutoff at 10 as suggested previously (14). Using the independent-samples *t*-test, we examined individual item score differences between the dichotomized groups. To examine the statistically significant differences in demographics and the PANSS, GAD-7, and RASS scores between patients diagnosed with SSDs with and without mania, we conducted independent-samples *t*-tests for continuous variables and chi-square (χ^2) tests for categorical variables. Using Spearman's r^2, we also explored correlations between YMRS scoring and PANSS total and subscale scores. Lastly, a linear regression model was developed to measure the association between the severity of positive symptoms according to PANSS total scoring and the presence of manic symptoms. To account for 125 comparisons in total, including the Spearman's correlations (r^2), we used Bonferroni correction by setting the level of significance at $p < 0.05/125$, that is, $p < 0.0004$. *Post-hoc* statistical power was calculated using G*Power version 3.1.9.7 (40) at $\alpha = 0.05$.

Data Availability

Data availability is restricted due to human subject involvement and is non-public. All data used in the analysis are available upon reasonable request to the corresponding author.

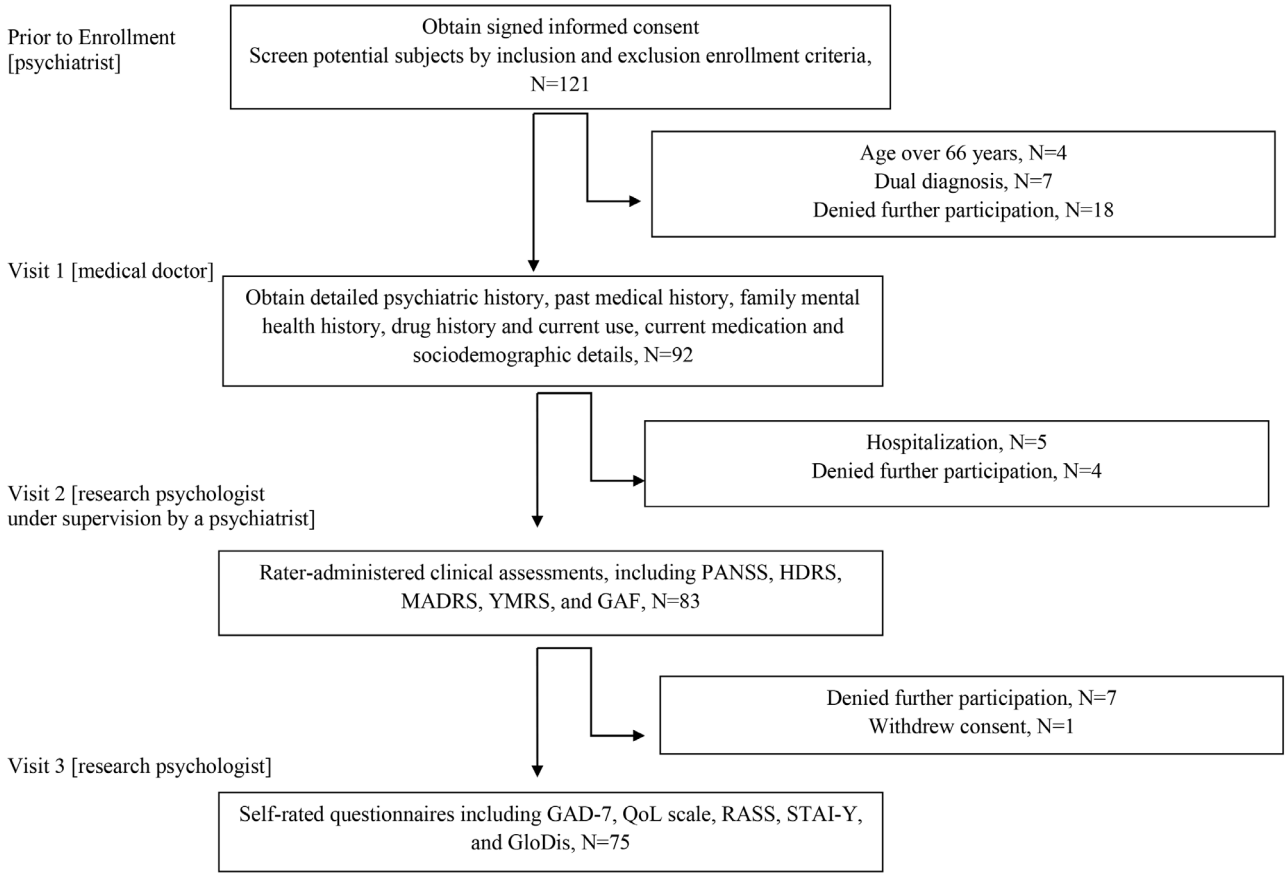

Figure 2. Recruitment flow chart.

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Author Contributions

E.M.T. oversaw clinical research coordination and organized, managed and analyzed the database of results. She was the primary author of the manuscript and orchestrated and contributed to the intellectual conceptualization of the perspective paper; she also participated as a clinical supervisor in data collection. She also acted as research coordinator. D.P. and M.K. conducted semistructured interviews on participants, collected clinical data under supervision and edited the manuscript. K.C. and S.F. collected clinical data and collated relevant data and edited the manuscript. G.K. conducted all primary assessments and screening. K.N.F. conceptualized the research project, was the primary investigator of this study and contributed to the writing and editing of this manuscript.

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Author Disclosures

The authors have confirmed that no conflict of interest exists. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript has been read and approved by all authors.

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