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Relationship of residual mood and panic–agoraphobic spectrum phenomenology to quality of life and functional impairment in patients with major depression

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Abstract

The aim of this study was to analyze the relationship of residual mood and panic–agoraphobic spectrum phenomenology to functional impairment and quality of life in 226 adult outpatients who had remitted from a major depressive episode. Quality of life and functioning were assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire and the Work and Social Adjustment Scale. Residual symptoms were assessed using the Mood and Panic–Agoraphobic Spectrum Questionnaires. Linear and logistic regression models were used to analyze the relationship of mood and panic–agoraphobic spectrum factors with quality of life and functioning. Poor quality of life was associated with the Mood Spectrum Self-Report Questionnaire factors ‘depressive mood’ and ‘psychotic features’ and the Panic-Agoraphobic Spectrum Self-Report Questionnaire factors ‘separation anxiety’ and ‘loss sensitivity’. Functional impairment was associated with the Mood Spectrum Self-Report Questionnaire factor ‘psychomotor retardation’ and the Panic-Agoraphobic Spectrum Self-Report Questionnaire factor ‘fear of losing control’. These relationships were held after controlling for the severity of depression at the entry in the continuation treatment phase. In conclusion, the spectrum assessment is a useful tool for clinicians to identify areas of residual symptomatology that can be targeted with focused and effective long-term treatment strategies.

Keywords

anxiety; depression; functioning; quality of life; remission; residual; unipolar

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Introduction

Evidence from clinical trials in major depression indicates that a substantial minority (20–50%) of patients treated for depression continue to suffer from persistent depressive symptoms at the end of acute treatment (Keitner *et al.*, 2006; Trivedi *et al.*, 2008). A number of studies have found a strong association between residual symptoms of depression and an increased risk of recurrence, poorer functioning over time and increased social and economic costs (Kupfer *et al.*, 1992; Paykel *et al.*, 1995; Judd *et al.*, 1998, 2000; Van Londen *et al.*, 1998; Pintor *et al.*, 2003; McIntyre *et al.*, 2004). For these reasons, residual symptoms after the acute treatment of major depressive episode (MDE) can be considered one of the few consistent predictors of relapse and poor psychosocial and functional outcomes during continuation and maintenance treatment (Prien and Kupfer, 1986; Papakostas *et al.*, 2004; Kennedy *et al.*, 2007; Mendlewicz, 2008).

Residual symptoms may be specific to the mood disorder, related to side effects of treatment, or secondary to comorbid Axis I or II disorders, especially anxiety disorders (Dombrovski *et al.*, 2007). It is well known that comorbidity with anxiety disorders is common among patients suffering from depressive disorders, and that anxiety symptoms delay time to response and interfere with functional impairment (Frank *et al.*, 2000; Lowe *et al.*, 2008).

The heterogeneity of residual symptoms could be, at least in part, responsible for the difficulty in finding effective long-term treatments for postacute and residual phases of depression (Fava *et al.*, 2004; Moller, 2008). This observation is confirmed by the evidence that drug treatments for acute depression may not be the most suitable for continuation treatments (Fava *et al.*, 1994), and that specific psychotherapeutic approaches targeted to residual symptoms of depression can reduce the risk of recurrence and help restore social functioning over time (Weissman *et al.*, 1974, 1981; Fava *et al.*, 2002, 2004; Papakostas *et al.*, 2004; Fava *et al.*, 2007).

Recently, Zimmerman *et al.* (2005, 2007) compared remitted patients with different scores on the Hamilton Rating Scale for Depression (HRS-D) and found that patients with a score of 0–2 reported significantly less psychosocial impairment and better quality of life than those with a score of 3–7. This is probably reflective of the fact that the instruments commonly used to assess the severity of depression and residual symptoms are focused on typical aspects (Kennedy and Paykel, 2004; Papakostas *et al.*, 2004; Dombrovski *et al.*, 2007) and overlook atypical symptoms (i.e. symptoms not mentioned in the *Diagnostic and Statistical Manual*, fourth edition or International Classification of Diseases, Tenth Revision), behavioural traits and temperamental features that are associated with depression. A number of studies, starting from a spectrum approach to mood and anxiety disorders, have shown that such symptoms and traits are associated with considerable suffering and disability and poorer treatment outcome, even in the absence of threshold-level psychiatric disorders (Frank *et al.*, 2000; Cassano *et al.*, 2004).

The aim of this study is to examine the relationship between residual features belonging to the mood and panic-agoraphobic spectrum to psychosocial functioning and quality of life.

Materials and methods

The study sample consists of adult patients with nonpsychotic unipolar depression recruited from February 2002 to March 2007 at the outpatient clinics of the Departments of Psychiatry of the Universities of Pisa and Pittsburgh in the framework of the study ‘Depression: the search for treatment-relevant phenotypes’ (Frank *et al.*, 2008) who remitted

from the index depressive episode. Remission was defined as a mean HRS-D_{17} score ≤ 7 over 3 consecutive weeks.

In the beginning of the acute treatment phase, participants were randomly assigned to a pharmacotherapeutic (citalopram or escitalopram) or a psychotherapeutic intervention (interpersonal psychotherapy – IPT) (Klerman and Weissmann, 1987).

The acute treatment phase of the study involved three assessment and triage points, at weeks 6, 12, and 20. Those participants assigned to pharmacotherapy who did not evidence a response, defined as a 50% reduction of baseline score on the HRS-D_{17}, were first increased from the initial daily dose of citalopram (20 mg) or escitalopram (10 mg) to a dose of 40 or 20 mg, respectively, at week 3. If patients did not evidence a response by week 6, they were given psychotherapy in addition to pharmacotherapy. IPT was added by week 12 if they did not meet stabilization criteria (as in the case of initial improvement followed by worsening). Those patients assigned to psychotherapy who did not evidence a response after 6 weeks of acute treatment, had pharmacotherapy added to their treatment. Patients who showed an initial response at week 6 but who later worsened, had a second opportunity to receive pharmacotherapy augmentation at week 12. All patients still on monotherapy at week 12 who had not met the criteria for remission (average HRS-D_{17} ≤7 over 3 weeks) had the other treatment (pharmacotherapy or psychotherapy) added to their treatment regimen. Patients who had not achieved remission with combined IPT plus pharmacotherapy at week 20 continued IPT and were switched to a second antidepressant following the guidelines provided by the Texas Medication Algorithm Project (Trivedi *et al.*, 2004). Participants who did not meet criteria for remission following an 8-week trial of this second antidepressant were offered an alternative treatment. When remission was achieved, participants entered a 6-month continuation phase throughout which they received the same treatment that lead to stabilization.

Study procedures were approved by the Institutional Review Board of the University of Pittsburgh and the Ethics Committee of the University of Azienda Ospedaliero-Universitaria of Pisa. All patients signed a written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

Measures

The diagnostic assessment was carried out using the Structured Clinical Interview for *Diagnostic and Statistical Manual*, fourth edition Axis-I disorders by mental health professionals who were trained and certified in the use of the study instruments. The severity of the depressive episode was assessed at baseline, weekly during the acute treatment phase and monthly during the continuation phase using the interview-based HRS-D_{17} (Hamilton, 1960).

Consistent with the method of Dombrovski *et al.* (2006, 2007), we defined the presence of residual core mood symptoms as a score of ≥ 1 on the HRS-D_{17} core symptoms subscale including the depressed mood, guilt, suicide, and anergia/anhedonia items. Persistent insomnia was defined as a score of ≥ 1 on the HRS-D_{17} sleep subscale including the early, middle and late insomnia items. Persistent anxiety was defined as a score of ≥ 2 on the HRS-D_{17} anxiety subscale including the agitation, psychic and somatic anxiety and hypochondriasis items.

At the beginning of the continuation phase, patients completed the Mood Spectrum Self-Report Questionnaire (MOODS-SR) (Fagiolini *et al.*, 1999) and the Panic–Agoraphobic Spectrum Self-Report Questionnaire (PAS-SR) (Shear *et al.*, 2001) to assess mood and panic-agoraphobic spectrum symptoms, respectively occurring in the last month. The

MOODS-SR consists of 161 items coded as present or absent for one or more periods of at least 3–5 days during the past month, whereas the PAS-SR consists of 114 similarly coded items. The factor analysis of the items of the MOODS-SR Questionnaire has identified six depressive factors and nine manic–hypomanic factors (Cassano *et al.*, 2009a, 2009b). The factors of depression are: depressive mood, psychomotor retardation, suicidality, drug/ illness-related depression, psychotic features and neurovegetative symptoms. The factors of mania/hypomania are: psychomotor activation, creativity, mixed instability, sociability/ extraversion, spirituality/mysticism/psychoticism, mixed irritability, inflated self-esteem, euphoria and wastefulness/recklessness. The factor analysis of the PAS-SR has identified 10 factors: panic symptoms, agoraphobia, claustrophobia, separation anxiety, fear of losing control, drug sensitivity and phobia, medical reassurance, rescue object, loss sensitivity, and reassurance from family members (Rucci *et al.*, 2009).

Quality of life and functioning were assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott *et al.*, 1993; Rucci *et al.*, 2007) and the Work and Social Adjustment Scale (WSAS) (Mundt *et al.*, 2002), at weeks 1, 6, 12 during the acute phase and at the beginning and the end of the continuation phase. The WSAS consists of five items rated on an 8-point ordinal scale. The total score is obtained as the sum of the five items and ranges from 0 to 40. Mundt *et al.* (2002) suggested the use of two cut-off scores to define three severity classes: no impairment (0–9), mild impairment (10–19), moderate-to-severe impairment (20–40). The Q-LES-Q is a self-report form composed of 16 items, measuring the degree of enjoyment and satisfaction experienced in eight areas, including physical health/ activities, feelings, work, household duties, school/course work, leisure time activities, social relations, and general activities. The three areas of work, household duties and school/course work are filled out by the respondent only if applicable. Items are rated on a 5-point scale. Higher scores denote higher levels of satisfaction. Two items explore medication satisfaction and life satisfaction and contentment over the last week. The total score is the sum of the first 14 items and is expressed as a percentage of the maximum possible score, calculated as: (raw score – minimum possible score)/(maximum possible score – minimum possible score) (Schechter *et al.*, 2007).

Statistical analyses

Summary statistics are presented as means and standard deviations (SDs) for continuous variables, and percentages for discrete variables. The association between quantitative variables was analysed using Spearman correlation coefficients, to take into account skewed distribution of some variables. A Mann–Whitney test was used to analyze sex differences in residual symptoms, quality of life and impairment.

Backward stepwise linear regression models were used to analyze the relationship of mood and panic–agoraphobic spectrum factors with quality of life. Backward methods start with a model that includes all the predictors. At each step, the predictor that contributes the least is removed from the model, until all the predictors in the model are significant. The Hamilton Scores at the beginning of the continuation phase and the presence/ absence of lifetime panic disorder and agoraphobia were forced into the models to adjust for their effects.

Backward stepwise logistic regression models were used to analyze the relationship of mood and anxiety panic–agoraphobic spectrum factors with functional impairment. This model was chosen because the distribution of the total WSAS was skewed to the right and linear regression was not appropriate. For these analyses, the total WSAS was dichotomized at the score of ≥ 10 that separates participants with and without impairment according to Mundt *et al.* (2002).

Results

The study sample includes 226 patients who remitted from a depressive episode and entered the continuation phase of treatment. Of these, 161 (71.2%) patients were female and 65 (28.8%) male, with a mean age of 40.6 years (SD 11.8 years), a mean educational level of 13.9 (SD = 3.6) years, 38.1% married, 67.7% employed. The median duration of illness at the study entry was 9.3 years. About one-third (27.9%) of these patients were in their first episode, the other two-thirds had a median of three lifetime episodes. Ongoing treatment at the point of remission was monotherapy in 127 patients (IPT alone: n=62, 27.4%; SSRI alone: n=65, 28.8%), and the combination of the two in 99 patients (n=50, 22.1% with IPT plus SSRI and n=49, 21.7% with SSRI plus IPT).

Overall, 63.7% of patients had no functional impairment, 26.1% had mild impairment and 10.2% had severe impairment according to the WSAS. The mean raw score on the Q-LES-Q was 48.3 (SD=9.5), or 61% of the maximum total possible score [by comparison, in a large sample of 529 individuals not in treatment for a psychiatric disorder the corresponding figure is 78.3% (Schechter *et al.*, 2007)]. Areas of higher dissatisfaction were finances, sexual interests and housework. No sex differences were found on quality of life and functioning.

Association of functioning and quality of life with residual Hamilton Rating Scale for Depression symptoms

The mean HRS-D_{17} Score was 4.1 (SD=2.1) at the beginning of the continuation phase. One or more core residual symptoms (including mild anergia/anhedonia, depressed mood and guilt) were found in 62.4% of patients, sleep problems in 49.6%, psychic and/or somatic anxiety in 16.3%. Although core symptoms were associated with poorer quality of life (r= −0.256, P < 0.001) and functional impairment (r=0.434, P < 0.001), sleep problems and somatic/psychic anxiety were unrelated to functioning and quality of life.

Relationship between mood and panic–agoraphobia spectrum factors, quality of life and functioning

On average, patients endorsed 19.6 (SD=14.9) mood spectrum items and 8 (SD=10.6) panic–agoraphobic spectrum items. Women had significantly higher scores than men on the mania spectrum factors: psychomotor activation, mixed instability and euphoria, and on panic–agoraphobic spectrum factors: panic symptoms, claustrophobia, fear of losing control, rescue object and family reassurance (Table 1). No sex difference was found on the depressive component of mood spectrum and its factors.

Stepwise linear and logistic regression models were fit to examine the relationship of mood and panic–agoraphobia spectrum with quality of life and functioning. In these analyses, we used the factors of the mood and panic–agoraphobic spectrums as independent variables and the HRS-D_{17} score at the beginning of the continuation phase and the presence/absence of panic disorder or agoraphobia as covariates. Separate models were fit for the mood and panic–agoraphobic factors.

Quality of life was negatively associated with the mood spectrum factors: depressive mood and psychotic features and positively associated with sociability extraversion after controlling for the total HRS-D_{17} score at the beginning of the continuation phase in a linear regression model (Table 2). The model accounted for 29% of variance of quality of life.

Quality of life was also negatively associated with the panic–agoraphobic spectrum factors: separation anxiety and loss sensitivity after controlling for the HRS-D_{17} score and for the

presence of lifetime diagnosis of panic disorder or agoraphobia (Table 2). The model accounted for 24% of variance of quality of life.

Functional impairment (defined as a WSAS of 10 or more) was positively associated with mood spectrum factor 'psychomotor retardation', and negatively associated with 'euphoria' in a logistic regression model, after controlling for the HRS-D_{17} score (Table 3). A borderline positive association with psychomotor activation was also observed.

Functional impairment was also associated with the panic–agoraphobic spectrum factor 'fear of losing control' after controlling for the HRS-D_{17} score and lifetime panic disorder/ agoraphobia (Table 3).

Discussion

This study confirms that residual symptoms are frequent in patients who achieve remission from an MDE, in line with Dombrovski *et al.* (2007). Our study participants endorsed on average 19.6 mood spectrum items and 8.0 panic–agoraphobic spectrum items at the point of remission as defined by the HRS-D_{17}. Interestingly, manic/hypomanic spectrum features, including psychomotor activation, mixed instability, and euphoria, were more frequent among females. In a recent study based on the same study population, Rucci *et al.* (2009) found that the polymorphism of the 5-HTTLPR is related with the lifetime mania spectrum score only in women and that women with high scores on mania spectrum and the 'SS' genotype constitute a subgroup with higher severity of depression.

As previously suggested (Judd *et al.*, 2002), depressive symptoms wax and wane within the same patient along a continuum that can accompany the patient throughout life. Functional impairment and low quality of life follow the same direction of depressive symptoms so that only when patients are completely symptom-free psychosocially does functioning return to good or very good levels.

Core residual mood symptoms, as assessed with the HRS-D_{17}, were associated with poor quality of life and functional impairment, whereas sleep problems and somatic/ psychic anxiety were not found in this population.

Interestingly, specific factors of mood and panic–agoraphobic spectra were related to quality of life and work and social functioning even after controlling for residual HRS-D_{17} symptoms. The mood spectrum factors include depressive mood, psychotic features and psychomotor retardation. The presence of items belonging to the 'psychotic features' factor of the MOODS-SR among nonpsychotic patients is not surprising as this factor, reflecting the spectrum approach to mood disorders, includes subtle and less severe aspects, such as feeling very vulnerable, guilty or remorseful, being preoccupied with one's own problems, thoughts and feelings. Of note, psychotic features and psychomotor retardation have been described in a number of studies as clinical characteristics that are more common in bipolar depression, or in patients who convert to bipolar disorder over time, than in unipolar depression (Mitchell *et al.*, 2008).

The factors sociability-extraversion and euphoria were associated with better quality of life and better functioning. This result is consistent with the description of the 'sunny side' of hypomania with positive (driven euphoric) features (Akiskal *et al.*, 2003; Hantouche *et al.*, 2003). Such features are rarely perceived as a source of distress by patients (Akiskal *et al.*, 2000; Benazzi, 2003, 2004; Akiskal and Benazzi, 2006). Another report suggested that symptoms of hypomania are associated with significant increases in health service use, a need for public assistance and suicidal behaviour, thus denoting a 'dark side' with specific harmful dysfunctions (Judd and Akiskal, 2003).

The panic agoraphobic spectrum factors associated with poorer quality of life and functioning include separation anxiety, loss sensitivity and fear of losing control.

It has been already showed that panic–agoraphobic spectrum symptoms predict delayed response to sequential treatment with psychotherapy and drugs in women with recurrent major depression (Frank *et al.*, 2000). A recent study has highlighted the synergistic contribution of depression, anxiety and somatization to functional impairment during an index episode (Lowe *et al.*, 2008). This study adds to the existing literature by providing evidence that specific features of the panic–agoraphobic spectrum are linked with impaired psychosocial functioning even when remission is achieved. The relationship between childhood and adult forms of separation anxiety and major depression is well known (Lewinsohn *et al.*, 1997, 2008; Wijeratne and Manicavasagar, 2003). Our study suggests that these features could contribute to the maintenance of a low quality of life in patients who remit from a MDE. Panic–agoraphobic residual spectrum features are more common among female patients. This is in line with the findings of Verhagen *et al.* (2008), indicating that comorbidity with panic disorder is significantly more frequent in women than in men with a major depression.

A number of studies have proved that the lack of remission is associated with significantly higher psychosocial impairment (Murphy *et al.*, 1987; Ansseau *et al.*, 2009). The results of this study confirm the importance of residual features even when patients achieve clinical remission as assessed with the $HRS\text{-}D_{17}$.

To our knowledge, this is the first study assessing residual mood and panic–agoraphobic spectrum phenomenology in patients who remitted from an MDE.

We submit that the identification of residual spectrum psychopathology could help clinicians to identify sex-specific long-term pharmacological and psychotherapeutic strategies that might lead to more complete remission and, consequently, reduced risk of recurrence. Unfortunately, these aspects, especially when subthreshold, tend to be overlooked and underestimated by clinicians. The administration of the self-report spectrum measures allows a more accurate evaluation of the heterogeneous signs and symptoms that follow an MDE.

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Table 1

Sex differences in MOODS-SR and PAS-SR factors at remission

	Male (*N* = 65)	Female (*N* = 161)	Mann– Whitney *U* test	*P* value
MOODS-SR: manic/hypomanic component				
Total manic component	9.4 ± 9.4	9.2 ± 9.6	− 0.31	0.758
Psychomotor activation	1.48 ± 1.66	1.14 ± 1.74	− 2.02	0.043
Creativity	1.35 ± 2.14	0.94 ± 1.74	− 0.88	0.379
Mixed instability	0.26 ± 0.51	0.15 ± 0.46	− 2.17	0.030
Sociability/ extraversion	0.75 ± 1.18	0.79 ± 1.11	− 0.56	0.577
Spirituality/mysticism	0.03 ± 0.17	0.06 ± 0.29	− 0.62	0.537
Mixed irritability	0.80 ± 1.04	0.83 ± 1.10	− 0.03	0.976
Inflated self-esteem	0.35 ± 0.70	0.22 ± 0.48	− 1.38	0.166
Euphoria	0.95 ± 1.34	0.52 ± 0.97	− 2.54	0.011
Wastefulness/ recklessness	0.47 ± 0.78	0.45 ± 0.80	− 0.33	0.738
MOODS-SR: depressive component				
Total depressive component	5.9 ± 6.1	4.7 ± 5.2	− 1.34	0.180
Depressive mood	3.73 ± 4.29	3.91 ± 4.70	− 0.01	0.990
Psychomotor retardation	3.14 ± 3.47	2.55 ± 3.19	− 1.15	0.250
Suicidality	0.20 ± 0.59	0.24 ± 0.72	− 0.24	0.810
Drug illness-related depression	0.20 ± 0.54	0.17 ± 0.49	− 0.48	0.633
Psychotic features	1.42 ± 1.56	1.32 ± 1.63	− 0.76	0.448
Neurovegetative symptoms	2.69 ± 2.16	2.72 ± 2.39	− 0.10	0.920
PAS-SR				
Total panic–agora phobic component	5.1 ± 7.6	9.2 ± 11.4	− 3.49	< 0.001
Panic symptoms	1.18 ± 2.13	2.63 ± 3.35	− 3.35	0.001
Agoraphobia	0.80 ± 1.44	1.05 ± 2.09	− 0.11	0.914
Claustrophobia	0.28 ± 0.60	0.70 ± 1.40	− 2.17	0.030
Separation anxiety	0.46 ± 1.05	0.86 ± 1.77	− 1.94	0.052
Fear of losing control	0.48 ± 1.32	0.79 ± 1.62	− 2.43	0.015
Drug sensitivity and phobia	0.46 ± 1.09	0.60 ± 1.26	− 0.75	0.454
Medical reassurance	0.05 ± 0.21	0.15 ± 0.57	− 0.97	0.333
Rescue object	0.12 ± 0.41	0.30 ± 0.66	− 2.19	0.028
Loss sensitivity	0.54 ± 0.81	0.72 ± 0.87	− 1.70	0.088
Family reassurance	0.29 ± 0.63	0.76 ± 1.00	− 3.59	< 0.001

Data are presented as mean ± standard deviation (SD).

MOODS-SR, Mood Spectrum Self-Report Questionnaire; PAS-SR, Panic–Agoraphobic Spectrum Self-Report Questionnaire.

Table 2

Relationship of mood and anxiety spectrum factors to the quality of life (Q-LES-Q)

	Standardized β coefficients	*t*-test	*P* value
MOODS-SR			
Depressive mood	− 0.273	− 3.78	< 0.001
Psychotic features	− 0.197	− 2.79	< 0.001
Sociability extraversion	0.116	2.04	0.042
HRS-D_{17}	− 0.238	− 4.09	< 0.001
Constant		43.36	< 0.001
PAS-SR			
Separation anxiety	− 0.305	− 4.88	< 0.001
Loss sensitivity	− 0.153	− 2.56	0.012
HRS-D_{17}	− 0.270	− 4.57	< 0.001
Panic disorder or agoraphobia	− 0.036	− 0.59	0.553
Constant		44.18	< 0.001

Factors retained in stepwise linear regression models.

HRS-D, Hamilton Rating Scale for Depression; MOODS-SR, Mood Spectrum Self-Report Questionnaire; PAS-SR, Panic–Agoraphobic Spectrum Self-Report Questionnaire; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 3

Relationship of mood and anxiety spectrum factors to functional impairment (WSAS)

	OR	CI	*P* value
MOODS-SR			
Psychomotor retardation	1.27	1.14–1.41	< 0.001
Euphoria	0.51	0.34–0.78	0.002
Psychomotor activation	1.24	0.99–1.54	0.053
HRS-D_{17}	1.26	1.07–1.48	0.006
Constant	0.12		
PAS-SR			
Fear of losing control	1.33	1.08–1.64	0.008
HRS-D_{17}	1.33	1.14–1.54	< 0.001
Panic disorder or agoraphobia	0.59	0.26–1.32	0.198
Constant	0.15		

Factors retained in stepwise logistic regression models.

CI, confidence interval; HRS-D, Hamilton Rating Scale for Depression; MOODS-SR, Mood Spectrum Self-Report Questionnaire; OR, odds ratio; PAS-SR, Panic–Agoraphobic Spectrum Self-Report Questionnaire; WSAS, Work and Social Adjustment Scale.