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Clinical Characteristics of Patients with Late Life Bipolar Disorder in the Community: Data from the NNDC Registry

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Abstract

Objectives—To compare clinical characteristics of older and younger patients with bipolar disorder enrolled in the National Network of Depression Centers (NNDC) Clinical Care Registry (CCR).

Design—Multicenter, de-identified naturalistic data from the National Network of Depression Centers' Clinical Care Registry for all patients with a diagnosis of bipolar disorder who were enrolled in the Registry as of 4/25/13.

Setting—United States

Participants—Community-dwelling patients (N=218), ages 18 or older, with bipolar disorder diagnosis recruited by NNDC-affiliated medical centers to participate in the NNDC Clinical Care Registry (CCR). Subjects age 55 or older were compared with subjects younger than age 55 on clinical measures.

Measurements—Patient Health Questionnaire (PHQ-9); Quick Inventory of Depressive Symptomatology - Self-Report (QIDS); Altman Self-Rating Mania Scale (ASRM); Work and Social Adjustment Scale (WSAS); Frequency and Intensity of Burden of Side Effects Rating (FIBSER); and the Self-Administered Comorbidity Questionnaire (SCQ).

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The authors have no conflicts of interest to disclose. Brent P. Forester MD, MSc affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Results—A greater percentage of older patients were prescribed antidepressant medications (71.9% versus 50.0%), while the younger cohort had significantly more psychostimulant use (16.7% versus 0%). Younger patients endorsed significantly more depressive symptoms compared to older patients. The mean number of psychotropic medications was not different in both older and younger patients with bipolar disorder. There was no statistically significant difference in frequency, intensity or burden of psychotropic medication side effects as measured by the FIBSER.

Conclusions—Findings of higher antidepressant use rates in the older cohort, combined with lower depression symptom severity and a similar degree of manic symptoms, suggests the possibility that older adults with bipolar disorder may have improved antidepressant efficacy and lower switch rates into manic or mixed states compared with younger cohorts. Ongoing data collection by the NNDC CCR will add to current knowledge to inform the care of older patients with bipolar disorder by providing multi-site data regarding phenomenology, treatment response, and longitudinal course of late life bipolar disorder in community settings.

Keywords

Geriatric Bipolar Depression; Depression Severity; National Network of Depression Centers

Introduction

Community surveys indicate that bipolar disorder is approximately 1/3 less common in older people than in younger people, with lifetime prevalence rates estimated to be 0.5%-1% (1). Individuals with bipolar disorder are at increased risk for early mortality, which likely accounts for its lower prevalence rate among older adults (2). Older adults with bipolar disorder include individuals with early onset illness and those who develop the first episode of mania after age 50. While relatively rare in the community, high rates of geriatric bipolar disorder are seen in both inpatient and outpatient psychiatric treatment settings (3,4). Relapse and readmission is common among older patients with bipolar disorder, even among those individuals who have had the illness for many years (5).

While there has not been consensus about how to define late-life bipolar disorder most studies have used age cutoffs between 50 and 65 (14, 37). Reports on symptom presentation in older and younger patients with bipolar disorder have produced some conflicting results. Studies comparing the phenomenology of bipolar disorder in younger and older patients have reported that older bipolar patients tend to have less severe manias (6), are less likely to have psychotic symptoms (7), and are more likely to relapse into depression after a manic episode (8). A large 2-year prospective observational study found that elderly patients with bipolar disorder, especially early-onset bipolar disorder, were more likely to report a rapid cycling course (7). However, a recent study of outpatients with bipolar disorder found no association between age and acute bipolar depression or mood-elevation symptom presentation (9).

Both psychiatric and medical co-morbidity complicate clinical management of patients with late-life bipolar disorder. While older patients with bipolar disorder have comparable levels of cardiovascular disorder as older patients with depression, patients with late-life bipolar

disorder have higher basic metabolic indices, greater burden of endocrine and metabolic disorders and are more likely to be obese (12). Twelve-month prevalence rates of co-morbid anxiety disorders and alcohol use disorders are higher among older patients with bipolar disorder than among the elderly without bipolar disorder (13).

Although the clinical needs of patients with geriatric bipolar disorder are substantial, low prevalence rates in the population have made it a difficult condition to study. It has been noted that 85% of published studies are from a single institution, usually derived from “convenience samples” of hospitalized patients (14). Available studies on medication treatment of late-life bipolar disorder have included naturalistic prescription pattern reports of younger and older patients (16, 19) and retrospective analyses of larger clinical trial data sets of mixed age groups of bipolar patients (15). A naturalistic study of acutely ill elderly bipolar patients reported that combination therapy was more common than monotherapy (18). There have been few randomized controlled medication trials to date. Indeed, despite its widespread use in bipolar disorder patients, there are few studies of lithium in older patients. The first randomized controlled trial of lithium compared with divalproex for acute mania in older adults with bipolar disorder has been recently completed (17).

Over the next 20 years, the mental health needs of older individuals with bipolar disorder are expected to increase substantially. Yet little is known about the effects of aging on the course, symptom presentation, and response to treatment for patients with bipolar disorder. More information is needed to guide treatment and improve clinical outcomes for patients with geriatric bipolar disorder. Naturalistic, prospective studies of bipolar disorder can provide valuable data to better delineate the symptom profile and response to treatment of community-dwelling patients and to distinguish characteristics of the illness in older patients from younger patients.

The National Network of Depression Centers (NNDC) is a consortium of 21 academic medical centers that has the goal of advancing clinical knowledge of mood disorders through collaboration using common assessment tools and a central data coordinating center (20). Both naturalistic and longitudinal data are being collected prospectively in a Clinical Care Registry. The NNDC Clinical Care Registry (CCR) provides a unique opportunity to significantly add to current knowledge to inform the care of older patients with bipolar disorder by providing aggregate, multi-site data regarding the phenomenology, treatment response, and longitudinal course of geriatric bipolar disorder in the community.

This report presents findings from an exploratory analysis that was undertaken to compare clinical characteristics of younger and older patients with bipolar disorder using baseline clinical data from the NNDC CCR. We hypothesized that there would be differences in the pattern of medication use and mood symptom profiles of the older compared with the younger cohort with bipolar disorder.

Methods

The NNDC Clinical Care Registry (CCR) began in December 2010. Fifteen medical centers throughout the United States affiliated with the NNDC have enrolled patients in the long-

term, prospective Registry. Participating institutions contributing patients include: Duke University, McLean Hospital (Partners HealthCare, Harvard Medical School), Emory University, Johns Hopkins University, Lindner Center of HOPE, Medical University of South Carolina, University of Michigan, University of Pennsylvania, Brigham and Women's Hospital (Harvard Medical School), Mayo Clinic, Stanford University, UCSF Comprehensive Depression Center, University of Illinois at Chicago, University of Iowa, and University of Massachusetts. Each participating institution recruits and screens patients to participate in the Clinic Care Registry (CCR). Eligibility requirements include being 18 years or older with a diagnosis of a mood disorder, literate in English and able to provide informed consent. The institutional review boards at each site and the data coordinating center at the University of Michigan approved and monitor the registry.

Measures

Patients who provide informed consent to participate in the Registry are administered a standard battery of validated questionnaires that were selected for inclusion by the Network across all centers participating in the CCR at the time of enrollment. These include the Patient Health Questionnaire (PHQ-9); Quick Inventory of Depressive Symptomatology - Self-Report (QIDS); Altman Self-Rating Mania Scale (ASRM); Work and Social Adjustment Scale (WSAS); The Self-Administered Co-morbidity Questionnaire (SCQ) and Frequency and Intensity of Burden of Side Effects Rating (FIBSER). De-identified data from these questionnaires is sent to the central NNDC data coordinating center as well as information on demographic data, DSM IV mood disorder diagnosis, and list of current medications for each registry enrollee.

The PHQ-9 is a 9-item depression symptom severity scale based on the diagnostic criteria for major depressive disorder in the DSM-IV TR, ranging from 0 to 27 with higher scores indicating greater symptom severity over the past 2 weeks (21). Scores of 0-4 may be interpreted as minimal depression, 5-9 as mild depression, 10-14 as moderate depression, 15-19 as moderately severe depression and 20-27 as severe depression (22). The 16-item QIDS questionnaire is derived from the Inventory of Depressive Symptomatology (IDS) and assesses the 9 DSM-IV TR symptom criteria for a major depressive episode (23). Scores range from 0 to 3, with higher scores indicative of an increase in depression symptom severity over the last 7 days. Total scores range from 0-5 (normal), 6-10 (mild), 11-15 (moderate), 16-20 (severe) and 21-27 (very severe) (24).

The ASRM is a 5-item self-rating scale to assess the severity of manic symptoms in the past week (25). All items are scored from 0 (absent) to 4 (present to a severe degree). Total scores range from 0 (no manic symptoms) to 20 (significant manic symptoms). A cutoff score of 6 or higher on the ASRM indicates a high probability of a manic or hypomanic condition.

The WSAS is also a 5-item scale that assesses the impact of a patient's symptoms on his/her ability to work, manage affairs at home and socially, and to form and maintain close relationships. Each question is rated on a 0 (no impairment) to 8 (very severe impairment) Likert scale. Total scores range from 0-10 (typically associated with subclinical populations), 11-20 (significant functional impairment but less severe clinical

symptomatology) to 21-40 (suggesting at least moderately severe functional impairment or worse psychopathology) (26).

The FIBSER was developed to assess the frequency and intensity of the side effects of treatments patients have taken during the past week and the degree to which treatment side effects interfered with daily functions. Scores to each question range from 0 to 6 with higher scores indicating greater frequency, intensity or burden (27).

The SCQ measures self-reported medical co-morbidity based on the subject's perception of the current severity of 15 medical problems (e.g., cancer, back pain) and their impact on function (28). The total score ranges from 0 (no problems, treatment and limitation on activities) to 45 (problems, treatment and limitation on activities with each medical condition).

For the current study, de-identified data was requested from the CCR Registry for all patients with a diagnosis of bipolar disorder who were enrolled in the Registry as of 4/25/13. CCR subjects selected for this analysis had a diagnosis of bipolar disorder (DSM codes included 296.00-296.06, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.7, 296.8, 296.89). Patients older than age 55 were compared with patients younger than age 55 in terms of gender, number and type of psychotropic medications being taken, and responses on the PHQ-9, QIDS, ASRM, WSAS, and FIBSER scales from the time of initial enrollment. The decision to use age 55 years of age as a cutoff was related to the age distribution of the NNDC subject population (67% of subjects are less than 55 years of age, while 75% of subjects are less than age 57).

Analysis Methods

No *a priori* sample size / power calculations were made. Rather, the decision to conduct the analysis was based on including at least 200 CCR subjects with a primary diagnosis of bipolar disorder. A total of 229 subjects with bipolar disorder signed consent for CCR data collection. All non-missing data were included in analyses to maximize available information. Sample sizes varied depending on the degree to which consistent data were collected for each subject. For example, a total of 218 subjects had information on age, while 212 subjects were available to correlate age and gender (17 subjects missing either age or gender) and 90 subjects were available to assess age differences in medication use. Patients completed their self-administered scales between 73% (for FIBSER-Frequency) to 80% (for PHQ) of the time. Psychiatric medication treatment information was more difficult to obtain consistently in this voluntary registry study, with medication information available for only 42% of subjects. Comparison of age groups for categorical variables were assessed using Chi-square or Fisher's exact tests and for continuous variables using two-sample t-tests (with the Satterthwaite variance pooling method which assumes unequal variances). As a sensitivity analysis, we also assessed the relationship between age – as a continuous measure -- and medication use and symptoms using logistic and linear regression, respectively. We also assessed the impact of site differences on age, gender and outcomes using Fisher's exact tests and non-parametric Kruskal-Wallis tests. No adjustment of the p-values were made for multiplicity; two-sided p-values <0.05 were considered to be statistically significant, however, they should be interpreted cautiously from a hypothesis-

generating perspective rather than from a confirmatory framework. All analyses were performed using SAS 9.3 (Carey, NC).

Results

Fifteen NNDC sites contributed a mean of 15.3 (SD=12.9) subjects, ranging from 2 to 39 subjects, to the CCR study. There was a total of 218 patients who had age information: 147 (67%) under the age of 55 and 71 (33%) who were 55 years of age or older. There was a statistically significant difference in gender distribution between younger and older groups with more women than men in the younger cohort (72% vs. 46%; $\chi^2[1]=13.6$, $p<0.01$). Among the 60 younger patients, the mean number of psychotropic medications was 3.1 (SD=1.9) compared with 3.2 (SD=1.5) in the 32 older patients ($t(78.4)=0.11$; $p=0.91$). Table 1 documents use of psychotropic medication by class and age cohort. While there was no statistically significant difference in overall medication use, a greater percentage of older patients were prescribed antidepressant medications, while the younger cohort had significantly more psychostimulant use (Table 1). There was also no statistically significant difference in frequency, intensity or burden of psychotropic medication side effects as measured by the FIBSER (Table 2).

With regards to psychiatric symptoms and functioning, there were no statistically significant differences between age groups with the exception of depressive symptoms measured by the QIDS and with self-reported co-morbidity. Younger patients endorsed significantly more depressive symptoms and fewer co-morbidity problems compared to older patients (Table 2).

In a sensitivity analysis using age as a continuous variable, we found results were comparable in terms of the impact of age on clinical outcomes, both from a descriptive and inferential (i.e., statistical significance) framework. For medication use, we found similar results with respect to descriptive trends with age; however, there were some differences in the inferential findings. In contrast with the original analysis, there was a statistically significant relationship between increasing age and decreased use of lithium (odds ratio [OR] = 0.97, 95% CI: 0.94, 1.00; $\chi^2[1]=3.8$; $p=0.05$). Although significant relationships between age and antidepressant use (OR=1.02, 95% CI: 0.99, 1.05; $\chi^2[1]=1.5$; $p=0.22$) and stimulant use (OR=0.98, 95% CI: 0.94, 1.03; $\chi^2[1]=0.5$; $p=0.48$) were absent when using age as a continuous variable, the results were in the same direction. We chose to present the results categorically making the interpretation of data more straightforward (Table 1).

Site did not have a statistically significant impact on age, gender, ASRM and the FIBSER measures (data not shown). There were statistically significant differences among the 14 sites with outcome data in PHQ-9, QIDS and WSAS. PHQ-9 ranged from a mean of 4.0 (SD=5.9) in 7 subjects at MUSC to 14.8 (SD=9.8) in 4 subjects at Duke (Kruskal-Wallis $\chi^2[13]=34.6$; $p<0.01$). QIDS ranged from a mean of 7.0 (SD=5.5) in 7 subjects at MUSC and 7.1 (SD=5.0) in 6 subjects at McLean to 14.6 (SD=4.7) in 5 subjects at Duke (Kruskal-Wallis $\chi^2[13]=25.4$; $p=0.02$). WSAS ranged from 6.8 (SD=13.6) in 5 subjects at UMass to 25.8 (SD=15.1) in 5 subjects at Duke (Kruskal-Wallis $\chi^2[13]=23.8$; $p=0.03$).

Discussion

Our findings represent a cross sectional assessment of clinical characteristics of individuals with bipolar disorder comparing younger and older age patient cohorts in the NNDC collaborative registry at the time of enrollment. We found that gender ratio and medication use patterns, though not manic symptom presentation and functional status, differed between the younger and older bipolar disorder cohorts.

Patterns of antidepressant and psychostimulant use were different between the older and younger age cohorts. Specifically, antidepressant medication use was more frequent in older adults with bipolar disorder. Furthermore, the older cohort endorsed a lower frequency of depressive symptoms, possibly reflecting the higher use of antidepressant medication, although a prospective clinical trial would be required to conclude cause and effect. This finding is in line with a previous report from Oostervink and colleagues showing that older bipolar patients were more likely to be treated with antidepressants compared to younger patients (37). Studies of antidepressant-induced manic or mixed states have historically not included older bipolar cohorts (19). In their study of mixed aged patients between 18 and 65 years of age, Frye et al. found that antidepressant treatment emergent mania was not related to clinical characteristics but was related to the presence of minor symptoms of mania in the setting of bipolar depression (29). Our findings of high antidepressant use rates of nearly 72% of the study sample in the older cohort, combined with lower depression symptom severity and a similar degree of manic symptoms, raise the intriguing possibility that older adults with bipolar disorder may have improved antidepressant efficacy and lower switch rates into manic or mixed states compared with younger cohorts. Randomized controlled studies of antidepressant efficacy in older cohorts with bipolar disorder are sorely needed, especially given epidemiological data suggesting higher rates of depression episodes with advancing age (34). Longitudinal follow-up will help clarify whether depression severity or frequency of depressive episodes change with advancing age.

Although the overall numbers are small and not statistically significant, lithium usage was less prevalent among older adults with bipolar disorder. This is consistent with previous findings demonstrating a reduction of lithium use (16, 37) and increase in use of the mood stabilizer, divalproex, in the 1990s despite an absence of data to support the safety and efficacy of divalproex or other mood stabilizers for geriatric mania or maintenance therapy (30). Differences in antidepressant and psychostimulant medication use may be an artifact of missing data from the study sample. However, another plausible explanation for an absence of any psychostimulant use in the older cohort is an absence of co-morbid Attention Deficit Hyperactivity Disorder in older adults or avoidance of stimulant medications due to the presumption of a greater risk of cardiac side effects. Further data looking at medication use patterns for aging cohorts with bipolar disorder would help to better define best treatment practices for this under-studied population that is sensitive to medication effects. Despite the reality of a growing number of individuals with bipolar disorder aging into their 6th decade and beyond, there remains a dearth of double-blind placebo-controlled studies to determine the safety and efficacy of pharmacotherapies for aging individuals with bipolar disorder beyond the recently completed Geri-BD trial (17).

Our findings also highlight that, similar to younger adults, 50% of the older cohort was prescribed antipsychotic medications. Despite the 2005 FDA boxed-warning for increased mortality related to antipsychotic use in patients with dementia-related psychosis (31, 32), and an earlier FDA warning for the risk of cerebrovascular adverse events (31) (CVAEs), this NNDC community sample of older adults with bipolar disorder indicates that many older patients with bipolar disorder receive antipsychotic medication. Although the FDA warning identified the population of patients with dementia-related psychosis at risk for mortality and CVAEs, there is a relative lack of data regarding the efficacy and safety of these widely-used medications for the treatment of bipolar disorder in older adults, including the specific risk of increased mortality or CVAEs. However, one recent study from Bhalerao and colleagues did identify differential mortality risks of antipsychotic medications when used for treatment of bipolar disorder (33). Polypharmacy of psychotropic medications remains a factor in later life bipolar disorder with both younger (3.1) and older cohorts (3.2) prescribed a similar mean number of psychotropic medications. This finding is similar to the EMBLEM study (37) that also noted combined medication treatment was common in both younger and older patients with bipolar disorder. This underscores the complexity of clinical management of bipolar disorder in both early and later life. Interestingly, despite nearly identical rates of psychotropic medication use, the tolerability of the psychotropic medications, as measured by the FIBSER, were also similar between older and younger cohorts, suggesting that older subjects did not experience greater adverse effects despite a similar degree of polypharmacy. This finding would likely be highly unexpected by most clinicians. Older adults, in general, face increasing medical co-morbidity, co-prescription of non-psychotropic medications, differential absorption and metabolism of medications and enhanced sensitivity to medication related adverse effects. Further detailed information from a larger cohort of aging individuals with bipolar disorder may help inform safety and efficacy of treatment with advancing age.

Our results also highlighted a difference in gender ratio between the older and young bipolar cohorts. Previous studies demonstrate roughly equal gender ratios regardless of age with a slight preponderance of women amongst older study cohorts of bipolar patients (35, 36). In contrast, our sample noted a higher proportion of women in the younger cohort and an even distribution of men and women in the older cohort. These differences in gender distribution are likely due to our limited sample size and non-random sampling. It is possible, however, that treatment seeking is higher in older men compare to younger men. An alternative explanation is that younger men may be less likely to participate in treatment.

The database established by the National Network of Depression Centers represents a unique collaboration that provides an opportunity to better understand clinical presentation and treatment of individuals with mood disorders. Prior studies of older adults with bipolar disorder have been limited to small retrospective treatment studies or cross sectional data. The clinical value of the NNDC collaboration is the ability to obtain consistent, longitudinal and generalizable data on patients treated in clinical practice settings using standard assessment tools.

Our findings are limited by the cross-sectional nature of this analysis and by the extent of missing data, especially for medication use. Further, the assessments did not include

information on age of illness onset and/or duration of illness. The nature of data collection for the NNDC assessments hampers our ability to interpret age-related differences by reducing power and precision. Specifically, the research assessments are scheduled to coincide with clinical visits. Challenges in adequate completion of all study-related assessments remain one of the limitations of the NNDC database, in general. The pace of clinical practice may hinder complete data collection. Furthermore, some study sites encourage real-time, direct data entry by participants into the computerized database, while others rely on completion of paper documentation followed by data entry. The effect of this missing data includes a lack of power to detect meaningful differences by age cohort that might otherwise be apparent in larger sample sizes. The site differences observed may reflect the variability in clinical status of subjects recruited by each site at the time of study entry. For example, some sites only recruited from outpatient settings, whereas others recruited additionally from inpatient and partial hospital settings, where higher depression severity scores at the time of study entry are expected. Finally, we did not adjust for multiple comparisons and so the overall type I error may be inflated. Caution should be taken in interpreting p-values that are near the nominal 0.05 level.

There remain critical unanswered clinical questions regarding the effects of advancing age for individuals with bipolar disorder. Questions such as predictors of cognitive or functional changes with advancing age, risk of neurodegenerative dementia in an individual with a lifetime history of bipolar disorder and changes in treatment that must be considered given the efficacy and tolerability of psychotropic medications with advancing age. The NNDC's longitudinal database presents an opportunity to help answer some of these critical clinical questions. Furthermore, future data collection projects that could be considered include assessments of cognitive functioning, an important predictor of clinical outcome.

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Table 1

Medication Use by Age

	Young (Age < 55) N=59 to 60	Old (Age ≥ 55) N=31 to 32	p *
Lithium Use (n)	40.7% (24)	22.6% (7)	0.11
Lamotrigine Use (n)	32.2% (19)	29.0% (9)	0.81
Valproic Acid Use (n)	10.2% (6)	12.9% (4)	0.73
Any Anticonvulsant Use (n)	50.0% (30)	43.7 (14)	0.66
Antidepressant Use (n)	50.0% (30)	71.9% (23)	.05
Stimulant Use (n)	16.7% (10)	0%	.01
Antipsychotic Use (n)	50.0% (30)	59.4% (19)	0.51
Sedative Use (n)	41.7% (25)	40.6% (13)	>0.99

137 to 139 subjects are missing data on medication use.

* Two-sided p-value obtained from Fisher's exact tests

Table 2

Mean (Standard Deviation) Symptoms and Function by Age.

Scale (Range)	Young (Age < 55) N=109 to 123	Old (Age 55) N=51 to 61	T Value (df)*	p *
FIBSER Frequency (0 – 6)	1.99 (2.20) n = 101	1.81 (2.09) n = 52	–0.50 (107.9)	0.62
FIBSER Intensity (0 – 6)	1.78 (1.76) n = 102	1.60 (1.74) n = 52	–0.61 (106.8)	0.54
FIBSER Burden (0 – 6)	1.21 (1.63) n = 102	1.28 (1.61) n = 52	0.26 (109.5)	0.79
PHQ-9 (0-27)	10.3 (7.2) n = 112	8.9 (7.67) n = 55	–1.19 (102.0)	0.23
QIDS (0-27)	11.5 (5.9) n = 110	8.8 (5.6) n = 55	–2.82 (113.2)	<0.01
ASRM (0 -20)	3.4 (3.4) n = 111	3.0 (3.4) n = 55	–0.60 (106.8)	0.55
WSAS (0-40)	18.4 (13.0) n = 109	17.0 (12.4) n = 51	–0.70 (101.9)	0.49
SCQ (0 – 45)	2.9 (3.7) n = 123	4.7 (4.6) n = 61	2.76 (99.4)	<0.01

PHQ-9: Patient Health Questionnaire; QIDS: Quick Inventory of Depressive Symptomatology; ASRM: Altman Self-Rating Mania Scale; WSAS: Work and Social Adjustment Scale; SCQ: Self-Administered Comorbidity Questionnaire; FIBSER: Frequency and Intensity of Burden of Side Effects Rating.

* test statistic, degrees of freedom (df) and two-sided p-value obtained from two-sample t-tests (using Satterthwaite method)