Prevalence and clinical correlates of cognitive symptoms in depression: a naturalistic study

Prevalenza e correlati clinici della sintomatologia cognitiva nella depressione: uno studio naturalistico

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SUMMARY. Background. Treated mood disorder (MD) patients suffer from residual cognitive symptoms, even when treatment response is considered adequate. Here we estimated the prevalence of cognitive impairment and tested whether the severity of self-rated and clinician-rated cognitive symptoms differed between remitted and unremitted MD patients. **Methods.** Forty-three consecutive MD patients were recruited at an academic community mental-health centre at the University of Cagliari, Cagliari, Italy. Patients had to have a diagnosis of major depressive disorder (MDD), bipolar disorder (BD) type 1 or type 2, or unspecified depressive disorder according to the Diagnostic Statistical Manual (DSM)-5 criteria. Cognitive function was assessed using self-rated [Perceived Deficits Questionnaire – Depression, 5-item (PDQ-D-5)] and clinician-rated [Digit Symbol Substitution Test (DSST) measures and the short version of the Mini Mental State Examination (sMMSE)] tools. Standard statistical tests were applied. **Results.** The prevalence of cognitive symptoms ranged from 20.9% to 44.2%, depending on the assessment tool used. There were no statistically significant differences in self-rated and clinician-rated measures of cognitive function between remitted and unremitted patients as well as no statistically significant correlation between self-rated and clinician-rated measures of cognitive function. Patients with better education had higher mean scores at the sMMSE and the DSST. **Discussion and conclusions.** We confirmed that cognitive symptoms are highly prevalent in MD patients, irrespective of the mood state. This suggests that cognitive impairment in MD is a trait, rather than a state marker. The absence of a correlation between self-rated and clinician-rated (objective) measures of cognitive impairment suggests that each assessment tool captures a specific facet of cognitive function.

KEY WORDS: DSST, sMMSE, PDQ-D-5, cognitive impairment, clinician-rated measures.

RIASSUNTO. I pazienti con disturbi dell'umore (DU) manifestano sintomi cognitivi residuali, anche quando la risposta al trattamento farmacologico è considerata adeguata. In questo studio si è valutata la prevalenza delle disfunzioni cognitive e la presenza di differenze nella gravità di tale sintomatologia (esaminata sia con metodi soggettivi che oggettivi) tra pazienti in remissione e quelli con episodio depressivo in atto. **Metodi.** Quarantatré pazienti con DU sono stati reclutati presso la Clinica Psichiatrica dell'Università di Cagliari. I pazienti sono stati inclusi nello studio se avevano una diagnosi di disturbo depressivo maggiore (DDM), disturbo bipolare di tipo 1 o 2, disturbo depressivo senza specificazione. Le funzioni cognitive sono state valutate usando misure soggettive [il Perceived Deficits Questionnaire-Depression, 5-item (PDQ-D-5)] e oggettive [il Digit Symbol Substitution Test (DSST) e la versione ridotta del Mini Mental State Examination (sMMSE)]. Le analisi statistiche hanno impiegato metodi standard. **Risultati.** La prevalenza dei sintomi cognitivi variava, secondo lo strumento usato, dal 20,9% al 44,2%. Non abbiamo riscontrato differenze statisticamente significative nelle misure soggettive e oggettive di funzionamento cognitivo tra pazienti in remissione e quelli depressi, né tantomeno correlazioni tra le misure soggettive e oggettive di valutazione. I pazienti con più alti livelli d'istruzione avevano punteggi medi più alti alla scala sMMSE e alla DSST. **Discussione e conclusioni.** Il nostro studio ha confermato la presenza di un'alta prevalenza dei sintomi cognitivi nei pazienti con DU, indipendentemente dalla presenza o meno di alterazioni del tono dell'umore. Questo dato supporta l'ipotesi che le alterazioni cognitive siano un marcatore di tratto, piuttosto che di stato. L'assenza di una correlazione tra le misure soggettive e oggettive di valutazione suggerisce che ciascuno strumento identifichi una specifica sfaccettatura della funzione cognitiva.

PAROLE CHIAVE: DSST, sMMSE, PDQ-D-5, deficit cognitivo, valutazioni eterosomministrate.

INTRODUCTION

Major depressive disorder (MDD) is a severe mental illness characterized by low mood, anhedonia, negative thoughts, frequently accompanied by cognitive impairment, mainly consisting of reduced concentration or indecisiveness. Depressive episodes might also manifest in the context of a bipolar disorder (BD), a chronic psychiatric illness characteri-

zed by recurring episodes of depression and hypomania/mania alternating with intervals of well-being[1]. Treated mood disorders (MD) patients spend a substantial amount of time with residual affective symptoms, even when treatment response is considered adequate[2]. For instance, the residual morbidity amounts at 40%-50% of weeks of follow-up with standard treatment, and about three-quarters of it is depressive[2-5]. One of the most relevant (in terms of frequency and impact on functioning) cluster of symptoms affecting remitted and unremitted treated MD patients pertains to cognition[6,7]. A number of clinical studies have shown that cognitive impairment persists during euthymic phases in MD patients[8]. Several cognitive domains result to be affected, such as attention and executive function[8], processing speed, visual spatial memory and verbal working memory[9-12] and set shifting, planning, and verbal fluency[12]. Of interest, however, a qualitative data synthesis of the literature did not show significant alterations in cognitive function between diagnostic groups (i.e. BD versus MDD)[13].

One key aspect in the assessment of cognitive function in MD patients concerns the validity of self-rated (subjective) measures in detecting existing alterations with sufficient precision and accuracy. A recent large study in over 140,000 subjects of the UK Biobank cohort tested for the presence of differences in cognitive performance, assessed subjectively, between middle-aged adults with and without a lifetime history of MD features[14]. Inverse associations between lifetime history of bipolar or severe recurrent depression and cognitive performance were attenuated or reversed after adjusting for a series of confounders[14]. This finding appears in contrast with evidence based on clinician-rated measures, where cognitive impairment is significantly over-represented in MD patients compared to controls. Of note, the importance of targeting cognitive impairment in MD patients has led to the development of diverse novel assessment tools, that permit a comprehensive and clinically feasible longitudinal evaluation of cognition, particularly in relation to treatment effects[15].

In this context, our study had a threefold primary aim: 1) to estimate the prevalence of cognitive deficits in our sample of MD patients using self-rated and clinician-rated measures; 2) to test whether the severity of self-rated cognitive symptoms differed between MD patients currently depressed and in remission; 3) to assess whether the severity of clinician-rated cognitive symptoms differed between MD patients currently depressed and in remission. As an aside, we tested also the following secondary hypotheses: 1) to assess the correlation between self-rated and clinician-rated measures of cognitive function in our sample of MD patients; 2) to evaluate the patterns of association between indicators of personal and social functioning and cognitive function.

MATERIALS AND METHODS

Patient sample

We conducted a retrospective assessment of 43 consecutive MD patients followed longitudinally at the Section of Psychiatry of the Department of Medical Sciences and Public Health of the University of Cagliari, Cagliari, Italy. All patients gave written and verbal consent to allow reanalysis of clinical data for research purposes. We collected detailed clinical data on the recruited sample in the third trimester of 2018. Patients were included in the study if: 1) they had a diagnosis of MDD, BD type 1 or type 2, or unspecified depressive disorder according to the Diagnostic Statistical Manual five edition (DSM-5) criteria[16], 2) had an age between 18 and 70 years. Exclusion criteria were the following: 1) presence of a diagnosis of neurocognitive disorder of any severity according to the DSM-5 criteria, 2) inability to provide consent to the study. Recruited patients were assessed with a series of self-rated and clinician-rated tools, and deep-phenotyped on the basis of an accurate review of the clinical charts. We extracted socio-demographic and clinical data through a systematic chart review, performed at the time of the assessment of cognitive function. In light of the relatively small sample size, we created two new dummy coded categorical variables "Employment dichotomous" [employed (=0) and unemployed (=1)] and "Education dichotomous" [education level lower (=0) and higher (=1) than junior high school].

Data were extracted by one author (V.P.) and subsequently verified with senior investigators (M.M., F.P, M.G.O., B.C.). Disagreements in extraction and interpretation of data were resolved with consensus-based discussion.

Clinical assessment

Cognitive function was assessed using self-rated and clinician-rated tools. Specifically, as a self-rated measure we used the Perceived Deficits Questionnaire - Depression, 5-item (PDQ-D-5) an instrument initially developed for the assessment of patients affected by multiple sclerosis, subsequently validated in MDD[17]. The PDQ assesses 4 domains of cognitive functioning, which are reflected in the following subscales: attention/concentration, retrospective memory, prospective memory, and planning/organization[17]. For the purpose of this study we used the italian version of the short version (5-item) of the PDQ, the PDQ-D-5, practical for rapid assessment.

Clinician-rated measures of cognitive function included the Digit Symbol Substitution Test (DSST)[18], which is a pencil and paper test of psychomotor performance with a key grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consists of filling as many empty boxes as possible with a symbol matching each number. The score is the number of correct number-symbol matches achieved in 90 seconds. A component of the Wechsler Adult Intelligence Scale (WAIS)[19] and the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[20], the test explores executive function, perceptual speed and processing speed with high scores associated with intact motor speed, attention, and visuoperceptual functions (including scanning). The test has shown high test-retest stability[21] and has been proposed in the assessment of cognition in mood disorders[18]. We also used the short version of the Mini Mental State Examination (sMMSE)[22], whose accuracy in detecting cognitive decline is comparable with the long version of the test[23], to examine the global cognitive function. Given that each tool assesses diverse aspects of cognition, we implemented their combined use to perform an as comprehensive as possible assessment of cognition in a feasible manner. Clinician-rated psychopathological measures included the Clinical Global Impression severity (CGIs) scale[24], and the Global Assessment of Functioning (GAF)[25].

Data analysis

The rates of cognitive impairment were calculated using the median value of the empirical distribution of each scale score as

symptomatic cut-off. We studied continuous and categorical clinical variables using univariate analysis (t test or contingency tables as appropriate). When one or more cells had expected values of 5 or less Fisher's exact test was used in 2 x 2 contingency tables and bootstrap with 1,000 samples in larger tables. Non-parametric tests were used when data violated the assumption of normality. Statistical significance was set at =0.05. All statistical analyses were carried out with IBM® SPSS® Statistics version 25.0.0.1 (64 bit).

RESULTS

Clinical characteristics of the sample

The sample was comprised of 43 patients (female:male ratio=2.3). Twenty-one patients (about 50% of the sample) had a diagnosis of BD, 20 were MDD, and 2 were diagnosed with an unspecified mood disorder. The average age of the sample was 51.2 years [standard deviation (SD)=10.1], while the average age of onset was 27 years (SD=10.1). The mean duration of current or most recent depressive episode was 29.1 months (SD=51.2). Ten patients (23.3%) had psychiatric comorbidities, while 18 (41.9%) had medical comorbidities. More than half of the sample (55.8%) was assuming an antidepressant treatment at the moment of the assessment, while 11 patients (25.6%) were receiving psychotherapy. Further details of the sample are provided in Table 1.

Prevalence of cognitive dysfunction

Considering the median value of the empirical distribution as *symptomatic* cut-off we had the following rates: for the self-rated measures (PDQ-D-5), 11 patients out of 43 (25.6%) had values lower than the median; for the clinician-rated measures, using the median value of the DSST we found 19 *symptomatic* patients out of 43 (44.2%), while for the sMMSE there were 9 *symptomatic* patients out of 43 (20.9%).

Severity of self-rated and clinician-rated cognitive symptoms in MD patients currently depressed and in remission

Twenty patients (46.5%) were in remission, while 23 (53.5%) were depressed. As shown in Table 2, there were no statistically significant differences in self-rated and clinician-rated measures of cognitive function, including the DSST, between remitted and unremitted patients. Similarly, we did not detect a statistically significant overrepresentation of a specific socio-demographic or clinical variable in one of the two MD subgroups. As expected, the CGIs and the GAF scores were significantly lower ($t=2.1$, $p<0.05$) and higher ($t=4.3$, $p<0.00001$), respectively, in remitted patients. All these findings are summarized in Table 2.

Correlation between self-rated and clinician-rated measures of cognitive symptoms

Non-parametric analysis did not show a statistically significant correlation between self-rated and clinician-rated

Table 1. Socio-demographic and clinical characteristics of the sample.

Clinical variable	Total (N = 43)
Female, N (%)	30 (70)
Age (years), mean (SD)	51.2 (10.1)
Age class (years), N	
0-20	0 (0)
21-30	4 (9.3)
31-40	2 (4.7)
41-50	8 (18.6)
51-60	27 (62.8)
61-70	2 (4.7)
Marital status, N (%)	
Single	15 (34.9)
Married/Cohabiting	20 (46.5)
Divorced	7 (16.3)
Widowed	1 (2.3)
Employment, N (%)	
Employed	19 (44.2)
Housewife	10 (23.3)
Student	2 (4.7)
Retired	3 (7)
Unemployed	9 (20.9)
Main psychiatric diagnosis, N (%)	
Bipolar disorder	21 (48.8)
Major depressive disorder	20 (46.5)
Unspecified depressive disorder	2 (4.7)
Presence of a comorbid psychiatric disorder, N (%)	10 (23.3)
Depressive episode	
Current	20 (46.5)
In remission	23 (53.5)
Duration of current or most recent episode (months), mean (SD)	29.1 (51.2)
Age at onset (years), mean (SD)	27 (10.1)
Age at onset - current episode (years), mean (SD)	48.8 (10.7)
Presence of a comorbid medical disorder, N (%)	18 (41.9)
Presence of antidepressant treatment	24 (55.8)
Presence of psychotherapy	11 (25.6)
CGIs, mean (SD)	3.5 (1.1)
PDQ-5, mean (SD)	11.8 (5.2)
DSST, mean (SD)	30.9 (11)
GAF, mean (SD)	67.1 (12.8)
sMMSE, mean (SD)	14.1 (0.9)

Legend: SD= standard deviation; CGIs= Clinical Global Impression severity scale; PDQ-D-5= Perceived Deficits Questionnaire-Depression, 5-item; DSST= Digit Symbol Substitution Test; GAF= Global Assessment of Functioning; sMMSE= short version of the Mini Mental State Examination.

Table 2. Comparison of socio-demographic and clinical characteristics and of self-rated and clinician-rated measure of cognitive function between mood disorder patients with current depression and in remission.

Variable	Current depression (N=23)	In remission (N=20)	t test/Mann-Whitney or X^2	p
Female, N (%)	15 (65.2)	15 (75.0)	0.5	NS
Age (years), mean (DS)	50.1 (8.4)	51.5 (11.9)	2.3	NS
Age class (years), N (%)				
21-30	1 (4.3)	3 (15)	2.8	NS
31-40	1 (4.3)	1 (5)		
41-50	6 (26.1)	2 (10)		
51-60	14 (60.9)	13 (65)		
61-70	1 (4.3)	1 (5)		
Civil status, N (%)				
Single	8 (34.8)	7 (35.0)	1.2	NS
Married/cohabiting	11 (47.8)	9 (45.0)		
Divorced	3 (13.0)	4 (20.0)		
Widowed	1 (4.3)	0 (0)		
Employment, N (%)				
Employed	11 (47.8)	8 (40.0)	4.3	NS
Housewife	3 (13.0)	7 (16.3)		
Student	2 (8.7)	0 (0)		
Retired	2 (8.7)	1 (5)		
Unemployed	5 (21.7)	4 (20.0)		
Education				
Primary school	1 (4.3)	3 (15.0)	4.1	NS
Junior high school	11 (47.8)	5 (25.0)		
High school	5 (21.7)	8 (40.0)		
College/university	6 (26.1)	4 (20.0)		
Diagnosis, N (%)				
Bipolar disorder	11 (47.8)	10 (50.0)	0.04	NS
Major depressive disorder	11 (47.8)	9 (45.0)		
Unspecified depressive disorder	1 (4.3)	1 (5.0)		
Presence of psychiatric comorbidities, N (%)	7 (30.4)	3 (15.0)	1.4	NS
Duration of the most recent or current episode (months), mean (SD)	40.8 (67.1)	15.7 (15.4)	6.3	0.02
Age of onset (years), mean (SD)	25.6 (7.9)	28.7 (12.1)	3.1	NS
Age of onset, current episode (years), mean (SD)	47.7 (9.6)	50 (11.8)	1.2	NS
Presence of medical comorbidities, N (%)	10 (43.5)	8 (40.0)	0.05	NS
Presence of antidepressant treatment				
SSRI	5 (35.7)	2 (20.0)	5.1	NS
TCA	5 (35.7)	1 (10.0)		
SMS	2 (20.0)	2 (20.0)		

Continue

Continue Table 2.

Variable	Current depression (N=23)	In remission (N=20)	t test/Mann-Whitney or X^2	p
NaSSA	0 (0)	1 (10.0)		
SNRI	2 (14.3)	4 (40.0)		
Presence of psychotherapy	7 (30.4)	4 (20.0)	0.6	NS
CGIs, mean (SD)	3.8 (1.04)	3.1 (1.1)	-2.1	0.04
PDQ-D-5, mean (SD)	12.35 (5.7)	11.1 (4.7)	2.6	NS
DSST, mean (SD)	31.1 (12.1)	30.7 (9.8)	1.9	NS
GAF, mean (SD)	60.5 (8.4)	74.7 (12.9)	4.3	<0.00001
sMMSE, mean (SD)	14.2 (0.8)	13.9 (1.1)	3.2	NS

Legend: SD= standard deviation; CGI= Clinical Global Impression; PDQ-D-5= Perceived Deficits Questionnaire-Depression, 5-item; DSST= digit symbol substitution test; GAF= Global Assessment of Functioning; sMMSE= short version of the Mini Mental State Examination; TCA= tricyclic antidepressant; SSRI= selective serotonin reuptake inhibitors; SMS= serotonin modulator and stimulator; NaSSA= noradrenergic and specific serotonergic antidepressants; SNRI= selective noradrenergic reuptake inhibitors; NS= not significant.

measures of cognitive function (PDQ-D-5 versus DSST, rho=0.16, p=0.3; PDQ-D-5 versus sMMSE, rho=0.04, p=NS; DSST versus sMMSE, rho=0.14, p=NS).

Association between measures of cognitive function and indicators of personal and social functioning

Mood disorder patients with better education had higher mean scores at the sMMSE and the DSST, but not at the PDQ-D-5 compared to those with lower levels of education (mean sMMSE: 13.7 versus 14.3, p=<0.05; DSST: 25.6 versus 35.6, p=0.002; PDQ-D-5: 11.4 versus 12.0, p=NS). These differences were not present with regard to the level of employment (data not shown). Non-parametric analysis showed a statistically significant negative correlation between the GAF and the PDQ-D-5 (rho=-0.4, p<0.0001) and a positive one between the GAF and the DSST (rho=0.3, p=0.008). The CGIs showed a statistically significant positive correlation with the PDQ-D-5 (rho=0.4, p=0.001) and a negative one with the DSST (rho=-0.27, p<0.05).

DISCUSSION

This naturalistic retrospective study assessed the prevalence and severity of self-rated and clinician-rated cognitive symptoms in a sample of unremitted and remitted treated MD patients. Several findings deserve a comment. The prevalence of cognitive symptoms ranged, depending on the assessment tool used, from 20.9% to 44.2%. Of note, the rates were substantially similar when comparing self-rated with clinician-rated measures. This figure is consistent with previous estimates reported in the literature[26] and confirms the presence of significant cognitive impairment in MD[27,28].

Another important finding was the absence of statistically significant differences in the severity of cognitive symptoms between remitted and unremitted treated MD patients using self-rated or clinician-rated measures. This finding appears to be in line with the hypothesis that cognitive dysfunction in MD can be considered as a trait (or risk) – marker rather than a state-marker. To meet the criteria for being defined as a trait marker (or endophenotype), a clinical characteristic has to be associated with the illness in question, independently of clinical state[29]. Indeed, there is a substantial amount of evidence suggesting that cognitive impairment persists during inter-episodic phases, and even predates the onset of a MD[30]. Several studies have corroborated this observation in MDD[33,34] and in BD[34]. Concerning MDD, most of the evidence supporting the role of cognitive impairment as a trait-marker comes from twin[35] and high-risk[31,35] studies. For instance, the work of Belleau et al.[35] showed that the offspring of at least one parent affected by MDD (i.e. at high genetic risk) had significantly slower reaction times on an index of executive attention compared to healthy offspring, suggesting that this characteristic might predict the subsequent onset of a full-blown MD. Another study, using a longitudinal design[31], tested whether the manifestation of depressive symptoms in the mothers correlated with alterations of executive functions in their offspring (aged 2-6 years)[31]. Using a sample of 126 diads, these authors identified an association between mothers' depression and cognitive impairment that was strongly dependent on the duration of the exposure to affective symptoms[31]. Finally, a cross-sectional high-risk case-control study of healthy monozygotic (MZ) and dizygotic (DZ) twins with and without a co-twin history of affective disorder showed that healthy twins discordant for MDD showed lower performance on almost all measures of cognitive function, including selective and sustained attention, executive function, language processing and working and declarative memory[34]. In addition, healthy twins discordant for BD showed lower performance on tests measuring episodic and working memory[34]. In this context, our findings confirm that cognitive impairment remains active in MD patients even in the absence of active mood episodes. Ideally, further corroboration to our results should come from the assessment of healthy controls of similar age and education level of affected subjects.

Another finding of our study, that deserves some methodological considerations, is the absence of a statistically significant correlation between self-rated and clinician-rated measures of cognitive function. It is plausible that this lack of concordance depends on the specificity of each assessment tool in measuring a distinct facet of cognition. Indeed, DSST describes perceptual speed and processing speed, while PDQ-D-5 and sMMSE presents a global depiction of cognition. It is conceivable that using these measures, subjective and objective, jointly might give a more accurate description of cognition in MD than the one obtained with either assessment tool alone. In line with this finding are the reports from Yoo-Jeong et al.[36] and Petersen et al.[37]. In a sample of 207 persons living with HIV presenting clinical depression, subjective cognitive complaints did not correlate in a statistically significant manner with objective cognitive measures[36]. Furthermore, Petersen et al.[37] showed a substantial discrepancy between objective and subjective cognition measures in depressive patients, with certain clinical features, including illness duration and symptoms severity, associated with the degree of discrepancy. Finally, the finding of a discrepancy between subjective and objective measures of cognition is consistent also with data coming from the psychometric analysis of treatment response to antidepressants, where it was observed that self-report and clinician-rated measures each uniquely contributed to the prediction of antidepressant treatment outcome[38].

This study showed that indicators of personal and social functioning were associated with cognitive performance in our sample of MD patients. Specifically, we found higher cognitive functioning in patients with better education. Further, higher levels of global functioning (as expressed by GAF) correlated with lower PODQ-D-5 scores and higher DSST scores, corroborating the view that cognitive impairment exerts an impact on personal and social areas of functioning. This is in line with the literature, as recently shown by a qualitative data synthesis[32].

LIMITATIONS

Our results should be interpreted in the context of several limitations. First, clinical data were collected retrospectively, an aspect that could have increased the likelihood of recall bias. However, these data were based on accurate longitudinal observation started, in some cases, since the illness onset. Second, the absence of a healthy controls group did not permit to calculate normative values for the cognitive measures. Third, our sample size might not have had an adequate statistical power to detect signal of association of small to moderate effect size, thus increasing the likelihood of type 2 error (i.e. false negative rate). Our purpose is to continue the recruitment of MD patients in order to increase the statistical power of our sample. In addition, the relatively limited sample size did not allow for reliable multivariate analyses, due to the high propensity toward saturation of the models even with a few dependent variables. Another main limitation concerns the presence of concomitant pharmacological treatments. Indeed, the presence of mood stabilizing treatment might have influenced cognitive function, an effect previously described in anticonvulsants[39]. Fifth, it is plausible that the not negligible rate of medical comorbidities might have impacted on measures of cognitive function in our sample. This possible confounding effect could be increased by the presence of psychiatric comorbidities in a small proportion of MD patients. Finally, the diagnostic heterogeneity, determined by the inclusion of BD and MDD cases, might have also influenced our results.

CONCLUSIONS

Even in light of the existing limitations, we confirmed previous evidence that cognitive symptoms are highly prevalent in MD patients, irrespective of the mood state. This appears to indicate that cognitive impairment in MD is a trait, rather than a state-marker. Further, the absence of a correlation between self-rated and clinician-rated (objective) measures of cognitive impairment suggests that each assessment tool captures a specific facet of cognitive function, and that an exhaustive depiction of cognition in MD should include both subjective and objective measures. Should these results be confirmed also in a larger sample, and with a population of healthy controls, there will be further support for the hypothesis of cognitive impairment as a trait marker of MD.

Conflict of interests: the authors have no conflict of interests to declare.

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REFERENCES

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet 2016; 387: 1561-72.
2. Forte A, Baldessarini RJ, Tondo L, Vázquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. J Affect Disord 2015; 178: 71-8.
3. Joffe RT, MacQueen GM, Marriott M, Trevor Young L. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disord 2004; 6: 62-6.
4. Baldessarini RJ, Salvatore P, Khalsa H-MKM, et al. Morbidity in 303 first-episode bipolar I disorder patients. Bipolar Disord 2010; 12: 264-70.
5. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003; 64: 680-9.
6. Papakostas GI, Culpepper L. Understanding and managing cognition in the depressed patient. J Clin Psychiatry 2015; 76: 418-25.
7. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatry Clin Neurosci 2017; 71: 18-27.
8. Daniel BD, Montali A, Gerra ML, et al. Cognitive impairment and its associations with the path of illness in affective disorders: a comparison between patients with bipolar and unipolar depression in remission. J Psychiatr Pract 2013; 19: 275-87.
9. Godard J, Baruch P, Grondin S, Lafleur MF. Psychosocial and neurocognitive functioning in unipolar and bipolar depression: a 12-month prospective study. Psychiatry Res 2012; 196: 145-53.

10. Godard J, Grondin S, Baruch P, Lafleur MF. Psychosocial and neurocognitive profiles in depressed patients with major depressive disorder and bipolar disorder. Psychiatry Res 2011; 190: 244-52.
11. Xu G, Lin K, Rao D, et al. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J Affect Disord 2012; 136: 328-39.
12. Lin K, Xu G, Lu W, et al. Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: a prospective longitudinal study. J Affect Disord 2014; 168: 184-91.
13. Szmulewicz AG, Valerio MP, Smith JM, Samamé C, Martino DJ, Strejilevich SA. Neuropsychological profiles of major depressive disorder and bipolar disorder during euthymia. A systematic literature review of comparative studies. Psychiatry Res 2017; 248: 127-33.
14. Cullen B, Nicholl BI, Mackay DF, et al. Cognitive function and lifetime features of depression and bipolar disorder in a large population sample: cross-sectional study of 143,828 UK Biobank participants. Eur Psychiatry 2015; 30: 950-8.
15. Fiorillo A, Carpiniello B, De Giorgi S, et al. Assessment and management of cognitive and psychosocial dysfunctions in patients with major depressive disorder: a clinical review. Front Psychiatry 2018; 9: 1-8.
16. American Psychiatric Association. DSM-5. Washington, DC: APA Press, 2013.
17. Fehnel SE, Forsyth BH, DiBenedetti DB, Danchenko N, François C, Brevig T. Patient-centered assessment of cognitive symptoms of depression. CNS Spectr 2016; 21: 43-52.
18. Jaeger J, Domingo SZ. The digit symbol substitution test (DSST): psychometric properties and clinical utility in major depressive disorder. Eur Neuropsychopharmacol 2016; 2: S341.
19. Wechsler D. Manual for the Wechsler Adult Intelligence Scale. Psychological Corporation, 1955.
20. Wechsler D. WAIS-R Manual: Wechsler Adult Intelligence Scale-Revised. Psychological Corporation, 1981.
21. Matarazzo JD, Herman DO. Base rate data for the WAIS-R: test-retest stability and VIQ-PIQ differences. J Clin Neuropsychol 1984; 6: 351-66.
22. Stein J, Luppa M, Kaduszkiewicz H, et al. Is the Short Form of the Mini-Mental State Examination (MMSE) a better screening instrument for dementia in older primary care patients than the original MMSE? Results of the German study on ageing, cognition, and dementia in primary care patients (AgeCoD). Psychol Assess 2015; 27: 895-904.
23. Schultz-Larsen K, Lomholt RK, Kreiner S. Mini-Mental Status Examination: a short form of MMSE was as accurate as the original MMSE in predicting dementia. J Clin Epidemiol 2007; 60: 260-7.
24. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry 2007; 4: 28-37.
25. Aas IHM. Global Assessment of Functioning (GAF): properties and frontier of current knowledge. Ann Gen Psychiatry 2010; 9: 20.
26. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995; 34: 867-76.
27. Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. J Clin Psychiatry 2008; 69: 1122-30.
28. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatry Clin Neurosci 2017; 71: 18-27.
29. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636-45.
30. Allott K, Fisher CA, Amminger GP, Goodall J, Hetrick S. Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? Brain Behav 2016; 6: e00527.
31. Hughes C, Roman G, Hart MJ, Ensor R. Does maternal depression predict young children's executive function? A 4-year longitudinal study. J Child Psychol Psychiatry 2013; 54: 169-77.
32. Cambridge OR, Knight MJ, Mills N, Baune BT. The clinical relationship between cognitive impairment and psychosocial functioning in major depressive disorder: a systematic review. Psychiatry Res 2018; 269: 157-71.
33. Vöhringer PA, Barroilhet SA, Amerio A, et al. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. Front Psychiatry 2013; 4: 87.
34. Christensen MV, Kyvik KO, Kessing LV. Cognitive function in unaffected twins discordant for affective disorder. Psychol Med 2006; 36: 1119.
35. Belleau EL, Phillips ML, Birmaher B, Axelson DA, Ladouceur CD. Aberrant executive attention in unaffected youth at familial risk for mood disorders. J Affect Disord 2013; 147: 397-400.
36. Yoo-Jeong M, Anderson A, Rahman AKMF, Baumann M, McBroom J, Waldrop-Valverde D. Associations of mood on objective and subjective cognitive complaints in persons living with HIV/AIDS. J HIV AIDS 2018; 4.
37. Petersen JZ, Porter RJ, Miskowiak KW. Clinical characteristics associated with the discrepancy between subjective and objective cognitive impairment in depression. J Affect Disord 2019; 246: 763-74.
38. Uher R, Perlis RH, Placentino A, et al. Self-report and clinician-rated measures of depression severity: can one replace the other? Depress Anxiety 2012; 29: 1043-49.
39. Eddy CM, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. Ther Adv Neurol Disord 2011; 4: 385-407.