Relationship Between Residual Symptoms of Depression and Self-reported Cognitive Impairment

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ABSTRACT

Objective: The present study aimed to investigate the associations between residual symptoms of depression and specific self-reported symptoms in several cognitive domains.

Methods: The study investigated 117 patients with partially or fully remitted major depressive disorder (MDD) after treatment with antidepressant medications.

Results: Fatigue was significantly associated with inability to focus, alertness, and feeling "blue"; low interest and difficulty with concentration were associated with apathy. No associations were found between deficits in the cognitive domains considered and residual symptoms such as self-blaming, feeling worthless, feeling hopeless, having suicidal thoughts, difficulty with sleep, and lack of appetite.

Conclusion: Among MDD remitted patients endorsing residual symptoms such as fatigue

FOCUS POINTS

- Major depressive disorder (MDD) remitted patients may experience residual symptoms, which correlate with cognitive impairment.
- In the current study, fatigue correlated with focusing and attention, while apathy correlated with concentration.
- Cognitive impairment should be assessed among MDD remitted patients.

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and feeling "blue", deficits in a range of cognitive domains should be carefully assessed and treated.

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INTRODUCTION

Despite the availability of numerous antidepressants, many patients with major depressive disorder (MDD) receiving optimal pharmacological treatment do not remit or remit while still experiencing residual symptoms.[1,2] Fava and Davidson[1] observed that between 29% and 46% of depressed patients fail to fully respond to antidepressant treatment of adequate dose and duration. Further, it has been estimated that 30% to 50% of patients who remitted from depression continue to have residual symptoms.[1-3]

The presence of residual symptoms in remitted MDD patients has been associated with greater risk of relapse, higher rates of suicidal attempts and ideation, and impaired functioning.[2,4,5] Increasing indications that impairment is present even in subjects with few symptoms of depression have prompted researchers to identify those symptoms more prevalent in subthreshold depression. In a longitudinal study of 64 patients with MDD, 75% of patients with partial response experienced residual symptoms such as fatigue, psychic anxiety, somatic anxiety, genital symptoms, depressed mood, insomnia, or guilt.[4] The most prevalent residual symptoms among adult individuals with MDD who remitted after fluoxetine treatment were sleep disturbances and fatigue.[3] Among older patients Hybels and colleagues[6] noted that inner tension, depression, and lassitude were the residual symptoms most commonly reported by patients remitted after three months of treatment for MDD.

Deficits in a range of cognitive domains are prevalent in patients remitted from MDD who continue to experience residual symptoms and may play an important role in the course and phenomenology of depression. Fava and colleagues[7] observed that out of 117 patients with MDD meeting criteria for response after receiving antidepressants, over 30% reported cognitive symptoms such as apathy, inattentiveness, forgetfulness, word finding difficulty, and mental slowing. Weiland-Fiedler and colleagues[8] reported that patients with remitted depression had deficits with sustained attention and in the mnemonic and strategic aspect of working memory. Finally, Nebes and colleagues[9] noted that, in geriatric patients, cognitive impairment in the areas of working and episodic memory, attention, and information-processing speed persisted even when the depressive symptoms remitted. Cognitive impairment is not only prevalent in patients who remitted from MDD, but it also appears that some persistent cognitive deficits (eg, impaired attention) are associated with relapse.[10]

The impairment in a range of cognitive domains of patients with depression has been amply explored.[11] However, we are unaware of studies investigating relationships between specific residual depressive symptoms and cognitive deficits in specific cognitive domains among patients undergoing antidepressant treatment for MDD. During acute depressive episodes the cognitive dysfunction may simply represent a form of depressive symptomatology, while it is unclear whether cognitive symptoms in remitted patients are related to residual depression. Further knowledge regarding these relationships may improve patients' care by raising clinicians' awareness about correlates of residual symptoms of depression, guide the development of interventions targeting those specific symptoms, and shed light on possible common substrates among symptoms with different phenotypes.

This cross-sectional study aims to investigate, in a sample of patients with remitted or partially remitted MDD after receiving antidepressant medications, the relationships between specific residual depressive symptoms and reported symptoms of deficits in a range of cognitive domains.

METHODS

Procedure

For a more detailed description of the sample see Fava and colleagues.[7] Patients eligible for the study were enrolled between January 2003 and December 2004 in one of three clinical settings, the Massachusetts General Hospital (MGH) Depression Clinical and Research Program, the MGH Psychopharmacology Unit of the Outpatient Psychiatry Division, and the Hecker Outpatient Psychiatry Center in Ravenna, Italy. Inclusion criteria for the study were: ≥18 years of age and being considered with MDD in partial or full remission (responders) after having received antidepressants for at least 3 months for the treatment of MDD. Eligible patients were identified during the course of routine clinical care

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at the three sites by their treating psychiatrists and informed of the study. Interested patients, upon providing consent, were then provided a packet including a cover letter approved by the Institutional Review Board outlining the voluntary nature of study participation and several self-rated scales. Patients received no payment for their participation in this study.

The current study aimed at investigating the relationship between specific depressive symptoms and reported cognitive symptoms. Therefore, only the two questionnaires of interest were considered for our analyses. For a description of all the questionnaires administered in the study please refer to Fava and colleagues.[7] These questionnaires were self-administered and took ~10 minutes to complete.

Participants

The sample is fully described in Fava and colleagues.[7] Briefly, participants were 149 patients with MDD with a mean age equal to 41.6 years (SD=12.4), the majority of which were women (64%). Participants' MGH Cognitive and Physical Functioning Questionnaire[12] (CPFQ) total mean score was 18.90 (SD=5.38). Total mean score on the Harvard Department of Psychiatry National Depression Screening Day Questionnaire[13] (HANDS) was equal to 4.91 (SD=5.05). Out of the total sample, 117 (78%) met criteria for response according to the HANDS (score <9). Mean age of the sample was 43.4±12.6 (median age=43) and the majority were women (66.7%). Patients reported having been depressed on average 23.86±43.25 months (median=10 months).

Approximately two thirds of the participants were on one antidepressant (75.9%), and the rest were on two (16.2%) or three (7.8%). Overall, ~50% of the participants were on at least one adjunct medication in combination with an antidepressant. Less than one in five participants were taking two adjunct medications (17.9%) and one participant was on three medications in conjunction with an antidepressant (0.9%). With regard to medications with sedative side effects, 9.4% of patients were on tricyclic antidepressants (TCAs), 30.8% were on benzodiazepines, and 0.9% were on mirtazapine.

Measures

HANDS

The HANDS consists of 10 questions pertaining to depressive symptoms, which are rated depending on their frequency using a scale ranging from none of the time (0) to all of the time (3). The HANDS has shown good internal consistency and validity.[13] The HANDS was found to perform as well as the 20-item Zung Scale, the 21-item Beck Depression Inventory-II, and the 15-item Hopkins Symptom Depression Checklist in screening for depressive symptoms.[13]

Given that the current study focused on assessing residual symptoms of depression, only patients who were either in partial or full remission (responders) were included in the analysis. Patients were deemed responders if their score was <9 on the HANDS, as a total score between 0 and 8 on this scale is not considered to be consistent with the diagnosis of MDD.[13]

The MGH CPFQ

The CPFQ consists of 7 questions pertaining to a subject's cognitive and physical well-being. Each question is graded on a 6-point scale, ranging from greater than normal (1), to normal (2), to totally absent (6). The CPFQ has been shown to be reliable and valid.[12] The CPFQ has shown to be a unifactorial scale with strong internal consistency equal to 0.90 and adequate test retest reliability equal to 0.83. The CPFQ has shown to be sensitive to change and have convergent validity as it correlates with other validated measures of neuropsychological functioning.[12]

Data Analysis

Statistical analyses were conducted using the software Statistical Package for the Social Sciences (SPSS Inc., 2005).

To address possible differences in CPFQ total scores due to medication side effects we ran a series analyses of variance. We used Spearman correlations to measure associations between total scores and each item of the HANDS and the CPFQ. A correlation was considered significant and meaningful based upon two criteria. The first criterion was that the *P* value of the correlation be equal to or lower than a Bonferroni-adjusted *P* value of .0007, which corresponded to the N=70 correlations performed. Further, the correlation had to have a coefficient with magnitude of ≥0.30, indicating at least 9% of shared variance between the items. The analyses were performed on the 117 patients that were considered responders (HANDS total score <9).

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RESULTS

In a previous report[7] we noted that in this sample there was no statistically significant difference in CPFQ total score between patients on an antidepressant plus antipsychotics and patients on an antidepressant without concomitant antipsychotics (N=11 vs N=106; F=1.86; *P*>.05). Similarly, no difference was found in CPFQ total score between patients on an antidepressant plus an anticonvulsant and patients on an antidepressant without a concomitant anticonvulsant (N=20 vs N=97; F=1.88; *P*>.05).[7] To further examine differences due to medications we compared CPFQ total score of patients on antidepressants and a concomitant benzodiazepine (N=36) with CPFQ total score of patients on antidepressants without a benzodiazepine (N=81). We found that there was no statistically significant difference in CPFQ total scores (F=2.27; *P*>.05) of the two groups. Lastly, we found no statistical significant difference in CPFQ total score between patients taking either TCAs and mirtazapine and patients on other antidepressant medications (N=26; N=91; F=.97; *P*>.05).

The Spearman correlations between the items of the CPFQ and the HANDS are shown in the Table. Specifically, fatigue was associated with alertness, difficulty with sustaining attention and focusing, as well as with energy level. Feeling "blue", difficulty with concentration, and low interest were associated with apathy. Difficulty with concentration was also associated with inability to sustain attention and focus, and with mental acuity. Self-blaming, feeling worthless, feeling hopeless, having suicidal thoughts, difficulty with sleep, and lack of appetite were not associated with any of the CPFQ items.

DISCUSSION

Upon examining the relationships between specific items of the CPFQ and of the HANDS among depressed outpatients who had responded to antidepressant therapy, we observed several novel associations between residual depressive symptoms and reported cognitive impairment. Our findings add to the current knowledge by suggesting that fatigue is associated with impairment in specific cognitive domains (focusing and sustained attention). This enhances previous reports describing fatigue as a frequent residual symptom in remitted MDD patients[3,7] and associated with increased risk of MDD relapse.[14]

Apathy has been defined as a symptom indicating loss of interest or emotions distinct from anhedonia,[15] and it has been observed not only

TABLE.
Correlations Among Specific Symptoms Recorded by the HANDS and the CPFQ

CPFQ	Apathy/ Motivation	Wakefulness/ Alertness	Energy Level	Focus/Sustain Attention	Memory/ Recall	Word Finding Ability	Sharpness/ Mental Acuity
HANDS							
Fatigue	.24	.35*	.42	.32*	.45	.09	.23
Self-Blaming	.02	.01	–.04	–.09	–.04	–.02	–.03
Appetite	.11	–.12	.08	.04	–.04	.06	–.06
Sleep	–.04	–.07	.26	.09	–.12	.02	–.03
Hopelessness	.23	.13	.09	.18	.00	–.05	.09
Blue	.34*	.27	.27	.29	.04	.00	.18
Interest	.42*	.28	.29	.29	.08	.14	.24
Worthlessness	–.06	.13	.08	.04	.01	.049	.19
Suicide Thoughts	.10	.15	.09	.27	.17	.13	.11
Concentration/Making Decision	.32*	.29	.30	.52*	.29	.26	.38*

* *P*<0.0007

HANDS=Harvard Department of Psychiatry National Depression Screening Day Questionnaire; CPFQ=Cognitive and Physical Functioning Questionnaire; MGH=Massachusetts General Hospital.

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among remitted MDD patients[7,16] but in other illnesses with different etiologies. For example, apathy is found among patients with Parkinson's disease, Alzheimer's disease, and post stroke.[17-19] Previous studies have noted that apathy is associated with impaired memory and mental speed in patients with multiple sclerosis,[20] and with verbal fluency, working memory, and verbal abstraction among patients with Parkinson's disease.[21] We found an association between apathy and difficulty with concentration among MDD remitted patients; this suggests that apathy is associated with cognitive deficits in several cognitive domains in a range of illnesses. Furthermore, the associations among feeling "blue", difficulty with concentration, and apathy underline the need to further examine the presence of common subcortical neurocircuits underlying these symptoms.

As anticipated, difficulty with concentration, as measured by the HANDS, was associated with inability to focus and with mental acuity reported on the CPFQ. Moreover, fatigue was associated with reported problems of low energy. Predictably, lack of interest was associated with lower motivation and apathy. Given that the CPFQ was developed to measure cognitive and physical dysfunctions common in mood disorders, these associations provide further support for the convergent validity of the CPFQ. Patients who reported residual difficulty with appetite, sleep, self-blaming, worthlessness, hopelessness, and suicidal thoughts did not endorse cognitive symptoms.

Our study has several limitations. There may be a selection bias as not all patients invited to participate in this study agreed to do so. However, according the study clinicians' report, study participation refusal was uncommon. Another limitation is that cognitive symptoms were assessed only by a self-report measure , which asked for the subjective experience of the participants. The CPFQ has demonstrated to be correlated with a validated neuropsychological objective measure of cognitive impairment,[12] however further studies are needed to examine whether our findings are replicated when using standardized measures of cognitive deficits. Furthermore, results have to be interpreted with caution; we cannot determine whether the physical and cognitive symptoms were residual symptoms of MDD or side effects of antidepressant medications. We examined possible differences in CPFQ total score due to medications and we did not find any statistically significant differences.

Given the cross-sectional nature of the study we cannot evaluate any causal relationship between residual depressive symptoms and reported cognitive impairment or its direction. Future longitudinal studies, including multiple assessment points and objective measure of cognitive impairment, are needed to determine whether specific cognitive symptoms in partially or fully remitted MDD patients prevent improvement of specific depressive symptoms or vice versa. Lastly, our findings may not be generalizable to populations with different characteristics from the participants in our sample.

CONCLUSION

Our findings underline the importance of assessing cognitive deficits in remitted MDD patients reporting residual depressive symptoms such as fatigue, feeling "blue", and low motivation. Furthermore, given the significant psychosocial impairment found even with subthreshold symptoms of depression, and the call by Judd and colleagues[5] for treating MDD even when at a deceptively mild level of severity, these findings further underscore the importance to treat fatigue and feeling "blue" among MDD remitted patients. Lastly, our findings suggest the need for further studies of common clinical and neurobiological substrates among co-occurring symptoms in remitted MDD patients. ***CNS***

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