A Cross-Sectional Study of the Prevalence of Cognitive and Physical Symptoms During Long-Term Antidepressant Treatment

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Background: Antidepressant therapies have been associated with a variety of side effects of both physical and psychological nature. Until recently, however, the majority of the studies focusing on side effects of antidepressants have not routinely included assessment of cognitive side effects. The purpose of the present work is to examine cross-sectionally the prevalence of cognitive and physical side effects of antidepressants during long-term treatment of depression.

Method: Patients at least 18 years of age who were deemed responders to antidepressant therapy following at least 3 months of treatment for major depressive disorder (MDD) (diagnosed according to DSM-IV criteria) and whose MDD was considered to be in partial or full remission were eligible for inclusion in this study. Eligible patients were enrolled between January 2003 and December 2004. Study participants were administered the Harvard Department of Psychiatry/National Depression Screening Day (HANDS) scale, the Epworth Sleepiness Scale, the Brief Fatigue Inventory, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), and a study-specific questionnaire inquiring about the emergence of specific side effects such as apathy, fatigue, and inattentiveness.

Results: 117 MDD patients (mean ± SD age: 43.4 ± 12.6 years; women: N = 78 [66.7%]) met criteria for response according to the HANDS (score < 9). Cognitive symptoms (apathy, inattentiveness, forgetfulness, word-finding difficulty, and mental slowing) were each reported on both the CPFQ and the study-specific questionnaire by more than 30% of the responders on antidepressants. The physical symptoms of fatigue and sleepiness/sedation were reported by over 40% of the responders on both the CPFQ and the study-specific questionnaire. A significant, positive relationship was found between the CPFQ and the severity of residual depressive symptoms as measured by the HANDS total score ($F = 15.3$, $p = .0002$).

Conclusion: Physical and cognitive symptoms are frequently reported by MDD patients who have responded to antidepressants and are treated in the long term with these agents. It is likely that these symptoms are both side effects of the antidepressants as well as residual symptoms of MDD.

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Antidepressant therapies have been associated with a variety of side effects of both physical (e.g., sexual dysfunction) and psychological (e.g., anxiety) nature. Until recently, almost all studies on side effects of antidepressants have focused on those side effects emerging during acute, short-term treatment.[1] In addition, the majority of the studies focusing on side effects of antidepressants during the acute phase of treatment have not routinely included assessments of cognitive side effects. A recent study by Bolling and Kohlenberg[2] has identified for the first time several physical and cognitive side effects among depressed patients who had completed a course of treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant. In particular, nearly one fourth and one fifth of 161 major depressive disorder (MDD) outpatients treated with SSRIs in that study complained of "loss of creativity" and "apathy," respectively. A significant proportion of SSRI-treated MDD outpatients in the same study also complained of other cognitive side effects, including "poor concentration" (17.4%), "loss of ambition" (16.1%), "memory loss" (13.0%), and "problem-solving difficulties" (9.9%). The clinical relevance of cognitive symptoms during antidepressant treatment is supported by a study suggesting an increased risk for relapse among MDD responders who continue to experience cognitive problems, including abnormal initiation and perseveration.[3]

Unfortunately, however, to date, there is a paucity of studies examining the prevalence of cognitive and physical adverse events, including fatigue and sleepiness, during long-term treatment of depression.[1] The purpose of

the present work is to examine cross-sectionally the prevalence of cognitive and physical side effects of antidepressants during long-term treatment of depression.

METHOD

Patients at least 18 years of age, able to read and write in English, who were deemed responders to antidepressant therapy following at least 3 months of treatment for MDD (diagnosed according to DSM-IV criteria), and whose MDD was considered to be in partial or full remission were eligible for inclusion in this study. Patients with bipolar disorder or psychosis were excluded from the study. Eligible patients were enrolled between January 2003 and December 2004 in 1 of 2 clinical settings, the Massachusetts General Hospital (MGH) Depression Clinical and Research Program or the E. Hecker Outpatient Psychiatry Center in Ravenna, Italy. Patient recruitment in Italy was conducted by one of the investigators (F.B.), who directs a mood disorders clinic in Emilia-Romagna, an Italian region. The study questionnaires were translated from English to Italian by the same investigator (F.B.) for use among the latter population, and the translations were verified by another investigator who is also fluent in Italian (M.F.).

Eligible patients were first identified during the course of routine clinical care at these 2 sites by their treating psychiatrists, who approached all their MDD patients deemed in partial or full remission. In substitution of a typical consent form, participants were provided a 1-page cover letter, approved by the institutional review board, Human Research Committees of MGH, and describing the study protocol and its rationale. Patients received no payment for their participation in this study. Participants were then provided a questionnaire packet consisting of several self-rated scales, including the Harvard Department of Psychiatry/National Depression Screening Day (HANDS) scale,[4] the Epworth Sleepiness Scale (ESS),[5] the Brief Fatigue Inventory (BFI),[6] the MGH Cognitive and Physical Functioning Questionnaire (CPFQ) (Appendix 1), and a study-specific questionnaire inquiring about the emergence of specific side effects such as apathy, fatigue, and inattentiveness. These questionnaires were voluntarily self-administered and took approximately 10 minutes to complete.

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" (a score of 0) to "all of the time" (a score of 3).[4] Since this study focused on assessing the prevalence of residual symptoms of depression, only questionnaires of patients who were in either partial or full remission (responders) were included in the analysis. Patients were deemed responders if their score on the HANDS scale was less than 9, as scores between 0 and 8 on this scale are considered to be inconsistent with the diagnosis of MDD.[4]

The ESS[5] and the BFI[6] are self-rated measures of excessive sleepiness and fatigue, respectively, and their validity and reliability are well established.[5,6] The ESS consists of 8 questions pertaining to situations during which an individual may experience excessive sleepiness. Specifically, patients are asked to rate how likely they would be to fall asleep in each of those situations, ranging from "would never doze" (a score of 0) to "high chance of dozing" (a score of 3). The items are summed to give an overall score of 0 to 24, with higher scores indicating greater sleepiness. An ESS score of 8 or greater is considered indicative of pathologic sleepiness.[7] The BFI examines the degree to which fatigue interferes with daily life and consists of 9 questions, each of which is graded on a 10-point scale ranging from "no interference" (a score of 0) to "completely interferes" (a score of 10). Based on the BFI score, fatigue severity can be categorized as "mild," "moderate," or "severe": 1 to 3 for mild, 4 to 6 for moderate, and 7 to 10 for severe.[6] For the purpose of this study, we used a BFI score of 4 or more to identify patients with moderate to severe fatigue.

The MGH 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" (a score of 1), to "normal" (a score of 2), to "totally absent" (a score of 6) (Appendix 1). The CPFQ is currently being validated by our group.

In addition to these scales, patients were asked on a study-specific questionnaire to list the antidepressant they were prescribed, as well as the duration of use. Specific questions were also presented about potential side effects that could have been attributed to these medications, including inattentiveness, apathy, and cognitive slowing, and patients were to rate their occurrence from "not at all" to "a lot." Patients were also asked to list any other types of psychotropic medications they were prescribed.

Statistical Analyses

Appropriate parametric tests were used to compare groups on the basis of the presence of continuous (analysis of variance) as well as dichotomous (χ^2) variables. Relationships between continuous variables were assessed with the simple linear regression. For statistical significance, α was set at the .05 level (2-tailed).

RESULTS

During the course of the study, 150 MDD patients (mean ± SD age: 41.6 ± 12.4 years; women: N = 96 [64%]) were identified by their treating physician and administered the study questionnaires. Of these, 117 (78%) (mean ± SD age: 43.4 ± 12.6 years; women: N = 78 [66.7%]) met criteria for response according to the

Figure 1. Proportion of Responders With Cognitive and Physical Impairment (study-specific questionnaire) (N = 117)

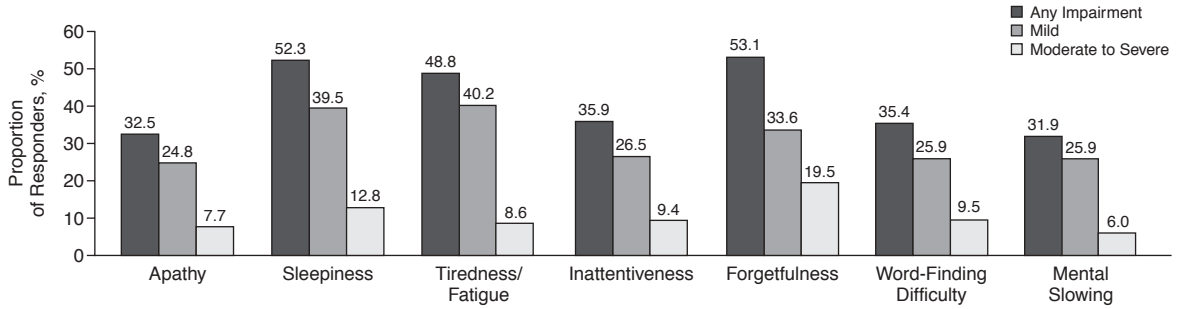
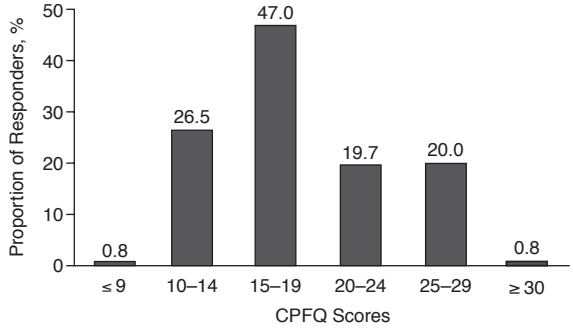


Figure 2. Frequency Distribution of Cognitive and Physical Functioning Questionnaire (CPFQ) Scores (N = 117)



HANDS (score < 9). Of these responders enrolled in the study, 11 (9%) received concomitant treatment with antipsychotics and 20 (17%) received concomitant treatment with anticonvulsants in addition to their antidepressant. We found no statistically significant ($F = 1.86$, $p = .18$) difference in CPFQ scores between responders on antidepressants plus antipsychotics (N = 11) and responders on antidepressants without concomitant antipsychotics (N = 106) (mean ± SD: 18.7 ± 5.9 vs. 17.1 ± 3.6, respectively). Similarly, there were no statistically significant ($F = 1.88$, $p = .17$) differences in mean CPFQ scores between responders on antidepressants plus anticonvulsants (N = 20) and responders on antidepressants without concomitant anticonvulsants (N = 97) (mean ± SD: 18.3 ± 4.5 vs. 17.0 ± 3.7, respectively). We therefore included in our analyses all patients, regardless of their concomitant treatment with antipsychotics or anticonvulsants. A significant proportion of the studied population were also taking other concomitant psychoactive agents including benzodiazepines (30.8%), trazodone (2.6%), modafinil (1.7%), and psychostimulants (4.7%), and they were included in the analyses.

As shown in Figure 1, cognitive side effects (apathy, inattentiveness, forgetfulness, word-finding difficulty, and mental slowing) were each reported on the study-specific questionnaire by more than 30% of the responders on antidepressants (N = 117). The physical symptoms of fatigue and sleepiness/sedation were reported by 48.8% and 52.3% of the patients, respectively.

Figure 2 depicts the frequency distribution of the total CPFQ scores among responders (N = 117). Overall, the percentage of patients who reported cognitive and physical impairment on the CPFQ was similar to that reported in the study-specific questionnaire (Figure 3). Cognitive impairments were reported by more than 30% of the responders on antidepressants, with motivation and recall difficulties being the 2 most prevalent. The percentage of responders reporting impairment in wakefulness and energy was slightly greater, reaching over 40%.

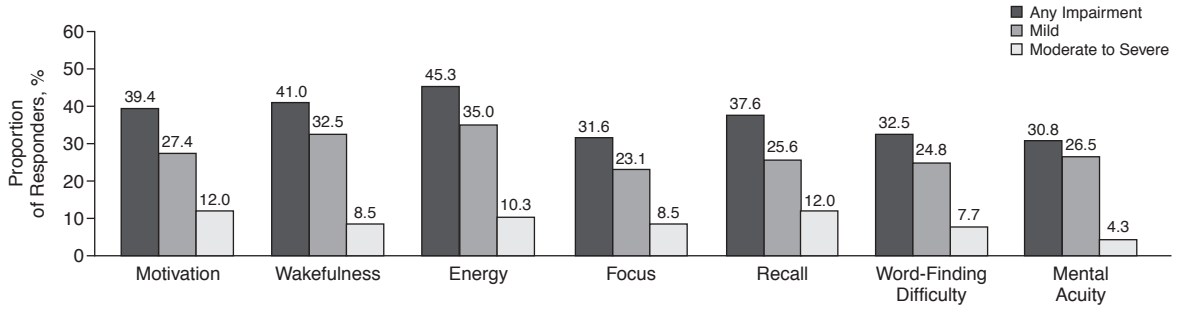
There was no significant difference ($F = 0.74$, $p = .39$) in total CPFQ scores between men and women (mean ± SD: 16.7 ± 3.8 vs. 17.4 ± 3.8, respectively). No significant relationship was observed between age and CPFQ score ($F = 0.27$, $p = .60$). A significant, positive relationship was found between CPFQ and the severity of residual depressive symptoms as measured by the HANDS total score ($F = 15.3$, $p = .0002$).

The percentages of patients who, based on their ESS and BFI scores, were experiencing significant fatigue (BFI score ≥ 4) or sleepiness (ESS score ≥ 8) were 24.8% and 41.9%, respectively.

DISCUSSION

Our study suggests that cognitive difficulties are relatively common among depressed outpatients who have responded to antidepressant treatment and continue to receive pharmacotherapy with antidepressants. In fact, approximately one third of our patients reported symptoms such as apathy and memory/concentration difficulties, and this is consistent with the findings of a recent study by Bolling and Kohlenberg,[2] in which a substantial proportion of 161 MDD outpatients treated with SSRIs complained of "loss of creativity," "apathy," and other

Figure 3. Proportion of Responders With Cognitive and Physical Impairment (Cognitive and Physical Functioning Questionnaire) (N = 117)



cognitive side effects. Their study, however, was retrospective and provided a relative underestimation of the problem compared to our study, which was cross-sectional in nature. Fatigue and sleepiness were also very common in our sample, and this is consistent with previous findings from our group, showing that sleep disturbances and fatigue were the 2 most common residual symptoms/side effects among remitters on fluoxetine treatment.[8]

Our findings suggest that our field has not paid sufficient attention to the presence of cognitive symptoms emerging or persisting during long-term antidepressant treatment, as this is the first cross-sectional study of the prevalence of these symptoms among patients who have responded to antidepressants and are maintained on these agents in the long term. These symptoms appear to be quite common, and their impact on patients' functioning needs to be investigated. Of course, the cross-sectional nature of our study does not allow us to establish whether the presence of these cognitive and physical symptoms among patients who have responded to antidepressant treatment can be attributed to an incomplete resolution of the depression itself (partial remission), to the antidepressant treatment (side effects), or to a combination of both. The significant relationship between degree of residual depressive symptoms in responders and total CPFQ score does suggest that it is likely to be a combination of both.

The main limitation of our study is that not all patients who had been asked to volunteer to participate in this study agreed to do so and that, therefore, these findings may potentially reflect a selection bias. Although we do not know the exact number of patients who had been contacted, based on the study clinicians' reports, we estimate that less than 25% of the patients asked to volunteer declined to do so. Another study limitation is that the study did not include objective measures of attention, concentration, and memory and relied on patients' self-report. In addition, while we collected information on agent and dose of antidepressants and concomitant psychoactive medications that patients were being treated with at the time of the assessment visit, we did not collect information on the reason the concomitant psychoactive medications were prescribed. This is particularly important in assessing residual symptoms and/or side effects in MDD remitters, since a significant proportion of the studied population was taking concomitant psychoactive agents including benzodiazepines (30.8%), trazodone (2.6%), modafinil (1.7%), and psychostimulants (4.7%), which are often used to target residual symptoms and/or side effects including insomnia, excessive sleepiness, fatigue, and cognitive impairment.[1] These concomitant medications may have affected our results, in that they may have increased or decreased the intensity of the symptoms reported, thereby leading to the underestimation or overestimation of the proportion of MDD responders who were experiencing physical and cognitive residual symptoms/side effects.

In summary, physical and cognitive symptoms are frequently reported by MDD patients who have responded to antidepressant treatment and are maintained in the long term on these agents. It is likely that these symptoms are side effects of the antidepressants as well as residual symptoms of MDD. Future studies need to tease out the specific contributions of both factors to the presence of these symptoms during long-term antidepressant treatment.

Drug names: fluoxetine (Prozac and others), modafinil (Provigil).

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Solvay, Somaxon, Somerset, and Wyeth-Ayerst; has been on the speakers boards of AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, PharmaStar, and Wyeth-Ayerst; and is a stock shareholder in Compellis and MedAvante. Dr. Iosifescu is a consultant for Forest and Pfizer; has received grant support from Aspect Medical Systems, Forest, Janssen, National Alliance for Research on Schizophrenia and Depression (NARSAD), and National Institute of Mental Health (NIMH); and has received honoraria from Cephalon, Eli Lilly, and Pfizer. Dr. Alpert has been a consultant for PamLab; has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Lichtwer Pharma GmbH, Lorex, Novartis, Pfizer, Roche, Sanofi-Synthelabo, Solvay, and Wyeth-Ayerst; has received research support and honoraria from Organon, PamLab, and Pharmavite; and has been on the speakers/advisory boards of Organon and Pharmavite. Dr. Papakostas has served as a consultant for Aphios Corporation, Evotec, GlaxoSmithKline, Inflabloc, Jazz, PamLab, and Pfizer; has received honoraria from Evotec, GlaxoSmithKline, Inflabloc, Jazz, PamLab, Pfizer, and Titan; and has received research support from Bristol-Myers Squibb, PamLab, and Pfizer. Dr. Benazzi, Ms. Graves, and Ms. Scalia report no additional financial or other relationship relevant to the subject matter of this article.

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Appendix 1 appears on page 1759.

Appendix 1. Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire[a]

Please answer all questions by **circling** the **correct answer** or the answer which seems the most **appropriate** to you (consider "normal" the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning).

a) How has your motivation/interest/enthusiasm been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

b) How has your wakefulness/alertness been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

c) How has your energy been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

d) How has your ability to focus/sustain attention been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

e) How has your ability to remember/recall information been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

f) How has your ability to find words been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

g) How has your sharpness/mental acuity been over the past month?

1	2	3	4	5	6
Greater Than Normal	Normal	Minimally Diminished	Moderately Diminished	Markedly Diminished	Totally Absent

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