

Research to Practice



Fatigue as a Residual Symptom of Depression

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Innov Clin Neurosci. 2011;8(10):40–43

INTRODUCTION

It is well recognized that many patients with major depressive disorder (MDD) do not achieve a full response to antidepressant medications despite adequate dose and duration of the treatment. One of the most common residual symptoms of a partially resolved depression is fatigue. Broadly defined, symptoms of fatigue can affect physical, cognitive, and emotional function, impair school and work performance, disturb social and family relationships, and increase healthcare utilization.

Furthermore, some of the medications we use to treat MDD can induce symptoms of fatigue as side effects. Given the importance and complexity of fatigue occurring in patients with MDD, I discussed this topic with Maurizio Fava MD, Slater Family Professor of Psychiatry at the Harvard Medical School. Dr. Fava is also Executive Vice Chair of the Department of Psychiatry, Executive Director of the MGH Clinical Trials Network and Institute (CTNI), and Director of the Depression Clinical and Research Program at the Massachusetts

General Hospital, in Boston, Massachusetts.

Dr. Fava, how often do we observe symptoms of fatigue in MDD?

Dr. Fava: We see prominent symptoms of fatigue in the majority of patients with depression. In fact, fatigue is one of the most prevalent presenting symptoms of MDD, the second most prominent residual symptom of MDD, and is often associated with impaired concentration, irritability, and reduced productivity.^{1–3} Further, up to one-third of MDD patients who have achieved remission or response still continue to experience some symptoms of fatigue.^{1,2} In one recent study, more than 90 percent of patients with MDD had severe fatigue despite the fact that more than 80 percent of these patients were already taking antidepressant medications.⁴ In this study of 66 patients with MDD, 81.5 percent were taking antidepressant medications: 48.2 percent were taking selective serotonin reuptake inhibitors (SSRIs) and 33.3 percent were taking serotonin norepinephrine reuptake inhibitors (SNRIs).

How do you define fatigue in depression?

Dr. Fava: Fatigue is one of the identified symptoms of MDD listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria where it is defined as physical fatigue or loss of energy. However, in my opinion, fatigue is much more than that. We see apathy and considerable emotional disturbance occurring as a consequence of fatigue. We have also seen high rates of diminished focus, word finding difficulties, and recall problems in fatigued patients with

MDD.² Recently, Arnold⁵ described three distinct categories of fatigue that commonly occur within a population of MDD patients: physical, cognitive, and emotional symptoms. The physical symptoms of fatigue include reduced activity, low energy, tiredness, decreased physical endurance, increased effort to do physical tasks, general weakness, heaviness, slowness or sluggishness, nonrestorative sleep, and sleepiness. The cognitive symptoms include decreased concentration, decreased attention, decreased mental endurance, and slowed thinking. The emotional (affective) symptoms of fatigue include decreased motivation or initiative (apathy), decreased interest, feeling overwhelmed, feeling bored, aversion to effort, and feeling low. Given the broad range of related, comorbid symptoms, it can be difficult to differentiate between independent symptoms of fatigue from symptoms directly related to MDD.

What are the consequences of residual symptoms of fatigue in MDD?

Dr. Fava: The key point is that patients with residual fatigue are more likely to get depressed again despite continued prophylactic treatment. There is a much greater likelihood that patients with MDD who have residual symptoms like fatigue will also have work, school, and/or social difficulties. As you know, there is a very high medical comorbidity associated with depression as well. Therefore, we need to identify these symptoms and intervene as early as possible.

How do you assess the symptoms of fatigue in MDD?

Dr. Fava: First, I want to confirm that the patient actually has a

diagnosis of MDD. There may be some patients who complain of many symptoms of fatigue but do not have MDD, or there may be some patients with comorbid illnesses that include some depressive symptoms and fatigue, but are not truly MDD. Second, it is really important to differentiate between symptoms of fatigue that have been caused by the drugs we are using to treat the MDD in contrast to symptoms that are present as residual symptoms of MDD.

I begin my assessment by obtaining a careful, detailed history of all of the symptoms that existed prior to the initiation of treatment,

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followed by identifying any symptoms that have persisted despite treatment, and then I ask about any new symptoms that have emerged during treatment. Treatment-emergent symptoms may or may not be caused by the medications we are using, but it is important to differentiate whether these symptom are new or were pre-existing to the treatment. Obviously, it is also important to explore whether the residual symptoms are more or less severe than they were before treatment commenced.

I may also have the patient fill out a comprehensive psychopharmacological history scale, such as the Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (MGH-ATRQ), as this type of tool is useful for this assessment.⁶ It is helpful to

know whether previous medications have had the same effects or caused different symptoms.

Based upon both my review of symptoms past and present and my psychopharmacological review, I can often pinpoint whether the identified fatigue symptoms are truly residual symptoms of MDD or side effects of treatment.

I also try to quantify the severity of the fatigue symptoms as a baseline for subsequent intervention.

How do you actually measure the symptoms of fatigue?

Dr. Fava: It is often helpful to rate the extent of fatigue in order to

track the progression from visit to visit. Some scales have been developed that evaluate the broad range of fatigue symptoms. For instance, the Fatigue Questionnaire and the Fatigue Associated with Depression scales (FasD) have been used in clinical trials to separately assess these symptoms in patients with MDD.^{4,7} I typically want to focus specifically on the wide range of fatigue symptoms and determine severity for these symptoms apart from any other symptoms of depression that may be present. For this reason, we have developed the patient-rated MGH-Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) as a tool to assess some of the physical and cognitive difficulties associated with depression.⁸ The MGH-CPFQ is a validated seven-item, self-rated

questionnaire assessing cognitive and physical functioning over the past month. Each of the following items is scored from 1 to 6 with increasing pathology: motivation/enthusiasm, wakefulness/alertness, energy, focus/attention, recall, ability to find words, and sharpness/mental acuity. Being particularly interested in quickly assessing the impact of fatigue symptoms on behavior and function, we have also developed a single-item scale to assess the global severity of fatigue.⁹ The Clinical Global Impression scale-severity (CGI-S) for fatigue is a one-item, validated, global assessment scale that assesses the effects of treatment interventions on the symptoms of fatigue and their impact on function. It is scored like other CGI-S scales from 1 to 7 with increasing global severity. The CGI-S for fatigue is a practical approach to quickly evaluate the impact of fatigue on behavior and function.

What antidepressant medications are most likely to cause fatigue in depression?

Dr. Fava: Although fatigue is viewed as a common side effect of the more sedating antidepressants, such as the tricyclic antidepressants, substantial rates of treatment-emergent fatigue have been reported with SSRIs and SNRIs. A pooled analysis by our group has shown that bupropion's use is associated with significantly lower levels of residual fatigue compared to the SSRIs.¹⁰

How do you treat residual fatigue in depression?

Dr. Fava: In clinical practice, evaluation of the treatment of fatigue as a residual symptom of MDD is complicated because it can be part of the symptom cluster of

MDD, can be a prodromal symptom of another disorder distinct from MDD, or could be a side effect of antidepressant treatment.^{2,3} Furthermore, treating fatigue by adding more medications can be risky because of the possibility of inducing additional adverse symptoms as a consequence of the intervention. Baldwin and Papakostas¹¹ describe the following three treatment strategies: 1) using antidepressant medications that are less likely to induce or exacerbate fatigue symptoms; 2) using antidepressant medications that are more likely to resolve the fatigue symptoms; or 3) using adjunctive treatments to specifically target residual fatigue and sleepiness in MDD patients.

What currently available medications are used to treat fatigue in depression?

Dr. Fava: There are several alternative pharmacological strategies to treat fatigue in depression. As adjunctive treatment, we can use psychostimulants (e.g., methylphenidate 20–80mg/day), modafinil (100–400mg qd),¹² bupropion (100–300mg qam), noradrenergic reuptake inhibitors (e.g., reboxetine, 2–4mg qam), atomoxetine (40–80mg qam), or protriptyline (10–30mg qam).

What is on the horizon for the treatment of residual fatigue?

Dr. Fava: Ongoing studies are currently evaluating some antidepressant medications that, in theory, may be much less likely to cause fatigue as a side effect, such as the triple uptake inhibitors and SNRIs with more prominent noradrenergic effects, as well as adjunctive treatments to minimize residual fatigue, such as norepinephrine reuptake inhibitors (NRIs).¹³

It is important to note that residual fatigue is not limited to patients with depression and that many drugs we use to treat other mental and medical conditions can induce fatigue well. For instance, we often see fatigue affect patients with schizophrenia that further compounds the apathy and negative symptoms that are core to that illness. Many of the medications we use for neurological conditions can cause symptoms of fatigue as well and that also exacerbates the existing condition for these patients. So, I would say that the topic of fatigue extends beyond depression and will become an important focus of assessment, treatment, and drug development in the next few years.

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- FUNDING:** There was no funding for the development and writing of this article.
- FINANCIAL DISCLOSURES:** Dr. Targum has served as a consultant to, received grant/research support/honoraria from, owns stock options in, or owns copyrights to the following companies: Acadia, Affectis, Alkermes inc., Amgen, AstraZeneca, BioMarin, BrainCells Inc., CeNeRx, Cephalon, Cypress, CTNI MGH, Dynogen, EnVivo Pharmaceuticals, Euthymics, Forest Research, Functional Neuromodulation inc, Eli Lilly and Company, Johnson & Johnson PRD, INC Research, Methylation Sciences Inc., Memory Pharmaceuticals, Naurex Inc, NeoSync, Neurophage, Novartis Pharmaceuticals, Novartis Bioventures, Nupathe, Prana Biotechnology Ltd., Sunovion, Targacept, TauRx, Transcept, Wyeth labs.
- Dr. Fava has served as a consultant to, received grant/research support/honoraria from, owns stock options in, or owns copyrights to the following companies: Abbott Laboratories; Adamed, Co.; Affectis Pharmaceuticals AG; Alkermes inc., Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma, Inc; Cephalon, Inc.; Clinical Trials Solutions, LLC; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DOV Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Eli Lilly and Company; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Gruenthal GmbH; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC.; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck & Co., Inc.; Methylation Sciences; Neuronetics, Inc.; Novartis AG; Nutrition 21; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmavite LLC.; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; PsychoGenics; Psylin Neurosciences, Inc.; Ridge Diagnostics, Inc.; Roche; RCT Logic, LLC; Sanofi-Aventis US LLC.; Sepracor Inc.; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Takeda Pharmaceutical Company Limited; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc.; and Wyeth Pharmaceutical.
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