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What is This?
Fatigue and occupational functioning in major depressive disorder

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Major depressive disorder (MDD) is typically accompanied by significantly impaired functioning. While definitions of functioning differ across individual and sociocultural contexts, it is evident that functional disruption can occur both globally as well as in specific domains such as occupational, interpersonal, or cognitive functioning. The association between MDD and occupational functioning has been the focus of particular scrutiny, not least because much of the global economic burden of MDD is a product of diminished occupational functioning. Numerous studies have documented that MDD is associated with high rates of sick leave or absenteeism, or time away from work. For example, depressed workers in the USA reported 1.5–3.2 more work-absence days per month compared to people who were not depressed (Kessler et al., 1999), while in the European Study of the Epidemiology of Mental Disorders (ESEMeD), depressed workers had 3–4 times more work-loss days per month than those without depression (Alonso et al., 2004). Furthermore, depression is associated with high rates of long-term disability and unemployment (Lerner et al., 2004). Notwithstanding the impact of absenteeism and disability, the greatest cost associated with MDD results from presenteeism or reduced productivity while at work (Lerner and Henke, 2008; Sanderson and Andrews, 2006; Stewart et al, 2003). Clearly, MDD is among the most costly of all health problems to employers in terms of work absence and productivity loss (Hilton et al., 2010).

In contrast to the extensive literature documenting the importance of occupational impairment in MDD, there is relatively less empirical evidence evaluating the impact of specific depressive symptoms on occupational functioning. Fatigue represents a particularly plausible contender as a symptom with high potential to erode workplace functioning. Yet, the role of fatigue in functional impairment has received little research attention, perhaps as a consequence of disproportionate emphasis on the emotional and cognitive domains in MDD (Demyttenaere et al., 2005). This viewpoint will reflect on the relationship between fatigue and functioning, with a particular focus on occupational functioning. Note that this paper focuses on fatigue as a symptom of MDD specifically, and not conditions such as chronic fatigue syndrome and fibromyalgia, in which fatigue is considered a pivotal symptom.

At a broad level, research does point to a central role for energy and fatigue in depression. First, fatigue is known to be highly prevalent in patients with MDD, especially those presenting in primary care settings. For example, in the Depression Research in European Society II (DEPRES II) collaborative study of approximately 2000 depressed primary care patients, 73% of the sample reported that they “felt tired”, with fatigue observed to be associated with depression severity (Tylee et al., 1999). Second, fatigue is known to be particularly difficult to treat, representing a common residual symptom among patients with MDD following antidepressant treatment. For example, over 80% of outpatients with MDD treated with fluoxetine in full remission continued to exhibit one or more residual depressive symptoms; fatigue, with a 39% prevalence rate, was amongst the three most common residual symptoms (Nierenberg et al., 1999). Third, the temporal relationship between fatigue and depression is known to be a two-way street; fatigue can be a precursor as well as consequence of depression. For example, Moos and Cronkite (1999) examined symptom predictors over a 10-year course, finding that baseline fatigue and loss of interest in usual activities were predictors of a lack of remission of depressive symptoms at 1-, 4-, and 10-year follow up. In

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Viewpoint
other prospective research, Addington et al. (2001) examined the prevalence of fatigue and its relationship with MDD over a 13-year period, observing that patients who had experienced unexplained fatigue for 2 weeks or greater periods in their lifetime showed an 11-fold greater risk of a lifetime diagnosis of MDD compared to non-fatigued participants. Participants with recurrent/chronic fatigue had a 28-fold greater risk of developing MDD than those without fatigue. Finally, in a secondary analysis of a World Health Organization primary care dataset spanning 14 countries, unexplained fatigue at baseline was found to be independently predictive of the development of a new episode of depression at follow up (Skapinakis et al., 2004). Further, depression at baseline was found to increase the risk of developing a new onset of unexplained fatigue at the 12-month follow up, after adjustment for confounding variables.

There exists a growing body of research to demonstrate that specific symptoms of MDD, such as insomnia and cognitive dysfunction, can have a particularly pronounced impact on functional outcomes (e.g. Buysse et al., 2008; Fava et al., 2006). It stands to reason that a similar relationship will exist between fatigue and occupational functioning. Although no controlled studies have examined the relationship between fatigue and occupational functioning in MDD, the veracity of this association is supported by findings from a naturalistic study of 573 primary care patients initiating antidepressant treatment in the USA (Swindle et al., 2001). The study, conducted in a sample of patients primarily diagnosed with MDD, dysthymia, or minor depression, produced three findings of particular note here. First, it was observed that fatigue was a common occurrence; over 91% of the sample endorsed the symptom. Second, examination of associations between work functioning scales and outcomes on other symptomatic and functional scales showed that fatigue was more predictive of impaired occupational functioning (specifically, rates of absenteeism and productivity) than a range of other depressive symptoms. Third, decreased fatigue was more predictive of improvement in work productivity at the 3-month follow up than was decrease in other depressive symptom constellations such as depressed mood, sleep disturbance, or guilt/ worthlessness. These findings provide the best evidence to date to suggest that the fatigue component of depression plays a key mediating link between improvements in depression and improved occupational performance. Elsewhere, a cross-sectional study of 164 outpatients with MDD found that low energy and daytime fatigue were subjectively reported to interfere with occupational functioning more so than other depressive symptoms (Lam et al., 2012).

The nascent literature on the relationship between fatigue and occupational functioning should not detract from the importance of attending to fatigue comprehensively and clinically, both in terms of assessment and treatment. With regards to assessment, the assessment of fatigue should be assigned importance, both in terms of baseline assessment of the presenting disorder and of the evaluation of response to treatment over time. Likewise, the assessment of occupational functioning should occur routinely in depressed workers; in keeping with clinical research and practice guidelines for other medical conditions, the assessment of functioning is now recommended as a routine and necessary component in the treatment of MDD (Greer et al., 2010). This stance also makes sense in terms of patient-oriented care, as many patients in treatment for MDD prioritize functional outcomes over symptomatic improvement (Zimmerman et al., 2006).

With regards to treatment, it is imperative that we develop and evaluate treatments targeted towards the full resolution of fatigue and functional impairment. Unfortunately, there are only limited data about current treatments that target fatigue and accelerate return to full occupational functioning. Pharmacological treatment studies have been of low quality with inconsistent results. For example, a Cochrane meta-analysis of psychostimulant studies in MDD found statistically significant effects on fatigue, but these were of questionable clinical significance (Candy et al., 2008). Physical and psychosocial treatment interventions targeting fatigue should be considered because it is possible that the reason why exercise is a useful adjunct treatment in depression is that it helps restore energy and lessen fatigue (Puettz et al., 2006).

Clearly, there are complexities inherent in terms of the optimal treatment of fatigue in MDD populations that warrant consideration. Research in this area has been hampered by the facts that DSM-IV and ICD-10 apply different descriptions of fatigue in MDD and that different depression rating scales show a different coverage of fatigue as a symptom. Determining the aetiological root of fatigue can be complex, especially as MDD is so commonly comorbid with conditions such as chronic fatigue syndrome. In fact, the lack of consistent results in treatment studies may be owing to the neurobiological heterogeneity inherent in fatigue. It may be more informative for future clinical trials to conceptualize fatigue into hypoaroused (associated with chronic fatigue syndrome and possibly atypical depression) and hyperaroused (associated with melancholic depression) subtypes (Hegerl et al., 2013). Further, in treatment trials for MDD, functional outcomes are rarely primary outcomes, despite compelling arguments for including functional outcomes as endpoints in both acute and maintenance phases of pharmacotherapy (Greer et al., 2010; Lam et al., 2011). Here, we advocate along with others (e.g. McKnight and Kashdan, 2009; Patten et al., 2009) that restoration of functioning should be considered a primary goal for treatment, over and above the longstanding...
clinical focus on reducing symptoms and, more recently, on achieving remission. To increase our likelihood of success in improving quality of life in working individuals with MDD, we further advocate for specific attention to be paid to the role of fatigue in determining occupational functioning.

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