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Review article

Restoring function in major depressive disorder: A systematic review

David V. Sheehan[a,1,*], Kazuyuki Nakagome[b,1], Yuko Asami[c], Elizabeth A. Pappadopulos[d], Matthieu Boucher[e]

[a] University of South Florida College of Medicine, Tampa, FL, USA
[b] National Center of Neurology and Psychiatry, Tokyo, Japan
[c] Pfizer Japan Inc, Tokyo, Japan
[d] Pfizer Inc, New York, NY, USA
[e] Pfizer Canada Inc. Kirkland, Quebec, Canada

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ABSTRACT

Background: Functional impairment contributes to significant disability and economic burden in major depressive disorder (MDD). Treatment response is measured by improvement in depressive symptoms, but functional improvement often lags behind symptomatic improvement. Residual deficits are associated with relapse of depressive symptoms.
Methods: A literature search was conducted using the following terms: “major depressive disorder,” “functional impairment,” “functional outcomes,” “recovery of function,” “treatment outcome,” “outcome assessment,” “social functioning,” “presenteeism,” “absenteeism,” “psychiatric status rating scales,” and “quality of life.” Search limits included publication date (January 1, 1995 to August 31, 2016), English language, and human clinical trials. Controlled, acute-phase, nonrecurrent MDD treatment studies in adults were included if a functional outcome was measured at baseline and endpoint.
Results: The qualitative analysis included 35 controlled studies. The Sheehan Disability Scale was the most commonly used functional assessment. Antidepressant treatments significantly improved functional outcomes. Early treatment response predicted functional improvement, while baseline disease severity did not.
Limitations: Clinical studies utilized various methodologies and assessments for functional impairment, and were not standardized or adequately powered.
Conclusions: The lack of synchronicity between symptomatic and functional improvement highlights an unmet need for MDD. Treatment guided by routine monitoring of symptoms and functionality may minimize residual functional impairments.

1. Functional impairment in depression: why is it important?

Depression is a very common mental illness, affecting an estimated 350 million people worldwide (World Health Organization, 2012). The clinical course of the disorder is highly recurrent with only 20% of patients recovering and remaining continuously well, while the other 80% have at least one recurrence during their lifetime (Burcusa and Iacono, 2007). The core features of major depressive disorder (MDD) include emotional, somatic, and functional impairments (American Psychiatric Association, 2013). Given its prevalence, highly recurrent nature, and multi-level impairments, MDD is a leading cause of disability worldwide (World Health Organization, 2008). The World Health Organization (WHO) predicts that MDD will be the leading

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; CBT, cognitive behavioral therapy; EQ-5D VAS, EuroQoL 5-Dimension Questionnaire Visual Analog Scale; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; LIFE, Longitudinal Interval Follow-up Evaluation; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NIMH-CDS, National Institute of Mental Health Collaborative Depression Study; NIRS, multi-channel near-infrared spectroscopy; NNT, number needed to treat; PHQ-9, Patient Health Questionnaire 9-item screen; QIDS, Quick Inventory of Depression Symptomatology; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; QOL, quality of life; SASS, Social Adaptation Self-evaluation Scale; SAS-SR, Social Adjustment Scale–Self-Report; SDS, Sheehan Disability Scale; SF-36/SF-12, Short-Form Health Survey; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression study; WHO-5, World Health Organization Well-being Index; WHO-DAS, World Health Organization Disability Assessment Schedule; WPAI, Work Productivity and Activity Impairment questionnaire; WSAS, Work and Social Adjustment Scale

* Correspondence to: Distinguished University Health Professor Emeritus, University of South Florida College of Medicine, Tampa, FL 33613, USA.
E-mail address: dsheehan@health.usf.edu (D.V. Sheehan).
[1] Contributed equally.

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cause of years lost to disability in 2030 (World Health Organization, 2008).

The disability and dysfunction associated with MDD exceeds that of other common chronic illnesses, including cardiovascular disease, diabetes, arthritis, and back problems (Wells et al., 1989). Functional impairments associated with depression result in social and occupational impairments that disrupt work, school, leisure, family life activities, and family responsibilities (American Psychiatric Association, 2013; Greer et al., 2010). Patients also experience reduced quality of life (QOL) and difficulty with interpersonal relationships. Among survey respondents with 12-month MDD, 97% reported some level of functional impairment, and 60% reported severe or very severe impairment based on the Sheehan Disability Scale (SDS) (Kessler et al., 2003). Respondents reported that moderate, severe, or very severe functional impairments led to an inability to function for a mean of 11, 33, and 97 days in the past year, respectively (Kessler et al., 2003). In comparison with adults with no mood disorder, adults with MDD reported limitations in the ability to perform work, household, or school activities 4.5 times more frequently (Shippee et al., 2011).

1.1. Economic burden

In 2010, mental health conditions cost approximately 2.5 trillion US dollars (Bloom et al., 2011), with approximately two thirds of the total cost related to indirect costs. Serious mental illness, including MDD, has been associated with a 33% reduction in earnings or approximately $16,000 per US worker (Kessler et al., 2008; Levinson et al., 2010). In the United States and other countries, depression is reported by approximately 10% of employees, and the economic burden of depression is driven by impairments in occupational functioning (Asami et al., 2015; Stewart et al., 2003; Wada et al., 2013). In the United States, MDD has been associated with 27 workdays lost (absenteeism and presenteeism combined) per employee per year, and an overall impact of 225 million lost workdays and $36.6 billion (Kessler et al., 2006). Although the severity of MDD correlates with lost work productivity, even minor depressive symptoms are associated with considerable lost productivity (Beck et al., 2011). The percentage of patients who reported missed or impaired work time increased from 30% for those with mild or minor depressive symptoms to 51% for those with severe depression. In the National Institute of Mental Health Collaborative Depression Study (NIMH-CDS), MDD patients were unable to carry out work activities during 21% of months assessed (mean, 33 months) (Judd et al., 2008). All symptoms of depression have been reported to interfere with work functioning; however, symptoms reported by more than 50% of patients as interfering very much or leading to missed work included lack of motivation, low energy, low mood, and feeling physically slowed down, anxious, tense, or nervous (Lam et al., 2012).

1.2. Relationship between depressive symptoms and functionality

Functional recovery is critical for patients to achieve and remain in remission of MDD and return to productive and fulfilling daily lives. In fact, depressed outpatients reported positive mental health (e.g., optimism and self-confidence); return to usual, normal self; and return to usual level of functioning at work, home, or school as key factors contributing to remission (Zimmerman et al., 2006).

Measures of psychosocial functioning generally move in parallel with depressive symptoms, such that as depressive symptoms increase, psychosocial disability worsens (Judd et al., 2000). In a pooled analysis including 3530 outpatients with MDD, improvement in functional impairment as measured by the SDS correlated with improvements in depressive symptoms assessed using the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) (Guico-Pabia et al., 2012). Following acute treatment of depression, psychosocial functioning returned to normal in patients who achieved remission of depressive symptoms (Miller et al., 1998). However, improvements in depressive symptoms and functionality do not always resolve in tandem. A pooled analysis of three randomized, double-blind, 8-week acute treatment studies found that 38% of patients achieved symptomatic remission ($HAM\text{-}D_{17} \leq 7$), while 32% achieved functional remission (SDS ≤6) and 23% achieved combined symptomatic and functional remission (Sheehan et al., 2011). In the NIMH-CDS, subthreshold symptoms of depression were associated with substantial psychosocial disability, particularly related to work function (Judd et al., 2000). Studies have shown that functional improvement lags behind symptomatic improvement and that greater symptom relief with treatment specifically focused on functional impairments may be necessary to achieve functional remission (Bijl and Ravelli, 2000; Papakostas et al., 2004; Rush, 2015; Sheehan et al., 2011).

Following initial monotherapy for MDD, only about 30% of patients achieve remission, indicating that approximately 70% of patients experience residual symptoms (Trivedi et al., 2006). Remission is increasingly difficult to achieve with each treatment failure, as an estimated one third of patients do not achieve remission after four optimized, well-delivered treatments (Greden, 2013; Thase, 2010). Patients with residual depressive symptoms are likely to also have residual functional impairment as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Work and Social Adjustment Scale (WSAS) (Dennehy et al., 2014). Importantly, impaired functioning is a predictor of subsequent relapse; patients whose depressive symptoms resolved with a Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) score ≤5 but had abnormal functioning based on Q-LES-Q and WSAS were at greater risk of relapse (defined as QIDS-SR score > 7) (IsHak et al., 2013). Moreover, patients who have psychosocial impairments are 22% less likely to achieve no symptoms of major depression over 8 weeks compared with those who do not have impairment (Solomon et al., 2008). Considering the lack of a strong correlation between depressive symptoms and functionality and the impact of substantial residual functional impairments that can remain after symptomatic recovery is achieved, functional status should be assessed routinely, in addition to typical measures of symptomatology, and even in light of successful reduction in depressive symptoms (IsHak et al., 2013; Rush, 2015; Trivedi et al., 2009; van der Voort et al., 2015).

1.3. Severity of depression and workplace functioning

It is not surprising that employed individuals with MDD experience substantially greater impairments in work productivity than individuals without depression (Greden, 2013). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, work productivity was assessed among patients with MDD who were employed at baseline (Trivedi et al., 2013). Of the 4041 patients with MDD who were evaluated in STAR*D, 2311 patients were employed at baseline, and 1928 had impairments in work productivity. Trivedi et al. reported that work productivity improved over several domains in parallel with reduction in the severity of depressive symptoms, but only during the acute phase of treatment. Although depressive symptoms continued to improve with subsequent treatment, improvements in work productivity were not sustained in patients who failed to achieve symptomatic remission early – these individuals continued to experience impairments at work (Greden, 2013; Trivedi et al., 2013).

Beck and colleagues investigated the relationship between depression severity and work place functioning using the Patient Health Questionnaire 9-item screen (PHQ-9) and Work Productivity and Activity Impairment (WPAI) questionnaire assessments in 771 employed patients with MDD, and observed a linear relationship between the severity of depressive symptoms and impairments in work productivity (Beck et al., 2011). Even minor depressive symptoms were associated with substantial decreases in work productivity. Specifically, each 1-point increase in PHQ-9 score was associated with a statistically