REVIEW ARTICLE

CNS Drugs 2010; 24 (4): 267-284
1172-7047/10/0004-0267/$49.95/0

Defining and Measuring Functional Recovery from Depression

Tracy L. Greer, Benji T. Kurian and *Madhukar H. Trivedi*

Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Contents

Abstract . . . 267
1. Functional Impairments Associated with Depression . . . 268
   1.1 Overall Function and Quality of Life . . . 268
   1.2 Work . . . 270
   1.3 Other Specific Domains Relating to Function . . . 271
      1.3.1 Insomnia, Daytime Sleepiness and Fatigue . . . 271
      1.3.2 Somatic Symptoms and Pain . . . 271
      1.3.3 Cognitive Function . . . 272
   1.4 Disability . . . 272
2. Assessing and Quantifying Functional Impairment . . . 273
   2.1 Defining Health-Related Quality of Life . . . 274
   2.2 Assessing Health-Related Quality of Life . . . 274
   2.3 Assessment of Specific Areas or Domains . . . 275
      2.3.1 Work . . . 275
      2.3.2 Sleep/Insomnia . . . 275
      2.3.3 Other Domains . . . 275
   2.4 Self-Reported versus Objective Assessment of Functional Impairment . . . 275
3. Defining Recovery . . . 276
4. Treating Residual Symptoms Associated with Functional Impairment . . . 277
   4.1 Common Augmentation Strategies in Major Depressive Disorder (MDD) . . . 277
   4.2 Targeting Augmentation Strategies for Specific Symptoms Associated with Functional Impairment in MDD . . . 278
      4.2.1 Insomnia . . . 278
      4.2.2 Daytime Sleepiness/Fatigue . . . 278
      4.2.3 Somatic Symptoms/Pain . . . 278
      4.2.4 Cognitive Impairments . . . 278
5. Conclusion . . . 279
6. Recommendations for Progress in this Area . . . 280

Abstract

Depression is associated with significant functional impairment and reduced quality of life. Disruptions occur both globally as well as in specific functional areas such as work, interpersonal relationships and cognitive function. From both a clinical and research perspective, much focus has been given to the resolution of symptoms associated with depression, while relatively little attention has been given to functional improvements. Definitions of remission in depression are most frequently based on achieving a cut-off score on clinical rating scales of depressive symptoms. Research in this area

has sparsely included psychosocial function or health-related quality of life as a primary outcome measure in clinical trials. However, the need to fully understand the impact of depression and its treatments on functioning is great, given the existing evidence of the profound effect that depression has on function. Even mild depressive symptoms and subsyndromal depression result in functional impairment and reduced quality of life, and untreated residual depressive symptomatology can result in an increased likelihood for relapse of the fully symptomatic disorder (i.e. major depressive disorder). Therefore, clinicians and researchers alike need to broaden the focus of treatment to encompass not only the specific symptoms of depression, but the functional consequences as well.

Many tools have been developed to assess function and quality of life, both globally as well as within specific domains. In addition, the effect of residual symptoms associated with functional impairment (i.e. insomnia, fatigue, pain [somatic] symptoms and cognition) in depression, even independently of depressive symptoms, warrants evaluation and monitoring. Recommendations for evaluating functional outcomes include: (i) adequately assessing functional impairment; (ii) identifying and/or developing treatment plans that will target symptoms associated with functional impairments; and (iii) monitoring functional impairments and associated symptoms throughout the course of treatment. The development of treatments that specifically target improvements in functional impairments is needed, and may require the use of novel treatment strategies.

This review describes some of the most common functional impairments in depression and the tools currently used to assess them. It also discusses currently available treatments for specific residual symptoms associated with functional impairment in depression, and recommends future areas of focus to increase the likelihood of adequate treatment of these symptoms in depressed individuals.

1. Functional Impairments Associated with Depression

1.1 Overall Function and Quality of Life

Major depressive disorder (MDD) causes significant functional impairment, which results in impaired psychosocial function, reduced quality of life and a host of impairments in specific areas such as at home, in the workplace, and with friends and family.[1-3] Much of the research in this area has shown that milder forms of the disorder, such as minor depression or dysthymia, and even subthreshold depressive symptomatology, adversely affect function and quality of life across the lifespan.[4-8] In addition, the amount of dysfunction and disability associated with depression exceeds that seen in many other common, chronic illnesses.[6,9,10]

Prior work in this area has included cross-sectional examinations of depressed persons with varying levels of depressive symptom severity. Wells et al.[11] examined functioning and well-being in persons with depressive disorders and depressive symptoms (n = 1137) and patients with no chronic conditions (n = 2577) who were participants in the MOS (Medical Outcomes Study), a large study of patient treatments and outcomes in the US. Wells et al.[11] found that depressive disorder or depressive symptoms in the absence of a disorder were both associated with poorer functioning (physical, social and role), worse perceived current health and more bodily pain compared with the absence of chronic conditions. Compared with eight other chronic medical conditions (history of hypertension,

history of diabetes mellitus, current advanced coronary artery disease, current angina only, current arthritis, current back problems, current lung problems, current gastrointestinal disorder), depression (whether symptoms or disorder) was associated with comparable or worse function, with the exception of a few cases in which depressed patients showed higher function than patients with coronary artery disease (physical functioning, role functioning, days in bed, current health), angina (physical functioning, current health) or arthritis (bodily pain). Social functioning was worse in depression than in any other chronic medical condition. Results from the LIDO (Longitudinal Investigation of Depression Outcomes) study,[12] which was conducted across six countries – Israel, Brazil, Australia, Spain, Russian Federation and the US – suggest that this effect is cross-cultural. Participants ($n = 18\,456$) with higher depressive scores had lower self-reported function and satisfaction, and higher utilization of health services across all of the countries that participated.[12]

Longitudinal studies of functional outcomes are being increasingly conducted. Coryell et al.[13] evaluated psychosocial functioning in 148 bipolar probands and 240 unipolar probands and relative comparison subjects based on the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression clinical studies.[14] Probands were followed every 6 months for 5 years, and comparison subjects received a baseline and 6-year follow-up evaluation. Both bipolar and unipolar probands had lower incomes than their respective comparison groups ($t = -3.14$, $df = 138$, $p = 0.002$ and $t = -3.69$, $df = 227$, $p = 0.0003$, respectively), and their incomes were less likely to increase by follow-up than the comparison groups. Mean education levels were slightly higher at baseline for bipolar probands compared with their comparators ($t = -2.12$, $df = 147$, $p = 0.04$), but they were less likely to increase their educational status at follow-up ($\chi^2 = 4.0$, $df = 1$, $p < 0.05$). Mean education levels for unipolar probands were lower than their comparison group at both baseline and follow-up ($t = 1.94$, $df = 239$, $p = 0.05$ and $t = 2.62$, $df = 237$, $p = 0.009$, respectively). With respect to marital status, both bipolar and unipolar probands were half as likely to ever have been married, and for those who were married, they were twice as likely to have been divorced or separated. Married unipolar probands were significantly more likely than nondepressed comparators to rate the quality of their relationship as poor (14.5% vs 1.2%, $\chi^2 = 7.7$, $df = 1$, $p < 0.01$) and to be dissatisfied with sexual functioning (22.0% vs 4.9%, $\chi^2 = 8.5$, $df = 1$, $p < 0.005$). Probands were also significantly more likely to report poorer interpersonal relationships with friends, children and other important relatives, as well as decreased involvement and enjoyment of recreational activities and overall satisfaction and contentment compared with the comparison group (note that analyses appear to be pooled by diagnosis for these comparisons). Even with sustained recovery, impairment in unipolar depressive patients was not much different from the total depressed group, suggesting that impairments are pervasive. The authors acknowledge that there may have been sampling bias, since participants were recruited as they were referred to treatment and the impact of socioeconomic status may not have been adequately assessed.

Judd et al.[6] followed 371 patients with unipolar MDD who were participants in the NIMH CDS (Collaborative Depression Study).[14] This longitudinal examination allowed for participants' functioning to be assessed over an approximate 10-year period, and through variations in levels of depressive symptomatology. Participants entered the study while experiencing a major depressive episode, and psychosocial function was assessed via the Longitudinal Interval Follow-up Evaluation (LIFE). Psychosocial function was assessed both globally as well as with specific assessments of work/employment and relationships with spouse or partner. The study concluded that with each increasing level of depressive symptom severity, psychosocial impairment was significantly increased. This was true for global impairment, as well as work/employment and relationship with spouse or partner. Odds ratios of significantly greater functional impairment associated with stepwise increments in depressive symptom severity were 7.7 (95% CI 7.1,

8.3) for subthreshold symptoms versus asymptomatic; 13.3 (95% CI 12.2, 14.6) for minor or intermittent depressive disorder versus subthreshold symptoms; and 23.3 (95% CI 20.7, 26.2) for MDD versus minor or intermittent depressive disorder.

In 2008, Judd et al.[15] reported on additional data from the NIMH CDS study.[14] These data compared 358 participants diagnosed with unipolar depression (UP-MDD) with 158 diagnosed with bipolar I disorder and 133 diagnosed with bipolar II disorder.[15] The LIFE Range of Impaired Functioning Tool (LIFE-RIFT) was used to evaluate the most impaired role function (work, household duties or schoolwork), the most disrupted type of interpersonal relationships (spouse/mate, children, other relatives or friends), limitations in recreation or hobbies and overall negative subjective satisfaction. All three diagnostic groups had averages in the mild impairment range across all months in which ratings occurred (i.e. across well and ill periods), compared with 1718 comparison subjects with no current psychiatric disorder, whose mean score indicated good function with no impairment. The three diagnostic groups spent similar amounts of time in the different categories of function: 8–12% of assessed months with very good function – no impairment; 31–34% of months with good function – no impairment; 27–29% of months with fair function – mild impairment; 19–23% of months with poor function – moderate impairment; and 7–9% of months with very poor function – marked impairment. When the latter three ratings, indicating some level of disability, were combined, patients were impaired to some degree during the majority of follow-up (54–59% of months), with a substantial number of those months with moderate or severe impairment (26–31%). Of the LIFE-RIFT domains, work impairment was the only domain in which severe impairment was observed during a considerable portion of the follow-up period (20–30% of months); the other domains did not show severe impairment in >7% of evaluated months. This finding is important, considering the impact of work function on disability and lost productivity, which causally impacts both the personal and societal costs of mood disorders.

The consistent findings that subthreshold depressive symptoms are associated with psychosocial impairment and reduced functional ability make it clear that functional outcomes are essential to understanding an individual's response to treatment. Current antidepressant treatment trials emphasize somewhat arbitrary cut-offs, based on depressive symptom severity, to define treatment response. For instance, in general, response to antidepressant medication is defined as a ≥50% improvement from baseline in depressive symptoms.[16] Given the differences in baseline symptom severity, this is a variable definition that is unique to each patient. Furthermore, the goal of treatment in recent years has been to achieve remission,[16] but while the concept of remission is universally identified as being symptom free, in practice it varies among symptom severity measures. Assessing a patient's functional status and assigning functional recovery (ability to work, enjoyment of interpersonal relationships and overall quality of life) as a primary outcome along with symptom severity for depressed patients may provide a clearer picture of MDD treatment response.[17] However, while many existing antidepressant treatment studies are designed to assess functional status as a secondary endpoint, very few power their study based on achieving functional recovery. Additionally, if functional outcomes are left unevaluated and unmonitored throughout the course of treatment, it is likely that residual impairments will remain, despite the patient's remission or response status. Residual impairments reduce an individual's productivity and quality of life, and increase the likelihood of relapse to another major depressive episode.[18] It is therefore essential that we more carefully evaluate and monitor functional outcomes when treating depressive disorders.

1.2 Work

Of the specific functional domains that can be measured, work-related impairment has received the most attention, likely due to the direct association with productivity and cost of illness. Kessler et al.[19] evaluated work performance

in unipolar and bipolar depression using a sample of 3378 workers from the National Comorbidity Survey (NCS-R). Diagnosis was based on the WHO Composite International Diagnostic Interview (CIDI).[20] Work performance was evaluated with the WHO Health and Work Performance Questionnaire,[21,22] which assesses self-reported absenteeism and presenteeism (i.e. low performance while at work because of a medical condition, which is transformed to lost workday equivalents). A summary measure of overall workdays lost was then generated to evaluate the month preceding the interview. Variables such as sex, age, race/ethnicity, education, occupation and expected number of weekly work hours were all controlled for in the analyses. Bipolar disorder was associated with 65.5 lost workdays (per worker, per year) and MDD was associated with 27.2 lost workdays (per worker, per year). Analysing by type of workday loss (i.e. absenteeism vs presenteeism), absenteeism was associated with 27.7 days of lost work for bipolar disorder and 8.7 days for those with MDD, whereas presenteeism was associated with 35.3 days of lost work for bipolar disorder and 18.2 days for those with MDD. This suggests that presenteeism may be more problematic than absenteeism. Estimates of the impact of these figures on the US workforce were 96.2 million lost workdays and $US14.1 billion salary-equivalent lost productivity per year for bipolar disorder, and 225.0 million workdays and $US36.6 billion salary-equivalent lost productivity per year for MDD (based on data from the 2002 Current Population Survey and projection to the total US civilian labour force). Individuals with serious mental illness such as MDD are also likely to receive lower wages than nondepressed counterparts,[23] likely due to disrupted functioning.

1.3 Other Specific Domains Relating to Function

Although slightly more difficult to quantify compared with work function, it is important to assess domains such as cognitive function and interpersonal relationships, which can often contribute to impairments in work function. For instance, cognitive impairments can significantly contribute to impairments at work, particularly with respect to presenteeism, or impaired performance during active workdays. In addition, it is also important to evaluate and quantify the sometimes very painful impairments associated with interpersonal relationships and other functional disruptions that impact work function. Finally, targeting specific symptoms (i.e. cognition, insomnia, somatic symptoms) associated with function, as discussed in more depth in section 4.2, provides potential treatments to improve overall functional outcomes.

1.3.1 Insomnia, Daytime Sleepiness and Fatigue

Complaints of insomnia, in some manner, are reported by a large percentage of the general population.[24] This is heightened in patients with MDD, in whom up to 90% present with co-morbid insomnia.[25] Insomnia is one of the nine core symptoms of MDD, and the frequency with which it occurs suggests how integral a role it plays in attaining symptom remission and functional recovery. Consistently, a number of studies have found that concurrent insomnia predisposes to future episodes of depression and anxiety.[24,26]

Another common residual symptom associated with MDD – and often concurrently occurring with insomnia – is daytime sleepiness and fatigue.[27] While fatigue is a hallmark of chronic fatigue syndrome and fibromyalgia, both of which are commonly co-morbid with MDD,[28] to date no controlled studies have assessed the impact of fatigue associated with MDD as it relates to functional outcome. However, it stands to reason that if a patient experiences daytime sleepiness and fatigue, this is likely to impair their functional capacity.

1.3.2 Somatic Symptoms and Pain

Physical (somatic) complaints are common symptom manifestations in MDD, and often persist even after traditional emotional symptoms improve.[29] In fact, a WHO report found that, of patients with depression, up to 69% reported having only somatic symptoms.[30] Additionally, patients with concurrent chronic pain disorders and MDD experience longer depressive

episodes than patients without chronic pain disorders.[31] A recent report further delineated this relationship by associating functional improvement with symptom improvement of nonpainful and painful somatic symptoms.[32]

1.3.3 Cognitive Function

Impaired cognitive functioning is one of the nine core symptoms of MDD, and it has a key role in depressed patients achieving functional recovery. Cognitive dysfunction has frequently been noted in depression, particularly in domains such as attention and executive function.[33] Jaeger et al.[34] noted that, despite the strong association between neurocognitive deficits and functional status in other psychiatric populations, there has not been adequate investigation into this relationship in depression. They examined the relationship between cognitive function (using a comprehensive testing battery) and life functioning (using the Multidimensional Scale of Independent Functioning [MSIF]),[35] and the degree to which cognitive function could predict functional outcome 6 months post-baseline (which occurred at hospitalization for a major depressive episode).[34] Limited baseline cognitive measures (i.e. one visuospatial measure and one learning measure) predicted life functioning at 6 months. However, impairments on measures of attention, ideational fluency, visuospatial function and learning were strongly associated with impaired life functioning at the 6-month visit, even after controlling for residual depression, psychosis and disabling medical co-morbidities, suggesting that cognitive function can adversely affect life functioning independent of improvement in depressive symptoms. In addition, participants showing cognitive improvements at follow-up were more likely to have better life functioning, whereas those who showed no improvement or worsened cognitive function were more likely to be significantly or totally disabled. The sample had patients using a variety of psychotropic medications and with mixed features (e.g. both psychotic and nonpsychotic), but these data strongly support a relationship between cognitive function and health-related quality of life, and they suggest that treatment directed specifically toward cognitive impairment is warranted.

Despite the fact that impaired concentration is a core symptom of depression, and evidence supports the role of cognitive impairment in depression, cognitive issues are often not assessed as well as they should be in depressive disorders. In fact, many mental health professionals fail to consider complaints of cognitive function during the course of treatment. One possible contributor to this oversight is the paucity of self-report measures used to assess cognitive function, as described in more detail in section 2.3.3. Thus, in addition to the need for targeted treatments of this functional domain, increased awareness and ease of assessment for these impairments is greatly needed.

1.4 Disability

One of the most damaging consequences of depression, both with respect to the individual who has the disorder and to society as a whole, is the profound disability that is associated with it. Depression is a leading cause of disability, both in the US and worldwide.[36,37] Murray and Lopez[38] projected that MDD will be second only to ischaemic heart disease in worldwide disability-adjusted life-years by the year 2020, and it is projected to remain in that position in the year 2030.[9] Not only are the costs in terms of pain, suffering and disability substantial, but the direct monetary costs of treatment, combined with the indirect costs from lost productivity, are significant.[39-41] These overall costs accounted for approximately $US77.4 billion inflation-adjusted dollars in 1990, rising to $US83.1 billion inflation-adjusted dollars in 2000.[42] Greenberg and Birnbaum[43] acknowledge that even these staggering costs are likely to be underestimates of the true costs because many costs, such as caregiver burden, are difficult if not impossible to capture.

Research on disability associated with depression in the workplace has focused on both short- and long-term disability claims. Kessler et al.[44] analysed data from two large national surveys – the National Comorbidity Study and the Midlife Development in the United States survey – to

assess short-term disability in the workplace that was associated with major depression. Participants were asked how many days in a 30-day period they were unable to work or carry out their normal daily activities, which were defined as work-loss days. In addition, days in which workers were present at work but either cut back on the time they worked or accomplished less than usual were counted as work cut-back days. A summary measure including both of these components was developed, and when data from the two national surveys were combined, 45.9% of individuals reporting depression had some short-term disability within the last 30 days compared with 19.9% of individuals without depression. The conditional mean number of work-disability days over a 30-day period was 7.6 among those who were depressed compared with 4.7 among those who were not depressed.

Less detailed information is available for long-term disability claims. With respect to long-term disability in the private sector, mental disorders, including depression, account for about 9% of claims through group long-term disability insurance.[45] Public sector long-term disability claims (as assessed by individuals receiving supplemental security income) for mental disorders (excluding mental retardation) have increased in the US in recent years – rising by 67% since 2007.[46] Long-term disability claims for mental disorders are associated with higher costs than claims for other disorders.[47] Employers are faced with decisions on how to manage costs associated with such mental health claims, which can be challenging. For example, there is some evidence that decreasing access to mental health benefits results in decreased outpatient treatment costs, but this in turn increases inpatient treatment costs.[47]

Many of the costs associated with depressive disorders are directly related to functional consequences of depression. For example, some evidence suggests that depression is associated with increased residential transience.[48,49] Davey-Rothwell et al.[48] conducted a study to assess the relationship between transience (defined as two or more moves in the last 6 months) and depressive symptoms as measured with the Centers for Epidemiological Studies Depression scale (CES-D)[50] in participants who were participating in an HIV prevention study. Most participants were intravenous substance users (cocaine or heroin) and had a low socioeconomic status. Participants who reported higher levels of depression (CES-D ≥16) were more likely to have been transient. While the contribution of drug use and low socioeconomic status cannot be ignored and the authors primarily discuss the impact of transience on mental health, these data also suggest that individuals with depression may have difficulty maintaining a residence and may therefore move more frequently than their nondepressed counterparts. Similarly, both initial and chronic (i.e. >18 months) homelessness has been associated with a higher presence and severity of mental health disorders, including major depression, although the results did not reach statistical significance.[49]

In addition, Naismith et al.[51] examined the relationship between quality of life and cognitive function in 21 patients with MDD who completed the Brief Disability Questionnaire,[52] the 12-item Short-Form Health Survey (SF-12)[53] and cognitive measures of psychomotor speed, initial learning, memory retention and executive function. The authors found moderate relationships between psychomotor speed and physical disability, as well as memory retention and mental health disability. Thus, depression and even some of its specific symptoms have been associated with increased disability. The staggering disability associated with depression truly underscores the need to better assess, treat and monitor functional outcomes associated with this disorder.

2. Assessing and Quantifying Functional Impairment

Given that depression is associated with functional impairment, it is essential that we begin to assess and monitor functional outcomes both in the research setting as well as in the course of clinical care. This section covers information on the definition of functional outcomes and the many instruments that have been developed to assess them.

2.1 Defining Health-Related Quality of Life

The term 'health-related quality of life' can represent many meanings, and it has often been used synonymously with terms such as 'functioning', 'quality of life', 'psychosocial function' and 'social functioning'. Health-related quality of life can assess patient perceptions of health, physical functioning, mental functioning, social participation, role participation and life satisfaction.[17,54,55] Bosc et al.[56] defined social functioning as ''the interaction of an individual with their environment and the ability to fulfil their role within the environment.'' This definition captures much of the intent of the evaluation of functional impairment, which is to assess the disruption in the function and quality of daily life that is due to a particular illness. It has not been until recently that we have begun to recognize the need for measures to distinctly evaluate function separate from symptomatic improvement in order to assess the effect of treatment in both areas.[17,56,57] Results from the evaluation of quality of life in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study[17] illustrate the need to evaluate multiple domains of quality of life and the need to control for sociodemographic variables, as these factors uniquely affect various functional domains in depressed individuals.

A wide variety of measures have been developed to assess function and quality of life. Some of these measures are global in nature and may provide a global summation of impairment across many domains (e.g. home life, work function, school function, interpersonal relationships), and some are designed to assess function specifically in one domain (e.g. work). Additionally, some are general in nature, and thus evaluate quality of life in a variety of medical conditions, while others are disease specific and are developed with consideration of a specific disease process.[58] We review some of the most commonly used measures, focusing on those that have been deemed most valid and reliable in the assessment of function in depression. The assessments are categorized below into those that have a more global assessment versus those that are more specific to a particular quality of life domain or specific related symptom.

2.2 Assessing Health-Related Quality of Life

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[59] is designed to measure satisfaction and enjoyment, as opposed to function *per se*, in various domains of function: physical health, feelings, work, household duties, school/course work, leisure time activities, social relations and general activities. A short version with 16 items is also available.

The LIFE-RIFT[60] is a subset of items from the LIFE. It was developed as a brief scale of functional impairment, since many other functional assessments are quite lengthy and therefore cumbersome to use. It is a semi-structured interview that targets functioning in four domains: work, interpersonal relationships, recreation and global satisfaction. It requires minimal training and takes only about 5 minutes to complete. The validity and reliability of the LIFE-RIFT was evaluated using a sample of patients with MDD from the NIMH CDS.[61]

The Satisfaction with Life Scale (SWLS)[62,63] is a five-item, self-report inventory that measures global life satisfaction.

The Short-Form Health Survey (SF-36, Version 2)[55,64] assesses health-related quality of life and was developed for the MOS.[65] The SF-36 contains eight scales measuring physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. Each scale score ranges from 0 to 100, with higher scores indicating better perceived health and functioning. Physical and mental summary scores can also be derived.

The Social Adaptation Self-evaluation Scale (SASS)[56,66] was developed to assess social function in patients in depression. The SASS has been shown to be differentially impacted by treatment with the selective noradrenaline reuptake inhibitor reboxetine compared with the selective serotonin reuptake inhibitor (SSRI) fluoxetine, with reboxetine treatment showing greater improvement in social functioning.[67] The SASS is

a self-assessment measure comprising 21 questions from several domains (work, relationships with family and friends, intellectual interests, hobbies, satisfaction with performance and the ability to manage one's environment), with each item having a possible score of 0–3. The SASS takes about 5–10 minutes to complete.

The Social Adjustment Scale – Self-Report (SAS-SR)[68] is a 54-item, self-report measure of instrumental and expressive role performance. Items are rated on a five-point scale with higher scores indicating impairment.

2.3 Assessment of Specific Areas or Domains

While some specific domains are most frequently evaluated in the context of a global functioning scale (e.g. interpersonal relationships), others, such as work, have instruments that are dedicated solely to the evaluation of that particular domain. A few examples of such measures are provided below.

2.3.1 Work

The Work and Social Adjustment Scale (WSAS)[69] is a five-item, self-report measure designed to identify functional impairment that is attributed to an identified problem or condition. Each question is rated on a 0–8 scale, with 0 indicating no impairment and 8 indicating very severe impairment. The WSAS has been used to study the treatment of depression and anxiety.

The Work Productivity and Activity Impairment questionnaire (WPAI)[70] measures the number of work hours missed during the last 7 days, the number of hours actually worked in the last 7 days and impairment while working or performing usual daily activities as a result of health problems. A 'health problem' is defined as any physical or emotional problem or symptom.

2.3.2 Sleep/Insomnia

The Pittsburgh Sleep Quality Index (PSQI)[71] assesses quality of sleep and sleep disturbances over a time frame of 1 month. It has 19 self-rated questions, as well as five that are rated by a bed partner or room-mate. Scoring of the PSQI results in a global score (with scores ranging from 0 to 21), as well as seven component scores reflecting sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction.

The Insomnia Severity Index (ISI)[72] is a seven-item, brief self-report assessing difficulties in sleep onset and maintenance, as well as satisfaction with sleep, and functional impairments related to sleep. Each of the items is rated on a scale of 0–4, resulting in a possible total score ranging from 0 to 28, with higher scores indicating more severe insomnia.

2.3.3 Other Domains

Specific measures exist for the evaluation of other relevant domains, such as cognitive function, anxiety and pain, all of which are relevant to functional outcomes as described previously. Cognitive measures vary widely, ranging from commonly used stand-alone measures to comprehensive testing batteries measuring many cognitive domains and, more recently, the development of computerized batteries. Specific scales to measure anxiety may be used, as well as subscales of depression rating scales, such as the Inventory of Depressive Symptomatology (IDS).[73,74] Somatic symptoms can also sometimes be measured in the context of depressive rating scales. Pain is most commonly assessed via visual analogue scales.[75-77]

2.4 Self-Reported versus Objective Assessment of Functional Impairment

The method by which functional impairment is assessed (i.e. self-report, informant, clinician-rated or objective [e.g. performance- or physiologically based] measure) is relevant to our understanding of such impairments. An important question in the assessment of functional impairment is the degree of accuracy of depressed individuals in the self-report of their level of functioning. This has been an important question in other mental illnesses, such as schizophrenia, where most evidence suggests little agreement occurs between clinical ratings and objective performance (e.g. neuropsychological task performance).[78,79] Even those instruments that are clinician rated rely on the information reported

by the patient (or sometimes an informant), and therefore may not be consistent with objective data. The assessment of many functional outcomes in depression – such as health status, level of satisfaction and enjoyment, and work performance – is most often conducted by self-report rather than by collection of objective data.

Other functional domains are more readily assessed by objective measures of performance. Cognitive function, for example, is more often assessed by objective neuropsychological tests that quantify performance; however, the relationship between this performance and self-reported cognitive complaints is not well understood, as some data suggest a discrepancy between the two,[80-82] whereas other studies report some degree of consistency.[83,84] Unfortunately, many of these studies have focused predominantly on older individuals, with much less information available on younger depressed subjects. Sleep is another functional outcome that can be readily assessed by both self-report and objective measures. As with cognitive function, studies examining perceived sleep and objective sleep measures (such as actigraphy or EEG) have shown strong positive correlations, suggesting agreement on this particular functional outcome,[85] whereas others show poor agreement.[86]

The influence of disease severity on the relationship between perceived and objective functioning may also be important, and should be better investigated. Some data suggest that increased severity of depression is associated with more functional impairments, such as cognitive complaints in the elderly,[87] although the relationship between these complaints and objective performance has been less frequently studied. Depression severity has been shown to increase both self-reported and objective measures of impaired sleep.[85]

It is also possible that noted discrepancies between self-reported and objective functioning could be because the assessments are not capturing the same information. This is particularly relevant in the cognitive function realm, where many cognitive domains are being assessed. It is conceivable that the existing cognitive tasks are limited in their ability to measure true cognitive deficits in depression that are being accurately reported by depressed persons. Such possibilities should be an aim of future research. In addition, it would be helpful to develop assessments that are more relevant to 'real-world' situations, such as conducting assessments of cognitive abilities on specific tasks in the workplace (i.e. simulations) and evaluating employers' observations of functional impairments.

3. Defining Recovery

Once assessment measures have been selected for use in evaluating function, they must then be included in the definition of recovery from depression. Currently, the most common definition for recovery from MDD is described in terms of remission. Remission is defined by the DSM-IV-TR as ≥2 months of no significant symptoms of MDD;[88] however; in practice this often leaves both the clinician and the patient with a vague and subjective endpoint for treatment. In research settings, a more objective line is used to define remission based on scales of the patient's symptom severity: for example, a 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) score ≤7, a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≤10 and a Quick Inventory of Depression Symptomatology (QIDS) score ≤5 are all synonymous with remission.[89-92] Each of these scales uniquely measures core symptoms of depression and the change therein over time. In recent years, achieving remission status has been identified by the American College of Neuropsychopharmacology (ACNP) Task Force[16] as the goal of treatment for patients with MDD.

Unfortunately, not achieving remission (i.e. partial response to treatment) is a common outcome for patients initially being treated for MDD. In fact, based on recent clinical trials evaluated in 'real-world' settings, first-step treatment with an SSRI antidepressant is only 33% effective in achieving remission of depressive symptoms.[93] Furthermore, a majority of depressed patients exhibit only a partial response to an initial antidepressant, and almost one-third are virtually nonresponsive.[94,95] The consequence of not

achieving remission (i.e. those with residual depressive symptoms) is manifested by increases in psychosocial impairments.[96] Additionally, nonremission increases the risk for and shortens the time to relapse of depressive symptoms.[18] Conversely, the presence of psychosocial impairments is also associated with a higher depression symptom severity and a lower chance for recovery.[97] In fact, in 2008 Solomon et al.[97] found that a one standard deviation increase in psychosocial impairment was associated with a 22% decrease in subsequent recovery from a major depressive episode (odds ratio = 0.78; 95% CI 0.74, 0.82; $Z = -3.17$; $p < 0.002$). This illustrates the need to fully assess, monitor and treat psychosocial impairment in patients with MDD.

While a scale such as the $HRSD_{17}$ effectively measures depression symptom severity, it has its own set of limitations.[98] Most notably, the cut-off score for remission ($HRSD_{17} \leq 7$) has been questioned as being too liberal (i.e. too high). Zimmerman and colleagues[98] argue that the current cut-off has not been "empirically derived" and, furthermore, allows remitters with residual symptoms the potential to still meet active criteria for MDD, based on DSM-IV criteria. In addition, symptom severity measures do not measure the functional recovery status of patients with MDD. From a quality-of-life standpoint, functional recovery status may be a more clinically meaningful proxy for course of illness than symptom severity. As described in section 1.2, productivity is significantly reduced by depression, and results in significant costs ranging from $US31 to almost $US37 billion dollars annually (2002 costings).[19] Thus, measuring and utilizing functional status to determine recovery status in patients with MDD is an important and novel way to gauge treatment response.

Currently, only a handful of MDD treatment studies have powered their primary outcome to measure functional status,[3] while the vast majority focus on depressive symptoms. Furthermore, while standard antidepressant treatment has been associated with improvements in psychosocial functioning,[3] it is all too common that functional impairments remain despite improvements or even resolution of depressive symptoms.[13]

4. Treating Residual Symptoms Associated with Functional Impairment

Given the importance of attaining remission from all depressive symptoms, in recent years increased attention has been given to treatment paradigms for nonremitters. Treatment strategies for nonremitters with residual symptoms (i.e. partial responders and nonresponders to antidepressant medications) consist of either switching to another agent or augmenting the original antidepressant with an additional medication. Recently, the STAR*D study, which was a 'real-world' effectiveness study, revealed that both strategies are efficacious, and the decision to switch or augment should be based on treatment response, tolerability (i.e. adverse effects) and patient preference.[99]

In general, if a patient has difficulty tolerating a medication, or an adequate dose and duration produces little or no response, switching to a new agent is considered. However, one potential drawback to switching medications is that the initial medication may have needed additional time to achieve efficacy. Additionally, for persons whose depression has responded but residual symptoms remain, switching may extend the time it takes to achieve remission. In these settings, augmentation strategies are often preferred.

4.1 Common Augmentation Strategies in Major Depressive Disorder (MDD)

Ideally, augmentation strategies enhance the action of the initial antidepressant medication, thereby reducing residual symptoms, achieving remission and enhancing functional recovery. A number of agents are currently used clinically for augmenting primary antidepressants, of which lithium and thyroid hormone (liothyronine; T_3) are most commonly used as first-line augmenting agents.[100] In addition to these conventional agents, recent studies have shown that nontraditional agents, such as modafinil, can be effective in reducing residual symptoms associated with depression (in the case of modafinil, fatigue).[101] While it is important to target augmentation treatments to reduce symptoms of the overall depressive syndrome, it may be necessary to

develop treatment approaches that target specific residual symptoms associated with functional impairments more directly. Insomnia, daytime sleepiness/fatigue, pain and cognitive dysfunction are common residual symptoms in patients with MDD and all have been uniquely associated with impairments in functional recovery.[27,29,102,103]

4.2 Targeting Augmentation Strategies for Specific Symptoms Associated with Functional Impairment in MDD

4.2.1 Insomnia

For a number of years clinicians have been prescribing hypnotic medications, such as benzodiazepines, to treat MDD and concurrent insomnia. However, due to the adverse effect profile associated with these older benzodiazepines, newer non-benzodiazepine hypnotics (i.e. zolpidem, zaleplon, eszopicolone) have emerged. Furthermore, recent studies have shown improvements in sleep for subjects taking an SSRI and zolpidem or eszopicolone concurrently.[104,105] Lastly, ramelteon, a novel medication that works as a melatonin receptor agonist and is indicated for primary insomnia,[106] worked favourably in a small number of patients with insomnia and generalized anxiety disorder.[107] These findings need to be replicated and studied in patients with MDD, but give hope for a novel treatment.

4.2.2 Daytime Sleepiness/Fatigue

Recent studies have assessed the use of treatments to augment conventional antidepressant medications in patients with residual daytime sleepiness/fatigue. Papakostas and colleagues[108] found preliminary evidence for the use of atomoxetine added to traditional antidepressants (mostly SSRIs). However, this was an open-label study that was additionally limited by a small sample size. With regard to randomized, placebo-controlled studies, Fava and colleagues[101,109] found modafinil augmentation to have a modest effect in treating residual fatigue in MDD. Larger, more definitive trials to assess the efficacy of atomoxetine and modafinil are necessary to solidify their place in the clinician's pharmacological armoury.

4.2.3 Somatic Symptoms/Pain

Treatment targets for physical symptoms have focused on shared neurobiological pathways for pain and depression. Specifically, increased availability of serotonin and noradrenaline (norepinephrine), which are key neurotransmitters in descending inhibitory pain pathways, is associated with the modulation of ascending pain signals. Clinically, serotonin-noradrenaline reuptake inhibitors, such as duloxetine, have proven efficacy and a US FDA-approved indication for treating pain conditions (i.e. fibromyalgia and diabetic neuropathy).[110] Older tricyclic antidepressants (TCAs), such as amitriptyline (which has an FDA-approved indication for polyneuropathy), have long been prescribed for a variety of chronic pain conditions. Tolerability and adverse effect profiles may limit the utility of TCAs for certain patients.

4.2.4 Cognitive Impairments

Few controlled studies have specifically assessed the impact of reducing symptoms associated with cognitive impairments in patients with MDD with an augmenting agent. Currently, antidepressant augmentation agents with potential cognitive benefits include psychostimulants,[111,112] modafinil[101,109,113] and cholinesterase inhibitors.[114,115] Two studies have assessed a psychostimulant (i.e. methylphenidate) combination with citalopram in geriatric depression, one of which was a placebo-controlled trial in 16 patients.[112] Although the results of this trial were promising, three of ten patients receiving the methylphenidate combination dropped out due to poor tolerability. Furthermore, because stimulants are controlled substances that require very close monitoring with regard to safety and tolerability, they may be too onerous for patients and providers. Fava et al.[101] conducted a pooled analysis of a number of prior modafinil augmentation studies in partial SSRI responders, but cognitive functioning was not detailed in these results. Finally, while Holtzheimer et al.[114] did specifically assess neurocognitive functioning, antidepressant augmentation with the cholinesterase inhibitor galantamine was not associated with significant benefit compared with placebo, and

Table I. Targeting residual symptoms associated with functional impairment in major depressive disorder

Residual symptom	Medication	Dosage range (mg/day)	Dosage schedule
Insomnia	Zolpidem	5–10	hs
	Zolpidem CR	6.25–12.5	hs
	Zaleplon	5–10	hs
	Eszopiclone	1–2	hs
	Ramelteon	8	hs
Fatigue, excessive somnolence	Modafinil	200	mane or qd
	Atomoxetine	40–80	qd
Pain (somatic) symptoms	Duloxetine[a]	30–60	qd
	Venlafaxine XR	75–225	qd
	Amitriptyline[b]	25–150	hs
Cognitive impairment	Methylphenidate	5–20	bid
	Donepezil[c]	5–10	hs
	Galantamine[c]	8–16	bid
	Modafinil	200	mane or qd
	Citicoline	500–2000	qd

a Duloxetine has FDA approval for use in fibromyalgia and diabetic neuropathy.

b Amitriptyline has FDA approval for use in polyneuropathy.

c Donepezil and galantamine trials were conducted in older adults with depression.

bid = twice daily; **CR** = controlled release; **hs** = at bedtime; **mane** = in the morning; **qd** = once daily; **XR** = extended release.

again tolerability was a limiting factor. The results of these studies suggest that an adequate treatment that is tolerable, efficacious and specifically designed for cognitive impairment in treatment-resistant MDD has not been identified, thus highlighting the need for new treatments in this population.

One potential candidate for the treatment of cognitive impairment in depression is citicoline. Citicoline (cytidine 5′-diphosphocholine) is an essential precursor in the synthesis of phosphatidylcholine, an essential element in cell membrane metabolism.[116] Although the mechanism of action through which citicoline appears to improve cognition and depression is unknown, animal studies reveal that at doses of 100 mg/kg, citicoline increases the essential monoamines (noradrenaline, dopamine and serotonin) involved in MDD in various regions of the brain.[117] Clinically, a recent, small, placebo-controlled study performed in outpatients with bipolar disorder and cocaine dependence suggested that citicoline is safe and well tolerated in humans, and may provide some cognitive benefits.[118] Specifically, the authors of this study reported a significant improvement in verbal learning and memory, measured by the Rey Auditory Verbal Learning Test (RAVLT), which supports prior results in other neurological disorders.[119,120] Although the data in depression are limited, a small trial with citicoline, administered intramuscularly at 500 mg/day, did achieve significant improvements in depressive symptoms in subjects diagnosed with a mood disorder.[121]

Taken together, insomnia, daytime sleepiness/fatigue, somatic symptoms (pain) and cognitive dysfunction are some of the most common residual symptoms associated with MDD. Table I provides dosage information for each of the targeted treatments for each of these residual symptoms. Although this table is not exhaustive, it does highlight key symptoms that are associated with functional impairment, with a list of pharmacological agents with some evidence for use.

5. Conclusion

Both cross-sectional and longitudinal studies of the effect of depression on functional outcomes suggest that function is significantly disrupted by depression, even by mild or subsyndromal

depressive symptoms. Functional impairment can occur globally, as well as in specific domains such as at work or home. Specific symptoms of depression, such as cognitive function or somatic symptoms such as insomnia, fatigue or pain, can also adversely affect function, even independently of the overall depressive syndrome. The costs of these impairments are great and comprehensive, affecting the individual with depression, their family, loved ones, co-workers and other individuals with whom they interact, and also society as a whole. A variety of measures are available to evaluate function, either global or symptom-specific, and these should more often be used both in clinical monitoring of patients as well as serving as a primary outcome measure in clinical trials investigating treatments for depression.

With the profound impact that depression has on function and quality of life, it is imperative that we develop and evaluate treatments that fully resolve functional impairments. While assessing and monitoring functional outcomes is an essential step in redefining clinical endpoints related to MDD, designing treatment strategies that target residual symptoms associated with functional impairments warrants further exploration and study. To date, treatment studies have assessed the impact of pharmacological adjuncts as they relate to classic symptoms of MDD. We advocate that future MDD studies include targeting insomnia, daytime sleepiness/fatigue, somatic symptoms and cognitive dysfunction, with change in functional status incorporated as part of the primary outcome. These treatments may take the form of augmentation strategies or novel agents, such as citicoline, and they may focus on specific targeted symptoms, such as cognitive function or somatic symptoms. It is only with the evaluation and resolution of functional impairment that we are likely to aid depressed individuals in achieving wellness and restored quality of life.

6. Recommendations for Progress in this Area

There are several strategies that can be implemented in order to fully evaluate, monitor and treat functional impairments. Goldberg and Harrow[122] note that while function in one area may be satisfactory, function in other areas may be low, and global assessment scales may be limited in their ability to isolate functional impairments in specific areas. Scales that comprehensively assess multiple functional domains may be ideal for both clinicians and researchers alike to utilize throughout the course of patients' treatment and in studies of depressed participants. Additionally, as noted by Bech,[57] social function should be assessed for a lengthy period of time, i.e. 1 year or longer, before meaningful improvements can be measured. As such, clinicians should plan to continually monitor and assess patients.

With respect to research, functional outcomes are too infrequently included as a primary outcome measure in clinical trials of treatments for depression. While they may be included as secondary outcomes, this designation may mean they are not adequately powered for the respective study design. Given the strong potential for adverse functioning associated with even mild depression, it is imperative that we thoroughly evaluate functional outcomes and the treatments that may improve function and quality of life in depression as a major goal of clinical research and clinical treatment. Recommendations for the evaluation, assessment and treatment of functional impairment and related symptoms in MDD are provided in table II.

Table II. Recommendations for evaluation, assessment and treatment of functional impairment and related symptoms in major depressive disorder

Evaluate function as an endpoint in clinical trials of depression, as well as in clinical treatment[17,57]
Use both general and disease-specific measures[58,122,123]
Evaluate multiple domains of quality of life, as well as specific, focused domains (e.g. work, cognitive function) and somatic symptoms (e.g. sleep/fatigue, pain)[17]
Consider the influence of sociodemographic variables[17]
Assess for an adequate period of time, typically at least 1 year[57]
Select treatments and/or treatment regimens that specifically target symptoms known to influence function[25,29,101-105,108,111-116]

Acknowledgements

The authors would like to thank Eric Nestler, Lou and Ellen McGinley, Distinguished Professor and Chairman, Department of Psychiatry, University of Texas Southwestern Medical Center as well as Carol A. Tamminga, M.D., Communities Foundation of Texas, Inc. Chair in Brain Science, and Interim Chair, Department of Psychiatry, University of Texas Southwestern Medical Center for administrative support. We would also like to thank Laura Cain and Shyma El Sayed for their assistance in preparing this manuscript.

No sources of funding were used to assist in the preparation of this review.

Tracy L. Greer has received grant support from the National Alliance for Research in Schizophrenia and Depression.

Madhukar H. Trivedi has been a consultant for Abbott Laboratories, Inc.; Akzo (Organon Pharmaceuticals Inc.); AstraZeneca; Bayer; Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Eli Lilly & Company; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; Johnson & Johnson PRD; Meade Johnson; Neuronetics; Parke-Davis Pharmaceuticals, Inc.; Pfizer, Inc.; Pharmacia & Upjohn; Sepracor; Solvay Pharmaceuticals, Inc.; Vantage-Point; and Wyeth-Ayerst Laboratories. He has served on speakers bureaus for Abdi Brahim; Akzo (Organon Pharmaceuticals Inc.); Bristol-Myers Squibb Company; Cephalon, Inc.; Cyberonics, Inc.; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; Eli Lilly & Company; Pharmacia & Upjohn; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories. He has also received grant support from Bristol-Myers Squibb Company; Cephalon, Inc.; Corcept Therapeutics, Inc.; Cyberonics, Inc.; Eli Lilly & Company; Forest Pharmaceuticals; GlaxoSmithKline; Janssen Pharmaceutica; Merck; National Institute of Mental Health; National Alliance for Research in Schizophrenia and Depression; Novartis; Pfizer Inc.; Pharmacia & Upjohn; Predix Pharmaceuticals; Solvay Pharmaceuticals, Inc.; and Wyeth-Ayerst Laboratories.

Benji Kurian has received research grant support from Targacept, Inc. and National Institute of Health.

References

1. Bakish D. New standard of depression treatment: remission and full recovery. J Clin Psychiatry 2001; 62 Suppl. 26: 5-9
2. Hirschfeld RM, Dunner DL, Keitner G, et al. Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biol Psychiatry 2002 Jan 15; 51: 123-33
3. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998 Nov; 59: 608-19
4. Gotlib IH, Lewinsohn PM, Seeley JR. Symptoms versus a diagnosis of depression: differences in psychosocial functioning. J Consult Clin Psychol 1995 Feb; 63: 90-100
5. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J Affect Disord 1997 Aug; 45: 5-17; discussion -8
6. Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry 2000 Apr; 57: 375-80
7. Judd LL, Paulus MP, Wells KB, et al. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. Am J Psychiatry 1996 Nov; 153: 1411-7
8. Judd LL, Rapaport MH, Paulus MP, et al. Subsyndromal symptomatic depression: a new mood disorder? J Clin Psychiatry 1994 Apr; 55 Suppl.: 18-28
9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006 Nov; 3: 2011-30
10. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997 May 17; 349: 1436-42
11. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1989 Aug 18; 262: 914-9
12. Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO study: functional status, health service use and treatment of people with depressive symptoms. Psychol Med 2002 Jul; 32: 889-902
13. Coryell W, Scheftner W, Keller M, et al. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993 May; 150: 720-7
14. Katz MM, Secunda SK, Hirschfeld RM, et al. NIMH clinical research branch collaborative program on the psychobiology of depression. Arch Gen Psychiatry 1979 Jul; 36: 765-71
15. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. J Affect Disord 2008 May; 108: 49-58
16. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006 Sep; 31: 1841-53
17. Trivedi MH, Rush AJ, Wisniewski SR, et al. Factors associated with health-related quality of life among outpatients with major depressive disorder: a STAR*D report. J Clin Psychiatry 2006 Feb; 67: 185-95
18. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995 Nov; 25: 1171-80
19. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. Am J Psychiatry 2006 Sep; 163: 1561-8
20. Kessler RC, Ustun TB. The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int J Methods Psychiatr Res 2004; 13: 93-121

21. Kessler RC, Barber C, Beck A, et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). J Occup Environ Med 2003; 45: 156-74
22. Kessler RC, Ames M, Hymel PA, et al. Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. J Occup Environ Med 2004; 46: S23-37
23. Kessler RC, Heeringa S, Lakoma MD, et al. Individual and societal effects of mental disorders on earnings in the United States: results from the national comorbidity survey replication. Am J Psychiatry 2008 Jun; 165: 703-11
24. Buysse DJ, Angst J, Gamma A, et al. Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep 2008 Apr 1; 31: 473-80
25. Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999; 60 Suppl. 17: 28-31; discussion 46-8
26. Buckner JD, Bernert RA, Cromer KR, et al. Social anxiety and insomnia: the mediating role of depressive symptoms. Depress Anxiety 2008; 25: 124-30
27. Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 2004; 65 Suppl. 16: 27-32
28. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med 2003 Jul-Aug; 65: 528-33
29. Trivedi MH. The link between depression and physical symptoms. Prim Care Companion J Clin Psychiatry 2004; 6: 12-6
30. Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999 Oct 28; 341: 1329-35
31. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry 2003 Jan; 60: 39-47
32. Wise TN, Meyers AL, Desaiah D, et al. The significance of treating somatic symptoms on functional outcome improvement in patients with major depressive disorder: a post hoc analysis of 2 trials. Prim Care Companion J Clin Psychiatry 2008; 10: 270-5
33. Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. J Clin Exp Neuropsychol 1997 Aug; 19: 587-603
34. Jaeger J, Berns S, Uzelac S, et al. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res 2006 Nov 29; 145: 39-48
35. Jaeger J, Berns S, Czobor P. The multidimensional scale for independent functioning: a new instrument for measuring functional disability in psychiatric populations. Schizophren Bull 2003; 29: 153-68
36. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998 Nov; 4: 1241-3
37. Murray CJ, Lopez AD. Evidence-based health policy: lessons from the Global Burden of Disease Study. Science 1996 Nov 1; 274: 740-3
38. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997 May 24; 349: 1498-504
39. Greenberg PE, Stiglin LE, Finkelstein SN, et al. Depression: a neglected major illness. J Clin Psychiatry 1993 Nov; 54: 419-24
40. Rice DP, Miller LS. The economic burden of affective disorders. Adv Health Econ Health Serv Res 1993; 14: 37-53
41. Stoudemire A, Frank R, Hedemark N, et al. The economic burden of depression. Gen Hosp Psychiatry 1986 Nov; 8: 387-94
42. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003 Dec; 64 (12): 1465-75
43. Greenberg PE, Birnbaum HG. The economic burden of depression in the US: societal and patient perspectives. Expert Opin Pharmacother 2005 Mar; 6: 369-76
44. Kessler RC, Barber C, Birnbaum HG, et al. Depression in the workplace: effects on short-term disability. Health Aff (Millwood) 1999 Sep-Oct; 18: 163-71
45. Salkever DS, Shinogle JA, Goldman H. Return to work and claim duration for workers with long-term mental disabilities: impacts of mental health coverage, fringe benefits, and disability management. Ment Health Serv Res 2003 Sep; 5: 173-86
46. US Social Security Administration. SSI annual statistical report, 2007 [online]. Available from URL: http://www.ssa.gov/policy/docs/statcomps/ssi_asr/ [Accessed 2008 Oct 31]
47. Salkever DS, Goldman H, Purushothaman M, et al. Disability management, employee health and fringe benefits, and long-term-disability claims for mental disorders: an empirical exploration. Milbank Q 2000; 78: 79-113, iii
48. Davey-Rothwell MA, German D, Latkin CA. Residential transience and depression: does the relationship exist for men and women? J Urban Health 2008 Sep; 85: 707-16
49. Schanzer B, Dominguez B, Shrout PE, et al. Homelessness, health status, and health care use. Am J Public Health 2007 Mar; 97: 464-9
50. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1 (3): 385-401
51. Naismith SL, Longley WA, Scott EM, et al. Disability in major depression related to self-rated and objectively-measured cognitive deficits: a preliminary study. BMC Psychiatry 2007; 7: 32
52. Von Korff M, Ustun TB, Ormel J, et al. Self-report disability in an international primary care study of psychological illness. J Clin Epidemiol 1996 Mar; 49 (3): 297-303
53. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 30: 473-83
54. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003 May; 56: 395-407
55. Ware Jr JE. Conceptualization and measurement of health-related quality of life: comments on an evolving field. Arch Phys Med Rehabil 2003 Apr; 84 (4 Suppl. 2): S43-51
56. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale: the Social Adaptation Self-evaluation Scale. Eur Neuropsychopharmacol 1997 Apr; 7 Suppl. 1: S57-70; discussion S1-3

57. Bech P. Social functioning: should it become an endpoint in trials of antidepressants? CNS Drugs 2005; 19: 313-24
58. Wisniewski SR, Rush AJ, Bryan C, et al. Comparison of quality of life measures in a depressed population. J Nerv Ment Dis 2007 Mar; 195: 219-25
59. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993; 29: 321-6
60. Leon AC, Solomon DA, Mueller TI, et al. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. Psychol Med 1999 Jul; 29: 869-78
61. Katz MM, Klerman GL. Introduction: overview of the clinical studies program of the NIMH clinical research branch collaborative study on psychobiology of depression. Am J Psychiatry 1979; 136: 49-51
62. Diener E, Emmons RA, Larsen RJ, et al. The Satisfaction With Life Scale. J Pers Assess 1985 Feb; 49: 71-5
63. Shevlin M, Brunsden V, Miles JNV. Satisfaction With Life Scale: analysis of factorial invariance, mean structures and reliability. Personality Individ Diff 1998; 25: 911-6
64. Ware JE, Snow KK, Kosinski M, et al. SF-36 Health survey manual and interpretation guide. Boston (MA): New England Medical Center, The Health Institute, 1993
65. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992 Jun; 30: 473-83
66. Bosc M. Assessment of social functioning in depression. Compr Psychiatry 2000 Jan-Feb; 41: 63-9
67. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol 1997; 11 (4 Suppl.): S17-23
68. Weissman MM, Prusoff BA, Thompson WD, et al. Social adjustment by self-report in a community sample and in psychiatric outpatients. J Nerv Ment Dis 1978 May; 166: 317-26
69. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002 May; 180: 461-4
70. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993 Nov; 4: 353-65
71. Buysse DJ, Reynolds 3rd CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May; 28: 193-213
72. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001 Jul; 2: 297-307
73. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatr Res 1986 May; 18: 65-87
74. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996 May; 26: 477-86
75. Carlsson AM. Assessment of chronic pain: I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983 May; 16: 87-101
76. de C Williams AC, Davies HT, Chadury Y. Simple pain rating scales hide complex idiosyncratic meanings. Pain 2000 Apr; 85: 457-63
77. DeLoach LJ, Higgins MS, Caplan AB, et al. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998 Jan; 86: 102-6
78. Bowie CR, Twamley EW, Anderson H, et al. Self-assessment of functional status in schizophrenia. J Psychiatr Res 2007 Dec; 41: 1012-8
79. Khatri N, Romney DM, Pelletier G. Validity of self-reports about quality of life among patients with schizophrenia. Psychiatr Serv 2001 Apr; 52: 534-5
80. Crane MK, Bogner HR, Brown GK, et al. The link between depressive symptoms, negative cognitive bias and memory complaints in older adults. Aging Ment Health 2007 Nov; 11: 708-15
81. Popkin SJ, Gallagher D, Thompson LW, et al. Memory complaint and performance in normal and depressed older adults. Exp Aging Res 1982 Fall-Winter; 8: 141-5
82. Zeintl M, Kliegel M, Rast P, et al. Prospective memory complaints can be predicted by prospective memory performance in older adults. Dement Geriatr Cogn Disord 2006; 22: 209-15
83. Chandler JD, Gerndt J. Memory complaints and memory deficits in young and old psychiatric inpatients. J Geriatr Psychiatry Neurol 1988 Apr-Jun; 1: 84-8
84. Squire LR, Zouzounis JA. Self-ratings of memory dysfunction: different findings in depression and amnesia. J Clin Exp Neuropsychol 1988 Dec; 10: 727-38
85. Lemke MR, Puhl P, Broderick A. Motor activity and perception of sleep in depressed patients. J Psychiatr Res 1999 May-Jun; 33: 215-24
86. Matousek M, Cervena K, Zavesicka L, et al. Subjective and objective evaluation of alertness and sleep quality in depressed patients. BMC Psychiatry 2004; 4: 14
87. O'Boyle M, Amadeo M, Self D. Cognitive complaints in elderly depressed and pseudodemented patients. Psychol Aging 1990 Sep; 5: 467-8
88. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision. Washington, DC: American Psychiatric Press, 2000
89. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967 Dec; 6: 278-96
90. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979 Apr; 134: 382-9
91. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003 Sep 1; 54: 573-83
92. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004 Jan; 34: 73-82

93. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006 Jan; 163: 28-40
94. Corey-Lisle PK, Nash R, Stang P, et al. Response, partial response, and nonresponse in primary care treatment of depression. Arch Intern Med 2004 Jun 14; 164: 1197-204
95. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001; 62 Suppl. 16: 10-7
96. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 2000 Sep; 157: 1501-4
97. Solomon DA, Leon AC, Coryell W, et al. Predicting recovery from episodes of major depression. J Affect Disord 2008 Apr; 107: 285-91
98. Zimmerman M, Posternak MA, Chelminski I. Is it time to replace the Hamilton Depression Rating Scale as the primary outcome measure in treatment studies of depression? J Clin Psychopharmacol 2005 Apr; 25: 105-10
99. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials 2004 Feb; 25: 119-42
100. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry 2006 Sep; 163: 1519-30; quiz 665
101. Fava M, Thase ME, DeBattista C, et al. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry 2007 Jul-Sep; 19: 153-9
102. Fava M. Pharmacological approaches to the treatment of residual symptoms. J Psychopharmacol 2006 May; 20: 29-34
103. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. J Clin Psychiatry 2006 Nov; 67: 1754-9
104. Asnis GM, Chakraburtty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999 Oct; 60: 668-76
105. Fava M, McCall WV, Krystal A, et al. Eszopiclone coadministered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol Psychiatry 2006 Jun 1; 59: 1052-60
106. Becker PM, Sattar M. Treatment of sleep dysfunction and psychiatric disorders. Curr Treat Options Neurol 2009 Sep; 11 (5): 349-57
107. Gross PK, Nourse R, Wasser TE. Ramelteon for insomnia symptoms in a community sample of adults with generalized anxiety disorder: an open label study. J Clin Sleep Med 2009 Feb 15; 5 (1): 28-33
108. Papakostas GI, Petersen TJ, Burns AM, et al. Adjunctive atomoxetine for residual fatigue in major depressive disorder. J Psychiatr Res 2006 Jun; 40: 370-3
109. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005 Jan; 66: 85-93
110. Sultan A, Gaskell H, Derry S, et al. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurol 2008 Aug 1; 8: 29
111. Lavretsky H, Kim MD, Kumar A, et al. Combined treatment with methylphenidate and citalopram for accelerated response in the elderly: an open trial. J Clin Psychiatry 2003 Dec; 64: 1410-4
112. Lavretsky H, Park S, Siddarth P, et al. Methylphenidate-enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry 2006 Feb; 14: 181-5
113. Thase ME, Fava M, DeBattista C, et al. Modafinil augmentation of SSRI therapy in patients with major depressive disorder and excessive sleepiness and fatigue: a 12-week, open-label, extension study. CNS Spectr 2006 Feb; 11: 93-102
114. Holtzheimer 3rd PE, Meeks TW, Kelley ME, et al. A double blind, placebo-controlled pilot study of galantamine augmentation of antidepressant treatment in older adults with major depression. Int J Geriatr Psychiatry 2008 Jun; 23: 625-31
115. Pelton GH, Harper OL, Tabert MH, et al. Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study. Int J Geriatr Psychiatry 2008 Jul; 23: 670-6
116. Fioravanti M, Buckley AE. Citicoline (Cognizin) in the treatment of cognitive impairment. Clin Interv Aging 2006; 1: 247-51
117. Petkov VD, Stancheva SL, Tocuschieva L, et al. Changes in brain biogenic monoamines induced by the nootropic drugs adafenoxate and meclofenoxate and by citicholine (experiments on rats). Gen Pharmacol 1990; 21: 71-5
118. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. J Clin Psychopharmacol 2007 Oct; 27: 498-502
119. Fioravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Cochrane Database Syst Rev 2005 Apr 18; (2): CD000269
120. Spiers PA, Myers D, Hochanadel GS, et al. Citicoline improves verbal memory in aging. Arch Neurol 1996; 53: 441-8
121. Salvadorini F, Galeone F, Nicotera M, et al. Clinical evaluation of CDP-choline (Nicholin): efficacy as antidepressant treatment. Curr Ther Res Clin Exp 1975 Sep; 18: 513-20
122. Goldberg JF, Harrow M. Subjective life satisfaction and objective functional outcome in bipolar and unipolar mood disorders: a longitudinal analysis. J Affect Disord 2005 Dec; 89: 79-89
123. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989 Mar; 27: S217-32

Correspondence: Dr *Madhukar H. Trivedi*, Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9119, USA.
E-mail: madhukar.trivedi@utsouthwestern.edu