

## Review Article

# Assessment, Determinants and Treatment of Work Disability Due to Major Depressive Disorder

Enns MW\*

Department of Psychiatry, University of Manitoba, Canada

**\*Corresponding author:** Enns MW, Department of Psychiatry, University of Manitoba, Canada**Received:** February 20, 2017; **Accepted:** March 14, 2017; **Published:** March 22, 2017**Abstract**

Major Depressive Disorder (MDD) is a major cause of work disability worldwide. Despite this, clinical studies of MDD have generally emphasized symptomatic rather than functional outcomes. In more recent years there has been increasing research interest in work disability due to MDD. This narrative review addresses the measurement and determinants of work disability due to MDD and summarizes recent evidence of the effectiveness of medication and non-medication treatments on work disability (2011-2016). Many potentially appropriate measurement tools can be used to assess work disability, but there is no clear evidence of superiority of any specific measure. Disability due to MDD has multiple determinants including features of the depressive disorder, individual characteristics and workplace features. There is convincing evidence that both medication and psychological treatments for depression can be effective in alleviating work disability, but the comparative efficacy of different forms of treatment has not been established. Potentially promising future research directions include investigation of psychosocial treatments that explicitly address work disability and medication treatments that specifically address impairing symptoms that remain after standard treatment.

**Keywords:** Depression; Major depressive disorder; Disability; Work; Assessment; Treatment

**Abbreviations**

MDD: Major Depressive Disorder; ICF: International Classification of Functioning Disability and Health; GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Functioning Assessment Scale; SDS: Sheehan Disability Scale; WHODAS: World Health Organization Disability Assessment Schedule; HPQ: Health and Work Performance Questionnaire; E-WPS: Endicott Work Productivity Scale; WLQ: Work Limitations Questionnaire; SPS: Stanford Presenteeism Scale; WPAI: Work Productivity and Activity Impairment Scale; WSAS: Work and Social Adjustment Scale; LEAPS: Lam Employment Absence and Productivity Scale; STARD: Sequenced Treatment Alternatives to Relieve Depression; NEMESIS: Netherlands Mental Health Survey and Incidence Study; FSS: Fatigue Severity Scale; NCS: National Comorbidity Survey; WHO: World Health Organization; RCT: Randomized Controlled Trial

**Introduction**

Major Depressive Disorder (MDD) is associated with extensive productivity losses as a result of absenteeism and presenteeism (illness-related functional impairment while attending work). In the Global Burden of Disease Study 2010, MDD was responsible for 8.2% of global Years Lived with Disability (YLD) and 2.5% of Disability-Adjusted Life Years [1]. The World Health Organization Mental Health Surveys found that depression accounted for over 5% of the population illness-related productivity loss; subjects with depression had a yearly mean of 34.4 “days out of role,” which was largely invariant by country [2].

Despite the importance of work disability in MDD, there has been a strong tendency until recent years to assess outcomes of MDD in terms of symptom measures rather than directly assessing work disability. However, symptomatic outcomes of treatment do not necessarily directly correlate strongly with functional outcomes such as work disability [3]. When patients describe important features of remission, they do not tend to focus primarily on the presence of specific depression symptoms. Instead, patients emphasize positive mental health and a return to usual level of functioning [4].

Various measures of work disability have existed for decades but they have not been routinely incorporated into clinical practice and few clinical trials have made work disability a primary outcome. In the last several years there has been a surge in clinical and research reports focusing on work disability related to MDD.

The present literature review sought to answer the following questions:

1. Are there clinically useful and valid measures of disability in MDD?
2. What are the determinants of work disability in MDD?
3. What is the impact of treatment on work disability in MDD?

Relevant articles were identified with PubMed using following search terms: [work disability or work impairment or work function] and [depression, or depressive]. Articles from the past 5 years (2011-2016) were identified (N=944). English language publications including adult subjects with MDD were selected for inclusion. Key references from earlier reports were selectively included as identified

through reviews of bibliographies. Supplementary searches were conducted to characterize work disability measurement tools used in key investigations.

### Assessment of work disability

There are both general and work-specific measures of disability. These measures are highly varied and include self-report measures, observer ratings, single-item global summaries and multi-dimensional measures. Examples will be reviewed below.

The World Health Organization International Classification of Functioning, Disability and Health (ICF) [5] provides a detailed, specific and global listing of multiple categories of functioning, which can be recorded in an extensive checklist format. The ICF has a complex structure and yields detailed data but not readily usable summary scores. There has been a paucity of studies on the use of the ICF in psychiatry [6].

The simplest of the general functional measures is the Global Assessment of Functioning (GAF) scale [7]. While the use of a simple, single-item, 100-point observer rating is intuitively and practically valuable, the GAF scale confounds functional ratings with symptom ratings and risks of harm. A revision of the GAF, the Social and Occupational Functioning Assessment Scale (SOFAS), removes all reference to symptom type and severity and focuses on global functioning across a range of activities [8].

Another simple, general measure of disability is the Sheehan Disability Scale (SDS) [9]. The SDS consists of three self-report questions assessing function in the areas of work/school, social life and family/home. The domain scores are added together to yield an overall disability score; subscale scores (based on single items) are sometimes reported separately. The SDS has found favor as a measure of disability in clinical trials.

The World Health Organization Disability Assessment Schedule (WHODAS 2.0) [10] is available in the public domain and appears in DSM-5 [11]. The WHODAS 2.0 assesses functioning in 6 domains including cognition, mobility, self-care, getting along with other people, life-activities (including domestic, leisure, work and school) and participation. The WHODAS 2.0 can be administered by either self-report or interview methods and both a 36-item and 12-item are available, though the full 36-items are required to generate separate domain scores. WHODAS 2.0 respondents are instructed to complete the work section only if they are working or going to school (though such circumstances may arise either because one is disabled or various other reasons).

Work specific disability can be conceptualized and assessed by focusing on either absenteeism (measured continuously or dichotomously as sick leave, disability leave, disability pensioning etc.) or presenteeism (lost productivity while still in attendance at work, typically assessed using psychometric measures). The following paragraphs review some of the frequently used specific work disability measures. Comprehensive reviews on this subject are available elsewhere [12,13].

The World Health Organization Health and Work Performance Questionnaire (HPQ) [14] is an extensive and relatively time-consuming scale but is a robust assessment tool for work disability.

The item content captures detailed and specific information on the nature of an individual's work, their time at and away from work and their productivity while at work. The extensive nature of assessment makes this scale an unlikely choice for routine clinical practice.

The Endicott Work Productivity Scale, (E-WPS) [15] is a 25-item questionnaire that assesses work productivity. Although it is described as a brief scale, it is relatively long for a single dimension scale, making it a relatively more cumbersome measure for clinical practice or research studies incorporating multiple measures.

The Work Limitations Questionnaire, (WLQ) [16] is a 25-item measure measuring the degree to which health problems interfere with the ability to perform in a work-related role. It generates a single score based on the assessment of 4 domains related to meeting demands including time scheduling, physical, mental-interpersonal and output. This scale shares the same practical limitations as the E-WPS.

The Stanford Presenteeism Scale, (SPS) [17] is a brief scale evaluating the impact of health problems on performance and productivity while at work. It has 6 items that generate a total score plus two factor scores related to completing work and avoiding distractions. The total score reflects ability to concentrate and accomplish work-related tasks, despite health problems.

The Work Productivity and Activity Impairment scale, (WPAI) [18] scale uses six items to assess work absences, productivity while working and ability to do other regular daily activities. The scale is intended to be applicable to various different disabling conditions.

The Work and Social Adjustment Scale, (WSAS) [19] consists of five items covering multiple domains of functioning including work, home management, and social and private leisure activities and interpersonal. Only one item of the WSAS is work-specific and being away from work is not differentiated from presenteeism.

The Lam Employment Absence and Productivity Scale (LEAPS) [20] is an 11-item rating scale designed to assess work functioning in a depressed population. It consists of four items that capture occupation, hours of work and hours missed from work followed by 7 Likert-rated items to assess productivity and troublesome symptoms (low energy, cognitive problems, anxiety/irritability, trouble getting along) which are totaled to yield an overall score. The symptoms included in the scale capture typical problems of depressed subjects, which may be a significant advantage for assessment in MDD, but it may reduce ability to compare between subjects with differing diagnoses.

There is considerable variability among disability measures in the domains of assessment, the emphasis on absenteeism versus presenteeism, the length of the scale and the relative specificity to assessment of subjects with depression. In light of this, it is difficult to make comparisons across studies using different measures. A recent review stated that the available evidence on measurement properties of such scales is based predominantly on studies of modest methodological quality and concluded that there was no clear evidence-based recommendation for which scale to prioritize for health-related work functioning [12]. Any of the validated scales with an explicit focus on occupational functioning may be a reasonable

choice until clearer psychometric and comparative evidence is available [12,13].

### Determinants of work disability

A broad range of factors may determine the nature and extent of work disability in individuals with MDD. The following paragraphs will emphasize the studies that have an explicit focus on work disability but will draw upon studies focusing on function as well, recognizing that there may be only partial concordance between the determinants of general functional status and work disability.

**Features of depressive illness and work disability:** Depression severity is one of the best established correlates of work disability in MDD [21-24]. The relationship of functional improvement with symptomatic improvement during treatment appears to be complex. A large study from STAR\*D found that reductions in symptoms during an initial medication trial were associated with improved work productivity (WPAI), but this finding did not hold true for treatment in the second step of treatment; even when patients were treated to the point of symptomatic remission at this stage, occupational impairment remained [24]. This could represent an aspect of treatment resistance or it may reflect a lag between symptomatic improvement and functional improvement. Duration of depressive symptoms has been associated with work disability due to depression [22,23,25-28]. A study of 558 depressed patients in primary care found that functional disability was particularly high among those with chronic major depression [26]. A five-year prospective study of patients with MDD found that the proportion of time spent depressed was a robust predictor of being granted pension [22,25]. The duration of untreated depression has been found to predict persistent occupational disability [27,29]. Chronic forms of depression showed slower and less complete recovery of function in the NEMESIS study [28]. Recurrent depression is also predictive of non-recovery of work productivity [24] and longer time to return-to-work among those receiving disability benefits [30].

The concept of remission, as opposed to “treatment response,” in MDD has emerged as a potentially more relevant measure of outcome in clinical trials. Making remission from an episode of depression the goal of treatment is intuitively reasonable. However, it should be noted that “remission” of MDD has routinely been assessed in clinical trials using a cutoff score on the same instruments used to measure response of depression symptoms—typically HAM-D score less than 7 or MADRS score less than 10 [31]. As such, patients meeting criteria for remission may have multiple persisting mild symptoms or a few more substantial symptoms of depression. Remission of MDD generally results in functional improvement but even remitted MDD may be associated with impairment due to residual symptoms such as fatigue, sleep problems and cognitive dysfunction [32-35]. A large MDD clinical trial (N=679) compared outcomes of patients who remitted, responded without remission and did not respond [36]. Patients who remitted showed significantly greater improvement in SDS and SDS-work scores compared to those who responded without remission or did not respond. In the STAR\*D trial (N=1928) patients who did not initially respond to treatment, but achieved remission in the second stage of medication treatment, showed no significant association between symptomatic improvement and reduction of work impairment [24].

Comorbidity of mental disorder diagnoses is common rather than an exception in MDD and is associated with greater general impairment, increased severity and reduced treatment responsiveness [37-40]. Comorbidity also predicts role disability [41], long-term disability and absenteeism [42] and recurrence of depression-related work disability [43]. Co-occurrence of depression with a wide range of chronic physical illnesses has also been shown to increase both general role impairment and work-related disability [22,42-51].

Early age of onset of depression has been associated with frequent comorbidity, longer episode duration and greater functional impairment [52-54]. A report from the STAR\*D study found that early age-of-onset (<18 years of age) was associated with absenteeism in outpatients with depression [24] and an Asian study of depressed outpatients found an association between early age-of-onset (<30 years of age) and limited social function [54].

A number of research reports have focused on the disability implications of one or more specific depression symptoms. The measurement of depressive symptom domains has varied significantly and the item content did not always reflect what the terminology suggests. For example, depressed mood has been found to predict future disability [42] but in this study “depressed mood” refers to scores on the self-report Inventory of Depressive Symptomatology. The “Diagnostic Apathia Scale” which aims to measure apathy, has been shown to predict impaired functioning [55]. This scale is inclusive of item content from several instruments incorporating symptoms of impaired concentration, memory complaints, indecisiveness, lassitude, tiredness, fatigue, insomnia and reduced ability to work. Lack of motivation has been associated with functional impairment [56] but the measurement of motivation included three items of the Hamilton Depression scale, (work and activities, psychomotor retardation and energy), each of which only indirectly measures motivation.

The Fatigue Severity Scale (FSS) [57] has been found to correlate with global, work and family/home disability as assessed with the SDS in patients with MDD [58]. Fatigue had a negative impact on functional outcomes of sequential treatments for depression in the STAR\*D trial; self-reported fatigue at baseline and failure of fatigue to improve during treatment were associated with worse functional impairment and reduced mental and physical function [59]. A post-hoc analysis of a large (N=429) clinical trial dataset evaluated fatigue as a mediator of the effect of levomilnacipran on function in MDD [60]. Change in motivation and energy accounted for 67% of the treatment effect and was a stronger mediator of treatment effects than depression symptom severity. Insomnia is another common and frequently distressing symptom in MDD. In the NCS Replication, various forms of sleep disturbance were frequently comorbid with MDD and contributed significantly to role impairment even when controlling for the effects of comorbid mental disorders [46]. A large study (N=1206) of subjects on long-term disability found a high level of co-occurrence of sleep disturbance, depression and pain and a prominent effect of sleep disturbance on functional ability in multiple domains [61]. The occurrence of anxiety symptoms in depressed patients has also been associated with functional disability [23] and loss of work productivity [24].

MDD-related cognitive problems include both subjective reports



of cognitive difficulties and objectively measured deficits in attention, memory, psychomotor speed and executive function [62]. Examples of instruments designed to quantify subjective cognitive complaints include the perceived deficits questionnaire [63,64] and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire [65,66]. Reviews of the objective neuropsychological measures used in studies of depressed subjects are available in a number of recent publications [67-69]. Cognitive deficits in MDD can be substantial in magnitude, are detectable by the first recorded MDD episode and may persist even when depression is in remission [68,70].

Cognitive deficits in MDD are associated with functional impairment [71]. Objective and subjective cognitive complaints generally show a modest correlation, but both have functional impact [72,73]. In a study of 48 hospitalized patients with MDD, neurocognitive performance was strongly associated with functionality ratings after controlling for residual depression symptoms and several neurocognitive domains tested at baseline were predictive of functionality at 6 months [74]. A cross-sectional epidemiological study found a strong association between depression and role functioning (path coefficient 0.43); self-reported cognitive problems were significant mediators (path coefficient 0.27) of the relationship between depression and work loss [75]. A study of 312 outpatients undergoing standardized medication treatment showed that patients with more severe perceived cognitive dysfunction had worse work-related productivity irrespective of depression severity [76].

Only a few studies of work disability in depression directly compared the impact of multiple individual depressive symptoms simultaneously. A study of 164 patients with MDD found that fatigue, insomnia, cognitive problems and anxiety were perceived to cause the most interference with work [77]. In STAR\*D, the four depressive symptoms most strongly correlated with work impairment (WSAS) were (in order of effect): impaired concentration, depressed mood, fatigue and initial insomnia. It was noted that different functional domains had different symptomatic determinants; for example, impairment in social activities was most strongly determined by loss of interests, depressed mood and impaired concentration [78]. A Canadian study compared employed and disabled patients with depression using the 17-item Hamilton Depression rating scale. They found that multiple symptoms were significantly more severe in the disabled group of patients, but in multivariate analysis, the only depressive symptom to discriminate between employed and disabled groups was loss of interests [79].

**Individual characteristics:** Personality factors exert a significant influence on the presentation, course and outcome of major depression [80]. A large (N=2770) epidemiological study in Norway found that any DSM-IV personality disorder was strongly associated with disability pensioning (OR=4.69), regardless of the primary disability diagnosis [81]. Another longitudinal study of 269 patients with DSM-III-R personality disorder found that a diagnosis of any personality disorder was predictive of overall functioning (SOFAS) 18 months later [23]. A cross sectional study of 161 patients with MDD found that low conscientiousness scores were associated with lower work productivity (WPS) [82]. Neuroticism has been found

to longitudinally predict worse social functioning in depressive disorders [23,28]. Introversion was also found to predict disability pension in MDD patients during 5 years of follow-up [25].

Several demographic factors have been associated with depression-related work disability. Older workers are more likely to be granted a disability pension [25,44,51] and are likely to take longer to return-to-work once granted short-term disability [30]. Age appears to be a robust predictor of disability pension; age above 50 showed an odds ratio for receiving a disability pension of 6.25 in a group of Finnish depressed patients [25]. Although increasing age is prone to confounding with the occurrence of other health conditions, the cited studies all considered concurrent medical illness in multivariate analyses. The impact of gender on disability has not been clearly established. One large Canadian study (N=10508 disability claimants with depression) found that compared to men, women were likely to take longer to return-to-work once granted short-term disability [30]. A large international study (N=1142 people with depression) found that woman had a lower probability of working with depressive illness [51]. However, many studies did not replicate these findings [25,44,83]. Differing social and familial contexts, role assignments and interpersonal issues are likely to impact on the relationship between gender and work disability.

Socio-economic status is an important determinant of work disability. Depressed individuals with higher pre-disability income are relatively protected against disability. A WHO study conducted in 29 countries found a gradient of progressively lower likelihood of work disability in depressed subjects across five income quintiles; in the highest income quintile 70.9% of individuals were working whereas in the lowest income quintile 32.5% were working [51]. A large Canadian study found that each incremental salary step of \$1000 per week showed a reduced time to closure of short-term disability claims (hazard ratio 0.872) [30]. Higher educational attainment also appears to be protective against work disability. Depressed patients (N=269) with specific vocational education were less likely to receive disability pension during five years of prospective follow up [25]. A low level of basic education showed a strong association with disability pension in people with common mental disorders including depression (odds ratio 2.67) [44]. A WHO study found a significantly higher level of education (average 12.5 years) in depressed patients who were working versus those who were not working due to illness (average 10.1 years) [51]. White-collar workers who were receiving disability income returned to work more quickly in comparison to blue-collar workers (hazard ratio 0.848) [30]. A Finnish registry study found that high socio-economic position was associated with lower onset of depression-related work disability, faster return to work and lower rates of recurrence [84]. These relationships are likely to be causally complex, implicating the pre-employment experiences, values and characteristics of workers, incentives for employment and the nature of work experiences.

Depression occurring consequent to childhood maltreatment may be more severe, persistent and treatment resistant [85-87]. Childhood maltreatment has also been associated with disability in MDD. In 91 outpatients in an internal medicine setting, disability leave for psychiatric illness was associated with a childhood history of trauma and the percentage of one's life spent on disability was

**Table 1:** Work function and disability outcomes in medication trials for MDD (2012-2016).

Ref	Study Population	Duration	Treatment Group	Comparison Group	Functional Measure	Main Findings	Additional Notes
<b>Acute Studies</b>							
98	6270 adult outpatients with MDD in general practice	12 wks	FP selected antidepressant medication (SSRI/SNRI)	N/A	SDS-W	89.8% response; 56.8% remission; -3.9 point change	Response: 1 point change in SDS-W Remission: SDS-W $\leq$ 2
24	1928 employed outpatients with MDD	8 wks	Citalopram 20-40 mg	N/A	WPAI	Baseline: 56% missed $\geq$ 1 hr; 22% missed > 10 hrs; 22% no presenteeism Endpoint: 46% missed $\geq$ 1 hr; 15% missed > 10 hrs; 37% no presenteeism	STAR*D trial
99	131 patients with severe MDD	6 wks	Fluoxetine 20 mg	N/A	WSAS	WSAS effect size = 0.77 (pre vs post). Baseline score = 23.8 6 wk score = 16.7	Effect size on the HamD was much larger = 2.4
100	36 employed adult outpatients with MDD	8 wks	Desvenlafaxine 50-100 mg	N/A	LEAPS HPQ SDS	Effect sizes (d) pre/post: LEAPS 1.35; HPQ 0.89; SDS 1.45	Patients who had significant improvement on neurocognitive measures had significantly greater improvement in work functioning
101	331 employed patients with chronic MDD	12 wk acute phase	Antidepressant combinations a) bupropion plus escitalopram b) mirtazapine plus venlafaxine c) escitalopram	N/A	WPAI	Baseline vs Week 12: - % Missing $\geq$ 1 hour 40% vs 14.1%; - % with $\geq$ 20 hours impairment 23.1% vs 6.8%; - absenteeism 12.34 vs 4.17 hours; - presenteeism 40.4 vs 19.8 hours; - overall impairment 44.9 vs 21.0 hours	These are combined results for the three treatment groups. All work productivity changes remained significant after controlling for depression symptom changes
102	41 outpatients with MDD	8 wks	Bupropion XL 150-300 mg n=19	Escitalopram 10-20 mg n=19	SDS-W E-WPS total	Bupropion SDS-W = -2.6; E-WPS = -16.7; Escitalopram SDS-W = -1.5; E-WPS = -3.6; Difference between groups NS	Verbal memory and fatigue improvement explained SDS improvement. Underpowered study
103	501 in- and outpatients (inadequate responders to SSRI/SNRI)	12 wks	Vortioxetine 10-20 mg n=252	Agomelatine 25-50 mg n=241	SDS-W; WLQ - Global productivity	Vortioxetine SDS-W = -2.95** WLQ = -0.06* Agomelatine SDS-W = -2.25** WLQ = -0.04* Vortioxetine superior ** p < 0.01* p < 0.05	Vortioxetine was also superior on the main symptom outcome (MADRS)
104	2496 adults with MDD in RCTs	7-13 wks	Duloxetine 60-120 mg n=1424	Placebo n=1072	SDS	Remission: 39.5% vs. 28.7%; Change scores -8.8 vs -6.3	Pooled analysis of 6 RCTs No drug - placebo difference at 24 wks; Remission defined as SDS $\leq$ 6
105, 106	310 employed outpatients with MDD	12 wks	Desvenlafaxine 50 mg n=208	Placebo n=102	WPAI SDS-W	Time missed (%)= NS; Presenteeism (%)= -7.4 p=0.02; Activity impairment (%) = - 6.5 p=0.03; SDS-W= -0.8 p=0.07	Used modified ITT sample with HamD $\geq$ 20
107	2598 patients with MDD	8-10 wks	Levomilnacipran ER 40-120 mg n=1566	Placebo n=1032	SDS-W	Levomilnacipran ER vs placebo: Moderate/Extreme to Mild/None 55% vs 40% Marked/Extreme to Mild/None 47% vs 33%	Pooled analysis of 5 RCTs using categorical change; Marked/extreme = 7-10 on SDS-W; Moderate/extreme impairment = 4-10 on SDS-W; Mild/none impairment = 0-3 on SDS-W
108	2193 patients with MDD	8-12 wks	Duloxetine 40-120 mg n=1029	Placebo n=329 SSRI n=835	SDS-W	Odds ratios for remission: DLX vs PBO = 1.79; SSRI vs PBO = 1.52; DLX vs SSRI =NS	Pooled analysis from 4 RCTs; High baseline SDS score predicted lower probabilities of improvement. SDS-W $\leq$ 2 = remission
60	429 adults with MDD	8 wks	Levomilnacipran 40-120 mg n=215	Placebo n=214	SDS-W;	Effect size SDS-W = 0.35	Improvement in motivation/energy mediated the effect of levomilnacipran on SDS scores
109	7031 patients with MDD	8-12 wks	Newer antidepressants (various) n=4722	Placebo n=2309	SDS-W	Effect size (SMD): 0.28 (CI: 0.23-0.33) Favoring antidepressant. Mean difference: 0.73 (0.60-0.86)	Meta-analysis of RCTs of newer antidepressants. 17 placebo-controlled trials used SDS and reported SDS-W

Longitudinal Studies							
35	3278 outpatients with depression and anxiety	48 wks	Escitalopram 5-20 mg (co-treatments permitted)	N/A	Able to work full-time (% of subjects). Complete sick leave (% of subjects)	Percentage able to work: Baseline 36.7% Wk 8 44.2% Wk 24 61.2% Wk 48 62.2% Percentage on complete sick leave: Baseline 35.9% Wk 8 26.1% Wk 24 11.9% Wk 48 8.8%	The most common symptom at study endpoint was lack of energy/motivation (23.5%)
110	1549 patients with MDD	6 months	Duloxetine 60 mg	SSRI (Various)	SDS-W	Duloxetine: Baseline 5.33 Post 0.75 SSRI: Baseline 5.54 Post 1.74 Effect size (difference) = -0.62 (favours Duloxetine)	The effect size favouring Duloxetine was larger in patients with pain complaints (-0.85)
111	548 responders to acute treatment with desvenlafaxine	11 months	Desvenlafaxine 50 mg n=272	Placebo n=276	WPAI	Desvenlafaxine vs placebo: Time missed (%) = -0.33 (NS); Presenteeism (%) = -8.2 (p=0.013); Activity impairment (%) = -7.6 (p< 0.001); Differences all favor desvenlafaxine	Maintenance treatment design

Acute studies = 14 weeks or less; Longitudinal studies = longer than 14 weeks  
MDD: Major Depressive Disorder; SSRI: Serotonin Reuptake Inhibitor; SNRI: Serotonin and Noradrenalin Reuptake Inhibitor; SDS-W: Sheehan Disability Scale Work item; WPAI: Work Productivity and Impairment scale; STAR\*D: Sequenced Treatment Alternatives to Relieve Depression; ITT: Intent to Treat; E-WPS: Endicott Work Productivity Scale; WLQ: Work Limitations Questionnaire; MADRS: Montgomery-Asberg Depression Rating Scale; HamD: Hamilton Depression Rating Scale; WSAS: Work and Social Adjustment Scale; LEAPS: Lam Employment Absence and Productivity Scale; HPQ: Health and Work Performance Questionnaire

significantly related to physical and emotional abuse [88]. In the National Comorbidity Survey Replication, childhood adversities were significant predictors of increased days out of role associated with depression. Increasing number of adversities was associated with incremental functional impairment [89]. Finally, a Canadian study found that MDD patients on disability in comparison to employed MDD patients reported a higher frequency of childhood physical or sexual abuse (29.1% vs 17.6%) [79].

Social support is an established protective factor which moderates the impact of stresses, reduces the likelihood of onset of MDD and improves the prognosis of depressive episodes [90,91]. Low social support was strongly associated with disability status at 6 months and 18 months of follow-up in a cohort of Finnish depressed patients [23]. Low social support was also associated with an increased likelihood of being disability pensioned at 5-year follow-up [25]. Marital status has not been consistently associated with disability outcomes in depression, probably because of its complex relationship with social support and the socioeconomic implications of single versus dual incomes and familial/household roles [23,25,51].

**Features of work and the workplace:** The impact of the workplace on depression-related disability is a complex issue as there are many different work types, non-random selection of workers, differences between individuals in how they perceive their workplace and impacts of depressive symptoms on perceptions about the workplace. Employees taking sick leave due to depression perceive that there are multiple complex factors involved [92]. These factors include the nature of the work, organizational climate, over-commitment, supervisor behaviors, relationships with others, mismatch between the individual and their work, the impact of experiencing depression symptoms while working and other factors such as complaints, negative evaluations and perceived injustice at work. A Delphi study

conducted with physicians experienced in disability assessment and scientists in the field of work and mental health identified several major predictors of sick absences due to depression [80]. The consensus among experts suggested the following major workplace factors: high-demand/low-control, stressful work events, effort-reward imbalance, lack of decision latitude, high psychological work demands. The factors identified by experts substantially overlap with those identified by depressed workers, though experts tend to group interactive factors together (e.g. high-demand/low-control; effort-reward imbalance).

Several empirical studies have examined individual workplace factors and found evidence of significant impact. Job strain, which may be best, understood as a combination of high demands and low control [93] was a predictor of future disability pension in the Finnish Health 2000 Study with an odds ratio of 1.78 for high job strain in a model controlling for depression and comorbidity of common mental disorders [44]. In the STAR\*D trial, it was observed that depressed patients with no employment insurance missed less work at baseline than those with insurance [24]. A Canadian study found that differing types of disability funding policies can also affect the time to closure of STD claims [30]. It is probable that specific occupations are associated with a higher likelihood of work disability, but it is not clear to what degree such observations result from pre-employment characteristics of those who chose the occupation versus particular experiences related to that occupation [94].

**Impact of treatment on work disability due to depression**

A recent Cochrane “Intervention Review” found mixed evidence for psychological interventions and no evidence of a difference in effect on sickness absence of one antidepressant medication compared to another [95]. Depression clinical trials frequently focus on acute

treatment effects over an interval of 6-12 weeks, but improvement in functional ability is often noted to lag significantly behind symptomatic improvement [96,97]. Longitudinal assessments over at least 3-6 months may be necessary to detect meaningful functional improvement [13]. There are many determinants of work disability other than depression symptoms including individual, illness and workplace-related variables suggesting a complex relationship between symptoms and ability to function at work. While decreases in depression severity with treatment are generally associated with reductions in disability, this association appears to be stronger for younger workers (older workers do not experience as much functional improvement with symptomatic improvement) and those with least moderately stressful work experience more functional improvement with depression symptom reduction [83].

Recent findings (2011-2016) on the effect of pharmacological treatments on work-related disability are summarized in (Table 1) [24,35,60,98-111]. There is replicated evidence that pharmacological treatments for depression have positive effects on work functioning. There is a high degree of variability in study design including treatment group assignments, study duration and the manner of reporting work-functioning measures. Studies that report an effect size based on pre-to post-treatment change suggest large effect sizes while studies using a placebo control condition indicate much more modest effect sizes. The most commonly used measure of work function in clinical trials has been the SDS-work item. Accumulated data from multiple clinical trials using this measure permitted a meta-analysis (N=7031 from 17 RCTs) [109]. However, the clinical trials using this measure did not generally incorporate inclusion criteria relating to employment status. The Evans meta-analysis found an effect size on the SDS-W (versus placebo) of  $d=0.28$ , which is only slightly smaller than the effect sizes estimated for antidepressant medications in reducing depression symptoms [109]. Recent studies have evaluated whether cognitive improvement during treatment for MDD mediates positive change in functional outcome. A randomized controlled trial of escitalopram versus bupropion in 41 outpatients with MDD found that both medications significantly improved verbal and non-verbal memory, as well as global function (SDS) and work productivity (E-WPS) [102] a strong association was observed between improvement in immediate verbal memory and improved global function (SDS total) which was independent of the effects on general depression symptoms. A small open-label study (N=36 employed adult outpatients with MDD) of desvenlafaxine examined the relationship among depressive symptoms, cognitive function and work functioning outcomes [100]. Significant improvements were seen in depression symptoms, cognition and work function over the course of 8 weeks. Subjects who demonstrated significant improvement (+1 S.D.) in cognitive function showed significantly more improvement in work functioning, even when controlling for overall symptomatic change.

The role of benzodiazepines in functional recovery also merits consideration. Anxiety is common in MDD and benzodiazepines are an evidence-based treatment for several anxiety disorders [112]. However, a large study of depression and employment status found that the use of benzodiazepines was associated with unemployment in depressed patients [79] and a study of depressed patients receiving ECT found that benzodiazepine use was a negative predictor of

return-to-work in the year following ECT [27]. While these findings may reflect the impact of concurrent anxiety, it is reasonable to hypothesize that benzodiazepines may also interfere with return to work given their known effects on cognition [113].

Recent findings (2011-2016) on the effect of non-pharmacological treatments on work disability are summarized in (Table 2) [30,114-121]. Like the pharmacological studies, there is a high degree of variability in study design and outcome measure selection. There are multiple different psychosocial treatments with potential efficacy in reducing work disability and little evidence to suggest a preferred psychosocial treatment approach. Effect sizes are highly variable but studies with active control conditions suggest modest sized effects. The strongest accumulated evidence is for collaborative care [120]. A meta-analytic study reported a standard-mean-difference of 0.23 for short-term collaborative care. However, collaborative care has a broad definition that focuses on an interdisciplinary approach in a primary care setting and does not stipulate a specific psychosocial treatment modality. Treatment approaches that are specific to work such as "Work Focused Cognitive Behavioral Therapy" [119], "Behavior Activation Therapy-Work" [115] or "Cognitive Work Hardening" [122] may be particularly appropriate interventions, but there is currently inadequate evidence to support this conclusion.

## Conclusion

Depression-related work disability is a major clinical and public health challenge due to the high prevalence of major depressive disorder and the substantial functional impairment caused by episodes of MDD. Research in the area of MDD has increasingly incorporated multi-modality assessment including one or more measures to evaluate functioning. Although there is agreement about the importance and utility of formally assessing functional outcomes, there is no agreement as to how that should be achieved. Multiple different assessment instruments have been developed to assess function, but the optimal measurement tools for assessment in various clinical and research contexts have not been determined. Because of the fundamental importance to patients, families, employers, disability insurers and the public at large, work function requires a dedicated assessment approach. Despite the lack of agreement on the optimal assessment approach, it may nevertheless be appropriate to incorporate one of several readily available measures of functioning into clinical practice.

There are many potential determinants of work disability in MDD including features of the depressive illness, individual characteristics and the workplace environment. The features of depressive illness for which there is strong evidence of impact on work function include depression severity, comorbidity, response and remission of illness, residual symptoms and some specific symptoms, notably fatigue, cognitive problems and insomnia. There are a number of individual characteristics that predict work disability (notably age, socio-economic status and history of childhood maltreatment). Features of the work environment may also be important determinants of disability but this area has been relatively under-studied. Job strain (high demands, low control) and the availability and features of disability compensation appear to impact on disability. It is likely that there are complex interactions among work types, individual differences and depressive features leading to work disability, but



**Table 2:** Work function and disability outcomes in non-pharmacologic treatment trials for MDD (2012-2016).

Ref	Study Population	Duration	Treatment Group	Comparison Group	Functional Measure	Main Findings	Additional Notes
<b>Acute Studies</b>							
114	523 patients with recurrent MDD	12-14 wks	Cognitive therapy 16-20 sessions	N/A	Composite of SAS and RIFT Scales	Effect size for functional measure $d=1.25$ (pre to post treatment)	- Improvement in functioning predicted improvements in symptoms during the course of treatment. - Function improved more slowly and less overall than symptoms
115	Patients with chronic depression, medication responsive but still unemployed N=16	12 wks	Behavior activation therapy-work	N/A	Hours of work; Hours of paid work; Work productivity	Effect Sizes (pre-post) Hours of work $d=0.83$ ; Hours paid work $d=0.54$ ; Work productivity $d=.48$	Treatment involved activity scheduling, problem solving, activity monitoring, skills training and relaxation training Small to medium sized effects were significant despite active treatment in both groups
116	Employed patients with MDD	12 wks	Escitalopram plus telephone administered CBT N=48	Escitalopram plus telephone adherence reminders N=51	SDS-W LEAPS HPQ (overall)	Effect Sizes: SDS-W $d=0.20$ (NS); LEAPS $d=0.49$ ; HPQ $d=0.48$	Small to medium sized effects were significant despite active treatment in both groups
<b>Longitudinal Studies</b>							
30	Disability claimants with MDD: LTD – 10,338 STD – 10,508	Maximum 2.5 years	Psychotherapy (broadly defined)	No psychotherapy	Time to STD closure; Time to LTD closure	Receipt of psychotherapy was associated with: longer time to STD closure HR=0.81 & shorter time to LTD closure HR=1.42	- Non randomized design - Non standardized psychotherapy - Secondary analysis of claims data from a disability insurer
117	2796 primary-care outpatients with depression & anxiety disorders	12 mo	Stepped care: psychoeducation, interpersonal psychotherapy, psychiatric consultation and antidepressant (led by lay-health-workers) N=1360 Public and private facilities	Treatment as usual N=1436	Change in total disability days	Public facilities: - 4.77 days, $p=.06$ favoring intervention; Private facilities: +0.34 days, NS	Clients of private facilities may have had better access to more options in TAU condition
118	Psychiatric outpatients with depression N=120	6 mos	"Body-mind- Spirit intervention" N=56	Treatment as usual N=64	WSAS	Effect size: partial-eta-squared = 0.169	Nursing-administered holistic intervention
119	Patients on sick leave or at risk of sick leave due to depression or anxiety N=1193	12 mos	Work-focused CBT N=630	Treatment as usual N=563	Proportion increasing or maintaining work participation at follow-up	W-CBT 44.2%; TAU 37.2%; $p=0.015$	The strongest benefits were for those already on LTD
120	Meta-analysis of 15 clinical trials N = 4754	6-12 mos	Collaborative Care (N varied by analysis)	Usual care or enhanced usual care	"Participative Social Function" from: SF-36 or SF-12 MOS-20 SDS WSAS WHODAS (Standardized to effect sizes)	Short term ( $\leq 6$ mos) effect size SMD=0.23; Longer term ( $\geq 7$ mos) effect size SMD=0.19	Collaborative Care was delivered in community or primary care settings
121	168 employees off work due to depression and anxiety disorders	12 mos	Work-focused CBT (W-CBT) N=89	Traditional CBT N=79	Median duration until Full-RTW; Partial-RTW	Full RTW occurred 65 days earlier with W-CBT. Partial RTW occurred 12 days earlier with W-CBT. $p < .05$	W-CBT incorporated special attention to graded exposure in the workplace

Acute studies = 14 weeks or less; Longitudinal studies = longer than 14 weeks

MDD: Major Depressive Disorder; SAS: Social Adjustment Scale (self-report); RIFT: Range of Impaired Functioning Scale; CBT: Cognitive Behavior Therapy; LTD: Long Term Disability; STD: Short Term Disability; SDS-W: Sheehan Disability Scale Work item; LEAPS: Lam Employment Absence and Productivity Scale; HPQ: Health and Work Performance Questionnaire; WSAS: Work and Social Adjustment Scale; TAU: Treatment as Usual; SF-36/12: Medical Outcomes Study Short Form; MOS-20: Medical Outcomes Study; WHODAS: World Health Organization Disability Assessment Schedule; SMD: Standardized Mean Difference

research elucidating the nature of these complex relationships is lacking.

Many investigations of the impact of treatment of MDD on work disability have been reported over the past five years. Available



evidence is sufficient to conclude that antidepressant medications and a variety of psychosocial treatments for depression have a significant positive impact on work disability, but persisting work disability remains a common outcome of depression treatment. Residual symptoms after treatment are a significant factor in persisting work disability. Meta-analytic evidence of the effectiveness of medication treatment is convincing (modest effect size), but differential effects of specific medication treatments have not been confirmed. Most studies on psychosocial treatments are un-replicated and the comparative efficacy of different psychosocial treatments on work disability is unknown. Some specific symptom domains have been shown to mediate the impact of effective treatment on work-disability, notably cognitive deficits and energy/motivation.

Promising future directions include psychosocial treatments that explicitly and directly address work function and pharmacotherapy approaches tailored to address the specific symptom domains that remain after standard treatment.

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