Patient-reported functioning in major depressive disorder

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Abstract

Objectives: Compared with the general population, patients with major depressive disorder (MDD) report substantial deficits in their functioning that often go beyond the clinical resolution of depressive symptoms. This study examines the impact of MDD and its treatment on functioning.

Methods: From the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, we analyzed complete data of 2280 adult outpatients with MDD at entry and exit points of each level of antidepressant treatment and again 12 months post treatment. Functioning was measured using the Work and Social Adjustment Scale (WSAS).

Results: The results show that only 7% of patients with MDD reported within-normal functioning before treatment. The proportion of patients achieving within-normal functioning (WSAS) scores significantly increased after treatment. However, the majority of patients (>60%) were still in the abnormal range on functioning at exit. Although remitted patients had greater improvements compared with nonremitters, a moderate proportion of remitted patients continued to experience ongoing deficits in functioning after treatment (20–40%). Follow-up data show that the proportions of patients experiencing normal scores for functioning after 12 months significantly decreased from the end of treatment to the follow-up phase, from 60.1% to 49% ($p < 0.0001$), a finding that was particularly significant in nonremitters. Limitations of this study include the reliance on self-report of functioning and the lack of information on patients who dropped out.

Conclusion: This study points to the importance of functional outcomes of MDD treatment as well as the need to develop personalized interventions to improve functioning in MDD.

Keywords: functional outcomes, functioning, major depressive disorder, Sequenced Treatment Alternatives to Relieve Depression trial

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Introduction

Functioning refers to one's ability to work, form and maintain relationships, and engage in leisure and other life activities, and can be rated by others or through self-reporting [Ustün and Kennedy, 2009]. In short, functioning describes a person's everyday performance. Compared with the general population, patients with major depressive disorder (MDD) report substantial deficits in their functioning [Lin *et al.* 2014b; Trivedi *et al.* 2013]. Some studies even documented that the severity of functional impairments associated with depression are comparable to or even worse than those associated with other major medical problems [Hays *et al.* 1995]. Functional impairment often overlaps with depressive symptom severity [Greer *et al.* 2010]. Importantly, these deficiencies in functioning seem to continue even after symptom resolution [Trivedi *et al.* 2013; Hirschfeld, 2002; Kennedy *et al.* 2007], leading to increased frequency of relapse and increasing cost of care [McKnight, 2009]. Moreover, symptom severity in MDD seems to explain a small proportion of variance in functioning impairment [Romera *et al.* 2013]. Functioning significantly improves with remission [Trivedi *et al.* 2009], especially with specific remission criteria of complete remission of symptoms, absence of residual

symptoms, maintenance of remission, quality of remission and early remission [Romera *et al.* 2013]. However, a number of studies showed that several factors other than remission of the depressive episode could directly influence functioning, such as comorbid pain with MDD [Lin *et al.* 2013], combining pharmacotherapy with psychotherapy [Lam *et al.* 2013], weight and body mass index [Lin *et al.* 2014a], demographics factors such as social class [Falconnier, 2010], presence of comorbid personality disorder, social support, Global Assessment of Function (GAF) score prior to the depressive episode [Ezquiaga *et al.* 1998], comorbid anxiety with depression [Hecht *et al.* 1989], family relations and family dysfunction [Puig-Antich *et al.* 1993], suicidal ideation [Marzuk *et al.* 2005], number of depressive episodes, family history of psychiatric disorders [Sanchez-Moreno *et al.* 2010], duration of depressive episode [Lagerveld *et al.* 2010], specific antidepressants [Venditti *et al.* 2000; Dubini *et al.* 1997], and patient's view of self and world [Zauszniewski and Rong, 1999]. Remission or decreasing symptom severity in depression might not be enough to demonstrate true recovery, and increased emphasis should be placed on functioning as an important indicator of treatment success [Langlieb and Guico-Pabia, 2010; Kongsakon, 2005].

In this current analysis, we sought to study functioning in MDD by analyzing the data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [Rush *et al.* 2004; Fava *et al.* 2003], the largest prospective, randomized study of treatment effectiveness for outpatients with MDD. Published STAR*D analyses of functioning in MDD [Rush *et al.* 2004, 2006] provided an initial understanding of functional impairments in MDD. The magnitude of impairments before treatment, how functioning changed in response to treatment, and the statistical or clinical significance of these changes, however, remained to be examined. The current analysis examines functioning and symptom severity data at entry and exit of each of the four levels of acute treatment phase and 12 months after the end of treatment in the STAR*D study in order to address the following questions.

(1) How extensive are the functioning impairments in patients with MDD before treatment?
(2) To what extent does functioning improve with each level of treatment, and how much

are improvements maintained 12 months after acute treatment ends?
(3) Does remission (after any treatment step) improve functioning relative to levels seen in the general population?

Methods

Study population
The STAR*D study was conducted at 18 primary care and 23 psychiatric care settings in the United States and funded by the National Institute of Mental health (NIMH). The authors of the present analysis obtained an NIMH Data Use Certificate to use the STAR*D Public Version 3 dataset. STAR*D enrolled 4041 treatment-seeking outpatients aged 18–75 years between 2001 and 2007 with a primary diagnosis of MDD. Full details of the study's methodology are described elsewhere [Rush *et al.* 2004; Fava *et al.* 2003]. To be eligible for the current analysis, participants needed to have complete data for each of the outcome measures detailed below, at both entry and exit for each level of the study. All patients entered treatment at level 1 and progressed through levels until they achieved remission. That is, patients who achieved remission from treatment at level 1 exited treatment at that point. Those who did not achieve remission progressed to level 2 of the treatment, and so on. Data were collected at the entry and exit points for each level, as well as follow-up data collected 12 months after exiting the final level of treatment. Because complete data on functioning measures were only available for 2280 patients, the analyzed dataset in this study contained 2280 level 1 participants, 749 level 2 participants, 190 level 3 participants, 56 level 4 participants, and 414 participants from all levels at 12-month follow up.

Treatments administered
The treatment interventions are fully detailed elsewhere [Fava *et al.* 2003; Rush *et al.* 2004]. Briefly, treatments were administered according to a fixed-flexible dosing schedule and modified based on each participant's response. Patients were transitioned out of acute treatment and to the follow-up phase if they achieved remission from the first level of treatment. If they did not achieve remission, they moved to the next level of acute treatment.

Participants were enrolled into the following STAR*D levels. Level 1: citalopram monotherapy; level 2: switching to sertraline, sustained release

(SR) bupropion, extended release (XR) venlafaxine, or cognitive behavioral therapy (CBT); *or* augmenting with bupropion SR, buspirone; *or* CBT; level 3: switching to nortriptyline or mirtazapine; *or* augmenting with lithium or triiodothyronine (T3); level 4: switching to tranylcypromine; *or* switching to venlafaxine XR plus mirtazapine.

The study used an equipoise stratified randomized design which allowed patients a choice between several switch or augmentation strategies, within the permissible limits of the study design. This approach was adopted in lieu of complete randomization to mimic clinical practice [Rush *et al.* 2006]. During the follow-up phase, patients were strongly advised to continue taking the previously effective drugs [Rush *et al.* 2012].

Outcome measures
The Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) was used to measure MDD symptom severity (0 = not depressed to 27 = most depressed) with remission defined as a score less than 5 [Rush *et al.* 2003]. Functioning was measured using the Work and Social Adjustment Scale (WSAS) where 0 = no impairment to 40 = severe impairment, with scores greater than 20 indicating moderate to severe impairment; 10–20 = significant impairment; and less than 10 = subclinical [Mundt *et al.* 2002]. The WSAS has fairly strong psychometric properties (Cronbach's α = 0.70–0.94, test–retest reliability r = 0.73 [Mundt *et al.* 2002]).

Statistical methods
Summary values are expressed as means (SD) for continuous variables and frequencies (%) for categorical variables. The paired t test was used for comparisons between entry and exit numerical outcomes, within each level. Clinical significance for numerical outcomes was estimated using effect sizes [Kraemer, 2006] in which Cohen's d values of 0.2, 0.5 and 0.8 describe small, medium and large effects, respectively [Cohen, 1988]. Entry to exit comparisons of binary variables within each level and follow up were assessed using the McNemar test for related proportions. The proportions of patients that scored 'within normal' on the relevant measures were compared between remitters and nonremitters at exit, using the χ^2 test (or Fisher exact test for small sample sizes). p values less than 0.05 were considered

Table 1. Demographic characteristics of STAR*D major depressive disorder sample.

Number of subjects	2280 (100%)
Age range	18.1–75.6
Mean age (SD)	42.6 (13.0)
Female	1432 (62.8%)
White	1846 (80.9%)
Hispanic	239 (10.5%)
College graduate	686 (30.1%)
Employed	1301 (57.1%)
Living with spouse/partner	1046 (45.9%)

STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

statistically significant. Analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics of the study population
The demographic characteristics of the analyzed patient sample (*n* = 2280) are depicted in Table 1. The majority of patients were white (81%), with nearly 63% women, 57% employed, 30% college graduates, and 46% living with spouse or partner.

Mean scores on measures of depressive symptom severity and functioning
Pre- and post-treatment scores for both depressive symptom severity (as measured by the QIDS-SR) and functioning (as measured by the WSAS) for each STAR*D level, in addition to scores at entry and exit from the 12-month follow-up phase are displayed in Table 2.

The pre- and post-treatment data from each level show that patients made statistically and clinically significant improvements on both outcome measures. Depressive symptom severity (QIDS-SR scores) showed the following effect sizes (Cohen's d) at the end of each treatment level: d = 0.93 at level 1, d = 0.65 at level 2, d = 0.43 at level 3 and d = 0.64 at level 4 (p < 0.0001 for all). Functioning (WSAS scores) yielded the following effect sizes: level 1 Cohen's d = 0.74 (p < 0.0001), level 2 d=0.58 (p < 0.0001), level 3 d=0.29 (p < 0.0001) and level

Table 2. Mean and SD of measures of depressive symptom severity (QIDS-SR) and functioning (WSAS), with mean (SD) of change and effect sizes from the STAR*D study.

Level*	N	QIDS-SR entry (SD)	QIDS-SR exit (SD)	Change (SD)	p	ES
1	2280	15.4 (5)	9.4 (6.5)	−6.0 (6.5)	<0.0001	0.92
2	749	14.3 (4.7)	10.5 (6.5)	−3.8 (5.8)	<0.0001	0.65
3	190	15.5 (4.8)	13.1 (6.3)	−2.4 (5.6)	<0.0001	0.43
4	56	16.4 (4.6)	12.3 (6.5)	−4.1 (6.3)	<0.0001	0.65
12-month f/u	414	5.6 (3.7)	7.7 (5.7)	2.2 (5.1)	<0.0001	0.42
Level*	**N**	**WSAS entry (SD)**	**WSAS exit (SD)**	**Change (SD)**	**p**	**ES**
1	2280	23.8 (8.9)	15.5 (12.1)	−8.3 (11.2)	<0.0001	0.74
2	749	23.6 (9.0)	17.7 (12.1)	−5.9 (10.2)	<0.0001	0.58
3	190	25.7 (8.6)	23.2 (11.4)	−2.5 (8.8)	<0.0001	0.29
4	56	28.1 (7.9)	23.5 (11.4)	−4.6 (9.4)	0.0006	0.49
12-month f/u	414	9.7 (10.0)	12.5 (11.6)	2.8 (8.5)	<0.0001	0.33

Levels of treatment are as follows. Level 1: citalopram monotherapy; level 2: switching to sertraline, sustained release (SR) bupropion, extended release (XR) venlafaxine, or cognitive behavioral therapy (CBT); *or* augmenting with bupropion SR, buspirone; *or* CBT; level 3: switching to nortriptyline or mirtazapine; *or* augmenting with lithium or triiodothyronine (T3); level 4: switching to tranylcypromine; *or* switching to venlafaxine XR plus mirtazapine.
*Values compared between entry and exit at each level and between entry to follow up and exit at 12 months of follow up. ES, effect size; f/u, follow up; QIDS-SR, Quick Inventory of Depressive Symptomatology Self Report; SD, standard deviation; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; WSAS, Work and Social Adjustment Scale.

Table 3. Proportions of patients with normal functioning before and after treatment.

Level*	N	Within normal functioning entry (%)	Within normal functioning exit (%)	McNemar test p value
1	2280	6.7	38.5	<0.0001
2	749	6.4	31.9	<0.0001
3	190	4.7	16.8	<0.0001
4	56	1.8	16	0.022
12-month f/u	414	60.1	49.0	<0.0001

'Functioning within normal' is defined as WSAS scores of less than 10 [Mundt *et al.* 2002]. Levels of treatment are as follows. Level 1: citalopram monotherapy; level 2: switching to sertraline, sustained release (SR) bupropion, extended release (XR) venlafaxine, or cognitive behavioral therapy (CBT); *or* augmenting with bupropion SR, buspirone; *or* CBT; level 3: switching to nortriptyline or mirtazapine; *or* augmenting with lithium or triiodothyronine (T3); level 4: switching to tranylcypromine; *or* switching to venlafaxine XR plus mirtazapine.
*Values compared between entry and exit at each level and between entry to follow up and exit at 12 months of follow up.

4 $d = 0.49$ ($p = 0.0006$). At 12-month follow up, patients showed significant mild to moderate worsening on both measures with effect sizes of QIDS-SR Cohen's $d = −0.42$ and WSAS $d = −0.33$ ($p < 0.0001$).

Proportions of patients scoring within-normal functioning

The proportions of patients scoring within-normal functioning (WSAS < 10) at entry and exit for each STAR*D level and 12-month follow up are displayed in Table 3.

Less than 7% of patients with MDD reported within-normal functioning prior to treatment at all four levels. The proportions of patients achieving within-normal functioning scores significantly increased with treatment, however no more than 40% scored within-normal functioning after exiting treatment at any level.

Follow-up data show that about 46.4% of patients were in remission 12 months after completion of acute treatment phase. The proportions of follow-up patients experiencing within-normal scores for functioning at 12 months from the time of

completing acute treatment significantly decreased from 60.1% to 49% ($p < 0.0001$).

Proportions of remitters versus nonremitters scoring within-normal functioning

Remission from MDD is defined as minimal or no symptoms, as measured by QIDS-SR score less than 5. As detailed in Table 4, achieving remission significantly increased the proportion of patients experiencing within-normal functioning after each level of treatment. However, despite meeting remission criteria, a significant proportion of patients were left with less than normal functioning at the end of treatment, with 20–40% of patients not attaining within-normal WSAS scores.

The proportions of follow-up patients in remission who experienced within-normal functioning after 12 months did not significantly change from immediately post treatment to the end of the follow-up phase. In contrast, nonremitters showed significantly decreased proportions of within-normal functioning from 47.3% immediately after treatment to 24.6% at 12-month follow up ($p < 0.0001$).

Discussion

The current analysis yielded four main findings: functioning is substantially impaired at baseline in patients with MDD; functioning *does* improve with psychiatric treatment of MDD, however the majority of patients continue to experience deficits in functioning following treatment; patients with MDD who achieve remission show more remarkable improvements in functioning than nonremitters, however a moderate proportion of patients with MDD who achieve remission still experience abnormal functioning; and follow-up data show that mean functioning scores declined after 12 months, and although the proportions of patients experiencing within-normal scores significantly decreased, neither significant reductions nor increases were observed in remitters. Though there have been a number of studies based on data from the STAR*D, this is the first to analyze how functioning changed as a result of treatment, both immediately following treatment and at 12-month follow up.

The fact that less than 7% of STAR*D entry patients, at any level, are experiencing within-normal functioning speaks of the daunting task of

Table 4. Proportions of remitters/nonremitters with normal functioning before and after treatment.

Level	Remitters				Nonremitters				Difference at exit
	N	Within normal function entry (%)	Within normal function exit (%)	McNemar test p value	N	Within normal function entry (%)	Within normal function exit (%)	McNemar test p value	χ^2 or Fisher test p value
1	812	10.2	80.5	<0.0001	1,468	4.7	15.3	<0.0001	<0.0001
2	208	11.5	74.0	<0.0001	541	4.4	15.7	<0.0001	<0.0001
3	30	6.7	60.0	0.0001	160	4.4	8.8	0.119	<0.0001*
4	8	0	37.5	0.25	48	2.1	12.5	0.112	0.108*
12-mo. f/u	192	74.7	76.8	0.64	220	47.3	24.6	<0.0001	<0.0001

'Functioning within normal' is defined as WSAS scores of less than 10 [Mundt *et al.* 2002]. Levels of treatment are as follows. Level 1: citalopram monotherapy; level 2: switching to sertraline, sustained release (SR) bupropion, extended release (XR) venlafaxine, or cognitive behavioral therapy (CBT); *or* augmenting with bupropion SR, buspirone; *or* CBT; level 3: switching to nortriptyline or mirtazapine; *or* augmenting with lithium or triiodothyronine (T3); level 4: switching to tranylcypromine; *or* switching to venlafaxine XR plus mirtazapine.
*Fisher exact test used due to small sample size.
f/u, follow up; WSAS, Work and Social Adjustment Scale.

not only treating depressive symptoms but also of restoring functioning. Significant improvements were seen in symptom severity and functioning with the largest effect observed in depressive symptom severity. The largest effect sizes for post-treatment improvements on the two dimensions were seen after the first level of acute treatment (level 1). However, the widely held expectation that functioning is expected to improve spontaneously after symptom remission was not supported by the 12-month follow-up data analysis in this study. If anything, this domain suffered from significant deterioration, particularly in those patients who were not in remission after 12 months, whereas it did not change significantly from end of acute treatment to end of follow-up phase in patients who maintained remission. The above findings are consistent with the limited literature on long-term follow-up of functioning in MDD [McKnight, 2009; Romera *et al.* 2013].

Evidence suggests that improving functioning is a crucial treatment area for patients with MDD [Judd *et al.* 1998]. More than 60% of the patient population continued to experience functional impairments after exiting level 1 of treatment. These ongoing impairments leave more to be desired. Our findings reveal that remission status does indeed have a pronounced effect on functional recovery. Patients who achieved remission showed a remarkable change in the proportions achieving within-normal functioning levels after treatment. For instance, in level 1 remitted patients, 10.2% had within-normal functioning at entry compared with 80.5% at exit ($p < 0.0001$). For nonremitters at the same level of treatment, 4.7% had within-normal functioning at entry compared with 15.3% at exit. These findings reinforce the notion that *remission* (minimal or no symptoms), as opposed to *response* (typically a 50% reduction in severity), should remain the primary goal of MDD treatment. Moreover, incomplete resolution of depressive symptoms following treatment is an important predictor of MDD relapse. Numerous studies have reported that patients who fail to achieve complete symptomatic remission often continue to have psychosocial impairment and are more likely to relapse into full depression [Lin *et al.* 2014b; Judd *et al.* 1998; Thase *et al.* 1992]. It is important to note, however, that for patients with treatment-resistant depression, remission is not always possible. For these patients, an emphasis on mitigating symptoms,

as well as individualized treatment for improved functioning, should be the goal.

Our results point to the importance of aiming treatment beyond symptom resolution and to functional improvement and restoration. A sizeable proportion of remitted patients had deficits in functioning even after treatment. At the end of level 1, 19.5% of remitted patients still did not attain a functioning level comparable to general population norms. By the end of level 3 this percentage leaps to 40%, suggesting that patients with treatment-resistant depression are especially prone to ongoing deficits and functioning. These ongoing deficits mean that remitted patients could feel incapacitated across multiple life domains, even after an otherwise clinically successful treatment regimen.

In treating their depression, patients hope to return to normal levels of functioning. The treatment outcomes that patients with MDD considered 'very important' in determining remission status for patients were: the presence of positive mental health, such as optimism and self-confidence (selected by 77.3% of respondents); a return to one's usual, normal self (75.6%); and a return to normal levels of functioning at home, work or school (74.3%) [Zimmerman *et al.* 2006]. In treating MDD, these results indicate that clinicians should become more in sync with patients' ultimate concern: their functioning.

The findings in the analysis suggest that full remission should be targeted initially in the course of MDD treatment, as strongly supported by many other studies [Kennedy, 2002], in the context of treatment that is centered on improving functional outcomes and not limited to symptomatic improvement. Initial evidence shows that the following interventions may contribute to functioning improvement: CBT [Wong, 2008], future-directed therapy [Vilhauer *et al.* 2012], augmentation with ω3 [Van der Watt, 2008], dopaminergic agents [IsHak *et al.* 2009], and combining medications with psychotherapy [IsHak *et al.* 2011]. Adjunct interventions with favorable preliminary findings also include nutrition [Ruano *et al.* 2011], exercise [Bartholomew *et al.* 2005], meditation [Nyklicek and Kuijpers, 2008], massage [Hamre *et al.* 2007], humor [Strean, 2009], and music [Maratos *et al.* 2008]. Additionally, identifying and addressing the specific poor functioning items on the measures might contribute to the overall treatment plan.

The above interventions still need to be systematically studied in large-sample randomized controlled studies that use functioning as a primary outcome, a recommendation strongly supported by other studies [Brockow *et al.* 2004]. Measurement challenges such as the lack of multidimensional assessment of MDD outcome continue to impede our efforts in the aspect. However, new methodologies such as ones that incorporate symptom severity, quality of life, and functioning, such as the Individual Burden of Illness Index for Depression [IsHak *et al.* 2013; Cohen *et al.* 2013], might offer innovative ways to quantify overall improvement or deterioration in MDD.

Limitations and strengths

Our study has a number of limitations. One limitation is that the sample is largely white, female, married, in a high socioeconomic status bracket, and employed, which is unique relative to other studies of patients with depression and depressed populations at large. A second limitation is the study's reliance on self-report, as the accuracy and precision of self-assessment of functioning have been debated. Nevertheless, the use of patient-reported outcomes (PRO) using valid and reliable instruments, such as the ones used in STAR*D, is a growing movement in healthcare and is widely supported by clinicians and researchers alike, in addition to the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS), World Health Organization, and the US Food and Drug Administration PRO initiatives. Functioning measures are often lengthy, and to date there is no single measure that is specific to MDD domains. The time and effort burden of administering and scoring functioning measures, and using them to guide interventions, needs to be placed in the context of the realities of practicing medicine today. Further limitations include the lack of data on patients who dropped out *versus* those who achieve remission after each study level, which could have potentially provided useful information about their functioning. Future studies should investigate these measures in patients who could not complete the trial; such studies will help us understand the nature of these patients' struggles. The present analysis has a number of strengths as well. It highlights the clinical significance that each level of treatment in the STAR*D trial has on functioning. Statistical significance does not necessarily reflect the clinical significance that is expected or observed in everyday clinical practice. To discern the clinical significance of a research finding, effect size calculation is an important step in this direction. Although there are some concerns with the generalizability of the results due to the demographic characteristics of the sample, one strength of the STAR*D sample is that it is composed of treatment-seeking patients with MDD from primary and psychiatry clinics, rather than ad-recruited research subjects. This sampling method makes the sample more representative of outpatients with depression seen in everyday practice (with the exception of racial and ethnic breakdown). Because the majority of the patients were white, future studies should enroll more Hispanic, African American, Asian and Native American patients in order to better understand functioning in depressed populations.

Conclusion

Like all mental illness, major depression has serious effects on one's ability to perform daily activities and function at his or her normal baseline level. While current treatment focuses on eliminating or reducing the symptoms of MDD, this study points to the limitation of symptom-focused treatment and calls for extending the scope to improve functioning as part of an effort to promote overall wellness in patients with MDD. Contrary to commonly held expectations, functioning did not show additional improvements with time after the completion of the acute treatment phase of treatment, but actually seems to show a significant decline after 1 year of follow up. Therefore, research and clinical efforts in MDD would benefit from incorporating functioning measurement to improve long-term functioning as well as symptom reduction. Thus, it is critical to overall MDD treatment success that researchers investigate and incorporate specific and personalized interventions to improve and restore functioning in addition to evidence-based MDD treatment.

Key points for decision makers

This study reached the following conclusions:

(1) Functioning is severely impaired at baseline in patients with MDD.
(2) Patient functioning improves with psychiatric treatment of MDD, however the majority of patients (>60%) continue to experience impaired functioning following treatment.
(3) Although patients with MDD who achieve remission (symptomatic improvement) show more remarkable improvements in

functioning than nonremitters, 20–40% of remitters continue to experience ongoing deficits in functioning.

Effective MDD treatment should be tailored according to each patient so as to address functioning as well as symptomatic remission.

Conflict of interest statement
The authors declare that there is no conflict of interest.

References
Bartholomew, J., Morrison, D. and Ciccolo, J. (2005) Effects of acute exercise on mood and well-being in patients with major depressive disorder. *Med Sci Sports Exerc* 37: 2032–2037.

Brockow, T., Wohlfahrt, K., Hillert, A., Geyh, S., Weigl, M., Franke, T. *et al.* (2004) Identifying the concepts contained in outcome measures of clinical trials on depressive disorders using the International Classification of Functioning, Disability and Health as a reference. *J Rehabil Med* 44: 49–55.

Cohen, J. (1988) *Statistical Power Analysis for the Behavioral Sciences*, 2nd edition. New Jersey: Lawrence Erlbaum Associates.

Cohen, R., Greenberg, J. and IsHak, W. (2013) Incorporating multidimensional patient-reported outcomes of symptom severity, functioning, and quality of life in the Individual Burden of Illness Index for Depression to measure treatment impact and recovery in MDD. *JAMA Psychiatry* 70: 343–350.

Dubini, A., Bosc, M. and Polin, V. (1997) Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. *J Psychopharmacol* 11: S17–S23.

Ezquiaga, E., García, A., Bravo, F. and Pallarés, T. (1998) Factors associated with outcome in major depression: a 6-month prospective study. *Soc Psychiatry Psychiatr Epidemiol* 33: 552–557.

Falconnier, L. (2010) Social class and work functioning in treatment for depression. *Psychiatr Serv* 61: 718–721.

Fava, M., Rush, A., Trivedi, M., Nierenberg, A., Thase, M., Sackeim, H. *et al.* (2003) Background and rationale for the sequenced treatment alternatives to relieve depression (STAR★D) study. *Psychiatr Clin North Am* 26: 457–494.

Greer, T., Kurian, B. and Trivedi, M. (2010) Defining and measuring functional recovery from depression. *CNS Drugs* 24: 267–284.

Hamre, H., Witt, C., Glockmann, A., Ziegler, R., Willich, S. and Kiene, H. (2007) Rhythmical massage therapy in chronic disease: a 4-year prospective cohort study. *J Altern Complement Med* 13: 635–642.

Hays, R., Wells, K., Sherbourne, C., Rogers, W. and Spritzer, K. (1995) Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. *Arch Gen Psychiatry* 52: 11–19.

Hecht, H., von Zerssen, D., Krieg, C., Pössl, J. and Wittchen, H. (1989) Anxiety and depression: comorbidity, psychopathology, and social functioning. *Compr Psychiatry* 30: 420–433.

Hirschfeld, R. (2002) Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. *Biol Psychiatry* 51: 123–133.

IsHak, W., Davis, M., Jeffrey, J., Balayan, K., Pechnick, R., Bagot, K. *et al.* (2009) The role of dopaminergic agents in improving quality of life in major depressive disorder. *Curr Psychiatry Rep* 11: 503–508.

IsHak, W., Greenberg, J., Saah, T., Mobaraki, S., Fakhry, H., Wu, Q. *et al.* (2013) Development and validation of the Individual Burden of Illness Index for Major Depressive Disorder (IBI-D). *Adm Policy Ment Health* 40: 76–86.

IsHak, W., Ha, K., Kapitanski, N., Bagot, K., Fathy, H., Swanson, B. *et al.* (2011) The impact of psychotherapy, pharmacotherapy, and their combination on quality of life in depression. *Harv Rev Psychiatry* 19: 277–289.

Judd, L., Akiskal, H., Maser, J., Zeller, P., Endicott, J., Coryell, W. *et al.* (1998) Major depressive disorder:

a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord* 50: 97–108.

Kennedy, N., Foy, K., Sherazi, R., McDonough, M. and McKeon, P. (2007) Long-term social functioning after depression treated by psychiatrists: a review. *Bipolar Disord* 9: 25–37.

Kennedy, S. (2002) Full remission: a return to normal functioning. *J Psychiatry Neurosci* 27: 233–234.

Kongsakon, R. (2005) The functioning and quality of life of depressive patients with 12 weeks of psychiatric care. *J Med Assoc Thai* 88: 1261–1266.

Kraemer, H. (2006) Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry* 59: 990–996.

Lagerveld, S., Bültmann, U., Franche, R., van Dijk, F., Vlasveld, M., van der Feltz-Cornelis, C. *et al.* (2010) Factors associated with work participation and work functioning in depressed workers: a systematic review. *J Occup Rehabil* 20: 275–292.

Lam, R., Parikh, S., Ramasubbu, R., Michalak, E., Tam, E., Axler, A. *et al.* (2013) Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. *Br J Psychiatry* 203: 358–365.

Langlieb, A. and Guico-Pabia, C. (2010) Beyond symptomatic improvement: assessing real-world outcomes in patients with major depressive disorder. *Prim Care Companion J Clin Psychiatry* 12. DOI: 10.4088/PCC.09r00826blu

Lin, C., Chen, C., Wong, J. and McIntyre, R. (2014a) Both body weight and BMI predicts improvement in symptom and functioning for patients with major depressive disorder. *J Affect Disord* 161: 123–126.

Lin, C., Yen, Y., Chen, M. and Chen, C. (2013) Relief of depression and pain improves daily functioning and quality of life in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 47: 93–98.

Lin, C., Yen, Y., Chen, M. and Chen, C. (2014b) Depression and pain impair daily functioning and quality of life in patients with major depressive disorder. *J Affect Disord* 166: 173–178.

Maratos, A., Gold, C., Wang, X. and Crawford, M. (2008) Music therapy for depression. *Cochrane Database Syst Rev* CD004517.

Marzuk, P., Hartwell, N., Leon, A. and Portera, L. (2005) Executive functioning in depressed patients with suicidal ideation. *Acta Psychiatr Scand* 112: 294–301.

McKnight, P. (2009) The importance of functional impairment to mental health outcomes: a case for

reassessing our goals in depression treatment research. *Clin Psychol Rev* 29: 243–259.

Mundt, J., Marks, I., Shear, M. and Greist, J. (2002) Work and Social Adjustment Scale: a simple measure of impairment and functioning. *Br J Psychiatry* 180: 461–464.

Nyklicek, I. and Kuijpers, K. (2008) Effects of mindfulness-based stress reduction intervention on psychological well-being and quality of life: is increased mindfulness indeed the mechanism? *Ann Behav Med* 35: 331–340.

Puig-Antich, J., Kaufman, J., Ryan, N., Williamson, D., Dahl, R., Lukens, E. *et al.* (1993) The psychosocial functioning and family environment of depressed adolescents. *J Am Acad Child Adolesc Psychiatry* 32: 244–253.

Romera, I., Perez, V. and Gilaberte, I. (2013) Remission and functioning in major depressive disorder. *Actas Esp Psiquiatr* 41: 263–268.

Ruano, C., Henriquez, P., Bes-Rastrollo, M., Ruiz-Canela, M., del Burgo, C. and Sánchez-Villegas, A. (2011) Dietary fat intake and quality of life: the SUN project. *Nutr J* 10: 121.

Rush, A., Trivedi, M., Ibrahim, H., Carmody, T., Arnow, B., Klein, D. *et al.* (2003) 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* 54: 585.

Rush, A., Fava, M., Wisniewski, S., Lavori, P., Trivedi, M., Sackeim, H. *et al.* (2004) Sequenced Treatment Alternatives to Relieve Depression (STAR⋆D): rationale and design. *Control Clin Trials* 25: 119–142.

Rush, A., Trivedi, M., Wisniewski, S., Nierenberg, A., Stewart, J., Warden, D. *et al.* (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR⋆D report. *Am J Psychiatry* 163: 1905–1917.

Rush, A., Wisniewski, S., Zisook, S., Fava, M., Sung, S., Haley, C. *et al.* (2012) Is prior course of illness relevant to acute or longer-term outcomes in depressed out-patients? A STAR⋆D report. *Psychol Med* 42: 1131–1149.

Sanchez-Moreno, J., Martinez-Aran, A., Gadelrab, H., Cabello, M., Torrent, C., Bonnin, C. *et al.* (2010) The role and impact of contextual factors on functioning in patients with bipolar disorder. *Disabil Rehabil* 32(Suppl. 1): S94–S104.

Strean, W. (2009) Laughter prescription. *Can Fam Physician* 55: 965–967.

Thase, M., Simons, A., McGeary, J., Cahalane, J., Hughes, C., Harden, T. *et al.* (1992) Relapse after

cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry* 149: 1046–1052.

Trivedi, M., Corey-Lisle, P., Guo, Z., Lennox, R., Pikalov, A. and Kim, E. (2009) Remission, response without remission, and nonresponse in major depressive disorder: impact on functioning. *Int Clin Psychopharmacol* 24: 133–138.

Trivedi, M., Morris, D., Wisniewski, S., Lesser, I., Nierenberg, A., Daly, E. *et al.* (2013) Increase in work productivity of depressed individuals with improvement in depressive symptom severity. *Am J Psychiatry* 170: 633–641.

Ustün, B. and Kennedy, C. (2009) What is 'functional impairment'? Disentangling disability from clinical significance. *World Psychiatry* 8: 82–85.

Van der Watt, G., Laugharne, J. and Janca, A. (2008) Complementary and alternative medicine in the treatment of anxiety and depression. *Curr Opin Psychiatry* 21: 37–42.

Venditti, L., Arcelus, A., Birnbaum, H., Greenberg, P., Barr, C., Rowland, C. *et al.* (2000) The impact of antidepressant use on social functioning: reboxetine

versus fluoxetine. *Int Clin Psychopharmacol* 15: 279–289.

Vilhauer, J., Young, S., Kealoha, C., Borrmann, J., IsHak, W., Rapaport, M. *et al.* (2012) Treating major depression by creating positive expectations for the future: a pilot study for the effectiveness of future-directed therapy (FDT) on symptom severity and quality of life. *CNS Neurosci Ther* 18: 102–109.

Wong, D. (2008) Cognitive and health-related outcomes of group cognitive behavioral treatment for people with depressive symptoms in Hong Kong: randomized wait-list control study. *Aust N Z J Psychiatry* 42: 702–711.

Zauszniewski, J. and Rong, J. (1999) Depressive cognitions and psychosocial functioning: a test of Beck's cognitive theory. *Arch Psychiatr Nurs* 13: 286–293.

Zimmerman, M., McGlinchey, J., Posternak, M., Friedman, M., Attiullah, N. and Boerescu, D. (2006) How should remission from depression be defined? The depressed patient's perspective. *Am J Psychiatry* 163: 148–150.

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