PATIENT-REPORTED OUTCOMES OF QUALITY OF LIFE, FUNCTIONING, AND DEPRESSIVE SYMPTOM SEVERITY IN MAJOR DEPRESSIVE DISORDER COMORBID WITH PANIC DISORDER BEFORE AND AFTER SSRI TREATMENT IN THE STAR*D TRIAL

Waguih William IsHak, Cedars-Sinai Medical Center
James Mirocha, Cedars-Sinai Medical Center
Scott Christensen, Cedars-Sinai Medical Center
Fan Wu, University of California Los Angeles
Richard Kwock, University of California Los Angeles
Joseph Behjat, University of California Los Angeles
Sarah Pi, University of California Los Angeles
A. Akopyan, University of California Los Angeles
Eric D. Peselow, New York University
Robert Cohen, Emory University

Only first 10 authors above; see publication for full author list.

**Journal Title:** Depression and Anxiety  
**Volume:** Volume 31, Number 8  
**Publisher:** Wiley: 12 months | 2014-08-01, Pages 707-716  
**Type of Work:** Article | Post-print: After Peer Review  
**Publisher DOI:** 10.1002/da.22152  
**Permanent URL:** https://pid.emory.edu/ark:/25593/rms8g

Final published version: [http://dx.doi.org/10.1002/da.22152](http://dx.doi.org/10.1002/da.22152)

**Copyright information:**
© 2013 Wiley Periodicals, Inc.

Accessed June 28, 2018 4:11 PM EDT
PATIENT-REPORTED OUTCOMES OF QUALITY OF LIFE, FUNCTIONING, AND DEPRESSIVE SYMPTOM SEVERITY IN MAJOR DEPRESSIVE DISORDER COMORBID WITH PANIC DISORDER BEFORE AND AFTER SSRI TREATMENT IN THE STAR*D TRIAL


1Department of Psychiatry, Cedars-Sinai Medical Center and David Geffen School of Medicine at UCLA, Los Angeles, California
2Department of Psychiatry, Cedars-Sinai Medical Center, Los Angeles, California
3Department of Psychiatry, Cedars-Sinai Medical Center and University of Southern California, Los Angeles, California
4Fielding School of Public Health at UCLA, Los Angeles, California
5University of California Los Angeles, California
6Department of Psychiatry, NYU School of Medicine, New York, New York
7Department of Psychiatry, Emory University School of Medicine, Atlanta, Georgia
8Department of Biostatistics, David Geffen School of Medicine at UCLA, Los Angeles, California

Abstract

Background—Panic disorder (PD) is highly comorbid with major depressive disorder (MDD) with potential impact on patient-reported outcomes of quality of life (QOL), functioning, and depressive symptom severity.

Methods—Using data from the sequenced treatment alternatives to relieve depression (STAR*D) trial, we compared entry and post-SSRI-treatment QOL, functioning, and depressive symptom severity scores in MDD patients with comorbid PD (MDD+PD) to MDD patients without PD (MDDnoPD). We also compared pre- and posttreatment proportions of patients with severe impairments in quality of life and functioning.

Results—MDD+PD patients experienced significantly lower QOL and functioning and more severe depressive symptoms than MDDnoPD patients at entry. Following treatment with citalopram, both groups showed significant improvements, however, nearly 30–60% of patients...
still suffered from severe quality of life and functioning impairments. MDD+PD patients exited with lower QOL and functioning than MDDnoPD patients, a difference that became statistically insignificant after adjusting for baseline measures of depressive symptom severity, functioning, and QOL, comorbid anxiety disorders (PTSD, GAD, social, and specific phobias), age, and college education.

**Conclusions**—Functional outcomes using QOL and functioning measures should be utilized in treating and researching MDD so that shortfalls in traditional treatment can be identified and additional interventions can be designed to address severe baseline QOL and functioning deficits in MDD comorbid with PD.

**Keywords**
depression; anxiety/anxiety disorders; quality of life; panic attacks/agoraphobia; antidepressants

**INTRODUCTION**

Major depressive disorder (MDD) is a leading cause of disability and premature mortality worldwide.\(^1\) Individuals with MDD often suffer from substantial quality of life (QOL) impairments and comorbid psychiatric and medical disorders.\(^2\) An analysis of the National Comorbidity Survey (NCS) showed that anxiety disorders are frequently comorbid with MDD with a 12-month prevalence of 51.2% for any anxiety disorder, 20% for social phobia, 15.4% for generalized anxiety disorder (GAD), 15.2% for posttraumatic stress disorder (PTSD), 12.6% for panic disorder (PD), in depressed individuals.\(^3\) Although PD is the least common comorbid anxiety disorder with MDD, studies showed that QOL is most compromised in PD (followed by PTSD) compared to other anxiety disorders.\(^4\) Further NCS analyses showed that about one-tenth of individuals with lifetime prevalence of MDD also met the criteria for lifetime prevalence of PD.\(^5\) A study by Reich et al. reported that the onset of MDD occurred before PD in 49% of MDD patients with comorbid PD (MDD+PD), while 32% of these patients had the onset of PD before MDD, and the remaining 19% developed PD and MDD within 3 months of each other.\(^6\) An NCS analysis by Roy-Byrne et al. demonstrated that individuals with both conditions have a more severe course and greater lifetime impairment than those experiencing either disorder alone. Individuals with both conditions tended to have higher utilization of general medical, mental health, and social services, more perceived role impairment, more attacks/episodes, and substantially higher prevalence of attempted suicide than either disorder alone. In MDD+PD, suicide attempts were 70% higher than MDD without PD and four times higher than PD without MDD.\(^7\)

The individual impact of each disorder on QOL has been well described in MDD\(^2,8\) and in PD.\(^9,10\) It has also been reported that the combination of MDD and PD could exert a remarkably negative toll on QOL \(^6\) and functioning.\(^11\) QOL is operationally defined as the subjective evaluation of life domains such as health, work, family and social relations, and leisure activities, within cultural and environmental context.\(^12\) Functioning refers to carrying out life activities (related to tasks and actions by an individual) and participation (involvement in life situations).\(^13\) Essentially, functioning denotes the individual’s actual performance in life activities (work, love, and play) as rated by self or observers, whereas
QOL reflects the individual’s satisfaction with the above life activities in addition to perception of health, as rated by self-report.\cite{14}

Although there is considerable evidence demonstrating that MDD+PD is associated with worse QOL and functioning than MDD without PD (MDDnoPD) at baseline,\cite{15–18} it remains unclear if this difference persists at the end of treatment. It is also unclear how much treatment impacts the proportions of patients with severe QOL and functioning, as well as MDD remission rates in patients with MDD+PD after treatment, compared to MDDnoPD. Studies of this topic have traditionally relied on small-sample size studies. We seek to enhance our understanding of how comorbid PD impacts treatment outcomes in MDD using a considerably large database of treatment-seeking depressed patients.

This study analyzed the data from MDD patients with and without PD who participated in the sequenced treatment alternatives to relieve depression (STAR*D) trial.\cite{19,20} Taking advantage of the large-sample size and the systematic collection of patient-reported QOL, functioning, and depressive symptom severity data, we examined the impact of panic disorder comorbidity in MDD by conducting a detailed analysis of QOL, functioning, and depressive symptom severity before and after Level 1 treatment with citalopram. We hypothesized that, compared to MDDnoPD:

1. Patients with MDD+PD would have worse QOL, functioning, and depressive symptom severity at entry and after SSRI-treatment.
2. The percentages of MDD+PD patients with severe impairments in QOL and functioning are higher at entry and after SSRI-treatment.
3. Patients with MDD+PD are less likely to achieve MDD remission.

**METHODS**

**STUDY POPULATION**

The STAR*D study is the largest study on MDD in modern times and was funded by the National Institute of Mental Health (NIMH). The details of the study are described in full details elsewhere.\cite{19,20} Briefly, the study enrolled 4,041 treatment seeking outpatients ranging from 18 to 75 years old, with a primary diagnosis of MDD recruited at 18 primary care and 23 psychiatric care settings in the United States from 2001 to 2007. The study used sequential treatment trials using up to four treatment levels as depicted in Fig. 1. The authors obtained an NIMH data use certificate to utilize the STAR*D Pub Ver1 dataset for the purpose of this analysis. We analyzed complete data on QOL, functioning, and depressive symptom severity resulting in a sample size of 2,280 patients.

**OUTCOME MEASURES**

QOL was measured using the quality of life enjoyment and satisfaction questionnaire—short form (Q-LES-Q),\cite{21} and the 12-item version of the medical outcomes study—short form (SF-12).\cite{22} Functioning and depressive symptom severity, were measured using the work and social adjust scale (WSAS),\cite{23} and the quick inventory of depressive symptomatology-self-report (QIDS-SR),\cite{24} respectively. Both the Q-LES-Q and the SF-12 scores range from

*Depress Anxiety. Author manuscript; available in PMC 2016 March 04.*
0 to 100 with 0 = lowest QOL score and 100 = highest. Community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3). Scores greater than 2 SD below the community norm indicate severe impairment, i.e. Q-LES-Q scores less than 55.7 are considered “severely impaired.”[25] The Q-LES-Q enjoys strong psychometric properties, with a Cronbach’s alpha of 0.90 and a test-retest reliability of 0.74.[21] For the SF-12, the population mean score is 50 (SD = 10) on both the physical composite score (PCS) and the mental composite score (MCS), thus patients with scores <30 are considered severely impaired.[22] The SF-12 has strong psychometric properties with a Cronbach’s alpha of 0.81 (PCS) and 0.84 (MCS), and a test-retest reliability of 0.89 (PCS) and 0.76 (MCS).[22] WSAS scores range from 0 = best functioning to 40 = worst functioning. Scores >20 indicate severe impairment.[23] The WSAS has fairly strong psychometric properties, with a Cronbach’s alpha ranging from 0.70 to 0.94, and a test-retest reliability of 0.73.[23] The QIDS-SR scores range from 0 = not depressed to 27 = most severely depressed. Remission is defined as a score of 5 or less.[24] The QIDS-SR is highly correlated with the widely utilized clinician-rated Hamilton rating scale[25] for depression with its three versions, the Montgomery Asberg depression rating scale,[26] as well as the Beck depression inventory,[27] and has a high internal consistency (Cronbach’s alpha = 0.86).[24]

STATISTICAL METHODS

Summary values are expressed as means (SD) for continuous variables and frequencies (%) for categorical variables. We analyzed only the Level 1 patients with complete entry and exit measurements (n = 2,280). We conducted both unadjusted and adjusted analyses to examine differences between the MDD+PD and MDDnoPD groups. Unadjusted analyses: Given the large size of the analyzed sample, we calculated effect sizes in order to assess clinical significance in addition to statistical significance, where Cohen’s d values of 0.2, 0.5, and 0.8 describe small, medium, and large effects, respectively.[28–30] Within-group changes from entry to exit (deltas) on continuous variables were assessed for significance using paired $t$-tests. Between-group differences on continuous variables were assessed for significance using independent samples $t$-tests. We calculated and compared the proportions of patients with severe impairments according to the parameters described above for the Q-LES-Q, SF-12-PCS, SF-12-MCS, and WSAS. Within group entry versus exit $P$-values were calculated using McNemar’s test for related proportions. The proportions of patients with severe impairments on the measures for MDD+PD were also compared to MDDnoPD at entry and exit, using Fisher exact tests. Five tests were performed for each outcome measure: two within group tests and three between group tests (entry, change, and exit). Thus, we used a Bonferroni-adjusted 0.01 significance level for each test. Adjusted analyses: We conducted multivariable linear regression analyses to examine the association between posttreatment numerical outcomes and PD, adjusting for age, college education, comorbid anxiety disorders (GAD, PTSD, social phobia, and specific phobia), as well as baseline QOL (Q-LES-Q, and SF-12), functioning (WSAS), and depressive symptom severity (QIDS-SR). We conducted multivariable logistic regression analyses to examine the association between posttreatment severe impairment outcomes and PD, adjusting for age, college education, comorbid anxiety disorders (GAD, PTSD, social phobia, and specific phobia), as well as baseline QOL (Q-LES-Q, and SF-12), functioning (WSAS), and depressive symptom severity (QIDS-SR).
Analyses were performed using the open source R programming language version 2.14.2 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

COMPARING DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MDD+PD AND MDDnoPD

The demographic and clinical characteristics of the analyzed patient sample (n = 2,280) and the differences between patients with MDD+PD and MDDnoPD are presented in Table 1.

In the study population, the majority were Caucasians (>80%), nearly two-thirds were women, about one-third graduated from college, and more than one-half were employed at entry into the study. The prevalence of MDD+PD was 4.4% (n = 101) in the analyzed sample. Demographic comparisons of patients with MDD+PD to those with MDDnoPD revealed differences in age and college education rates. The population with MDD+PD was younger (P = .014) and contained less college graduates (P = .028) (P values were no longer significant after Bonferroni adjustment to P = <.01). The MDD+PDD group also had a higher proportion of women and a lower percentage of employment; however, these differences were not statistically significant at all (P > .05).

Comorbid anxiety disorders were common especially GAD, PTSD, and social phobia. Compared to MDDnoPD, we found a significantly higher percentage of GAD, social phobia, PTSD, and specific phobia, in MDD+PD patients.

Patient-reported measures of QOL, functioning, and depressive symptom severity were significantly different between MDD+PD and MDDnoPD. Compared to MDD patients without comorbid panic disorder, the mean QOL scores were worse in MDD+PD patients at baseline when measured by the Q-LES-Q (P = .005). Similarly, baseline functioning was worse in MDD+PD as measured by the WSAS (P = .001). Baseline depressive symptoms were significantly more severe in MDD+PD (P = .001) compared to MDDnoPD.

IMPACT OF SSRI TREATMENT ON QOL, FUNCTIONING, AND DEPRESSIVE SYMPTOMS

STAR*D Level1 entry and exit scores for QOL (Q-LES-Q, SF-12-PCS, and SF-12-MCS), functioning (WSAS), and depressive symptom severity (QIDS-SR), are displayed in Table 2. It is important to note that the sample size (and statistical significance) of MDD+PD patients decreased with each level of treatment, precluding drawing any conclusions about Level 3 and Level 4 MDD+PD patients. Moreover, Level 2 consisted of multiple different treatment options. The different treatments in Level 2 could not analyzed separately due to the lack of a sufficient sample size in each of the treatment categories in the MDD+PD group.

MDD+PD and MDDnoPD patients showed both statistically (P values), and clinically (effect sizes) significant improvements after treatment. At the end of Level 1 treatment with citalopram, MDD+PD treatment effect sizes were generally large with d = 0.71 on the Q-LES-Q, d = 0.89 on the SF-12-MCS, d = 0.77 on the WSAS, and d = 1.02 on the QIDS-SR.
(all $P$ values <.001). For MDDnoPD, the values were $d = 0.78$ on the Q-LES-Q, $d = 0.99$ on the SF-12-MCS, $d = 0.74$ on the WSAS, and $d = 0.94$ on the QIDS-SR (all $P$ values <.001).

Although the pre/posttreatment “change” was not significant between MDD+PD and MDDnoPD groups on all measures, statistically significant differences were detected showing that mean functional scores were significantly worse in MDD+PD patients following treatment, as measured by the Q-LES-Q, SF-12-PCS, and WSAS in the unadjusted analysis. However, due to confounding variable differences at baseline highlighted in Table 1, we conducted regression analyses to examine the association between posttreatment outcomes and PD, adjusting for age, college education, comorbid anxiety disorders (GAD, PTSD, social phobia, and specific phobia), as well as baseline QOL (Q-LES-Q, and SF-12), functioning (WSAS), and depressive symptom severity (QIDS-SR). A common theme emerged from the multiple linear regression models: lack of college education, presence of PTSD, and low baseline QOL as measured by the Q-LES-Q were significantly associated with poorer posttreatment outcomes of QOL, functioning, and depressive symptom severity on all measures: Q-LES-Q, SF-12 PCS, WSAS, and QIDS-SR (all $P$ values <.001), except for the SF-12 MCS ($P = .027$). The presence of PD was not a significant predictor of poor outcome on any of the measures. Age was significantly associated only with poor physical QOL outcome (SF-12 PCS) ($P < .0001$). Baseline SF-12 PCS significantly predicted posttreatment Q-LES-Q, WSAS, and expectedly SF-12 PCS (all $P$ values <.001). Baseline depressive symptom severity was significantly associated with post-treatment scores of both physical QOL (SF-12 PCS) ($P = .0052$) and QIDS-SR ($P < .0001$).

**PROPORTIONS OF PATIENTS WITH SEVERE IMPAIRMENTS IN QUALITY OF LIFE AND FUNCTIONING**

STAR*D Level1 entry and exit proportions of patients with severe impairments in QOL (2SD below community norms, i.e., Q-LES-Q<55.7, SF-12-PCS<30, and SF-12-MCS<30), and functioning (WSAS>20), are displayed in Table 3. Data from Level 3 and Level 4 MDD+PD patients could not be interpreted due to small sample sizes. Level 2 data were not presented because dividing the different Level 2 treatment groups could lead to serious diminution of sample size in the MDD+PD group.

**Baseline Proportions**—Severe impairments in QOL and functioning at baseline were detected in the large majority of MDD+PD and MDDnoPD patients when measured by the Q-LES-Q (86.1% and 85.5%), the SF-12-MCS (75.2% and 71.2%), the WSAS (77.2% and 65.2%), and in a small proportion of patients on the SF-12-PCS (13.8% and 8.2%). No statistically significant differences were identified between the MDD+PD and MDDnoPD groups. However, in functioning using the WSAS, MDD+PD tended toward a significantly higher proportion of severely impaired patients at entry ($P = .013$).

**Posttreatment Proportions**

1. **Impact of treatment on MDD+PD and MDDnoPD:** The posttreatment data showed a statistically significant drop in the percentage of MDD+PD and MDDnoPD patients experiencing severe impairments in QOL and functioning. At the end of Level 1 treatment...
with citalopram, the percentage of MDD+PD patients with severe impairments dropped on
the Q-LES-Q from 86.1% to 56.4%, on the SF-12-MCS: from 75.2% to 32.7%, and on the
WSAS: from 77.2% 41.6% (all p values <0.001). For MDDnoPD, the percentages dropped
from 85.5% to 50.2% on the Q-LES-Q, from 71.2% 28.8% on the SF-12-MCS, and from
65.2% to 36% on the WSAS (all p values <0.001). The percentage of patients with severe
impairments on the SF-12-PCS in MDD+PD showed a numerical drop on the SF-12-PCS
that was not statistically significant, whereas MDDnoPD group showed a small numerical
increase that was statistically significant (P = .005).

2. Comparing treatment effects between MDD+PD and MDDnoPD: The proportions of
patients with severe impairments in QOL and functioning were not statistically significantly
different between MDD+PD and MDDnoPD groups on all measures when comparing the
two groups at treatment exit.

PREDICTORS OF SEVERE QOL AND FUNCTIONING IMPAIRMENTS
Using multiple logistic regression models, we explored the relationship between comorbid
PD and posttreatment severe QOL and functioning impairments while adjusting for age,
college education, comorbid anxiety disorders (GAD, PTSD, social phobia, and specific
phobia), in addition to baseline QOL (Q-LES-Q, and SF-12), functioning (WSAS), and
depressive symptom severity (QIDS-SR). The analysis consistently revealed the odds for
posttreatment severe QOL (as measured by the Q-LES-Q) and functioning (as measured by
the WSAS) impairments were not significantly associated with PD, were significantly
lowered in patients with college education (OR = 0.71; 95%CI = 0.58–0.87; P = .0011, and
OR = 0.72; 95%CI = 0.57–0.90; P = .0041, respectively), and were significantly increased in
the presence of PTSD (OR = 1.65; 95%CI = 1.06–2.56; P = .0274, and OR = 2.23; 95% CI
= 1.44–3.45; P = .0003, respectively).

THE IMPACT OF COMORBID PANIC DISORDER ON THE RATE OF MDD REMISSION
MDD remission rates were numerically lower in the MDD+PD group compared to the
MDDnoPD group in Level1 (26.7% vs. 36%), however this difference was not statistically
significant (P = .07). We tested the relationship between MDD remission and comorbid PD
using a multivariable logistic regression model. Adjusting for the above-described relevant
confounding variables, MDD+PD patients were not less likely to remit as hypothesized. In
this sample, the odds for MDD remission after treatment with citalopram, were higher in
patients with the following characteristics: younger age, college education, higher baseline
QOL (Q-LES-Q), higher baseline physical QOL (SF-12 PCS), and lower baseline depressive
symptom severity (QIDS-SR).

DISCUSSION
This analysis revealed three main findings: (1) Patients with MDD with comorbid PD
experienced worse QOL and functioning at entry compared to MDDnoPD; QOL and
functioning significantly improved after SSRI-treatment using citalopram, with no
significant differences between groups; (2) The large majority of MDD patients with or
without comorbid PD experienced severe impairments in QOL and functioning at entry, and

Depress Anxiety. Author manuscript; available in PMC 2016 March 04.
despite a significant drop in these percentages after treatment, at least 30–60% patients still experienced severe impairments, with no statistically significant differences between the two groups; (3) Patients with MDD+PD were as likely to achieve MDD remission as those with MDDnoPD, after SSRI-treatment with citalopram.

Panic disorder is a seriously disabling illness especially due to the recurrent unexpected nature of the episodes, the intensity of the episodes, and the constant concern about experiencing them or handling their consequences, leading to significant behavioral changes such as avoidance and isolation. The above experiences subsequently affect most life aspects especially when combine with MDD. Our study shows that MDD+PD patients who entered the study had worse QOL, functioning, and depressive symptom severity at entry, compared to MDDnoPD patients. These finding are consistent with the study by Watson et al., where depressive comorbidity with PD significantly diminished QOL, and the study by Hegel et al. where QOL and functioning were significantly impaired in depressed older adults with PD comorbidity. In contrast, Sherbourne et al. showed nonsignificant effects for PD or generalized anxiety disorder (GAD) on QOL. Additionally, Mittal et al. showed that PTSD and, GAD but not PD resulted in additional QOL impairment at baseline. It appears that the above two studies had fewer PD patients to detect a difference. Interestingly, the examination of predictors of poor outcome in our study showed that the presence of PTSD (not PD) significantly increased the odds for posttreatment severe impairment in QOL and functioning.

QOL and functioning significantly improved, statistically and clinically, in MDD+PD and MDDnoPD, after the first trial of antidepressants using the SSRI citalopram, with effect sizes of 0.71–0.78 on the Q-LES-Q, 0.89–0.99 on the SF-12-MCS, and 0.74–0.77 on the WSAS, at the end of Level 1. Despite treatment, a sizeable proportion of patients were left with severe QOL impairments (50–68% using the Q-LES-Q, and 29–40% using the SF-12-MCS) and severe functioning impairments (36–63% using the WSAS). Problems with QOL and functioning are linked to high relapse rates, ongoing suffering, and increased utilization of health services.

Although QOL and functioning improved in both groups at the end of treatment with citalopram, they remained worse for MDD+PD patients with mean exit scores indicative of severe impairments on the Q-LES-Q and the WSAS in the unadjusted analysis. Benvenuti et al., had shown that panic–agoraphobic spectrum symptoms were associated with posttreatment impairments in quality of life and functioning even after controlling for residual depressive symptoms in MDD. However, multivariable regression analyses in our study revealed that lack of college education, presence of PTSD, and low baseline QOL (Q-LES-Q) and not PD were significantly associated with poorer posttreatment outcomes of QOL, functioning, and depressive symptom severity as measured using Q-LES-Q, SF-12 PCS, WSAS, and QIDS-SR.

Depressive symptom severity was not significantly different in both after-treatment groups, probably due to SSRI effects on PD. MDD remission rates in MDD+PD were generally lower compared to MDDnoPD, although this difference was not significant at the end of treatment with citalopram. Logistic regression analyses showed that Level 1 treatment with
SSRI-citalopram yielded similar odds of MDD remission for MDD+PD compared to MDDnoPD. This finding is consistent with the ARTIST trial (A Randomized Trial Investigating SSRI Treatment) that showed that at month 6, after adjusting for baseline depression severity, there was no correlation between baseline panic and outcomes of depression treatment, with similar rates of remission or partial response.\[17\] In our sample, younger age, college education, higher baseline QOL (Q-LES-Q), higher baseline physical QOL (SF-12 PCS), and lower baseline depressive symptom severity (QIDS-SR) had higher odds for MDD remission. These findings are consistent with other studies of MDD.\[34\]

The literature clearly shows that patients experiencing comorbid depression and anxiety have more severe symptoms,\[31\] more chronic course,\[35\] increased rate of psychiatric admissions,\[36\] increased rate of suicide and suicide attempts,\[37\] serious impairment in social and occupational functioning,\[32\] and poor quality of life.\[38\] The concept of anxious depression introduced by Fava et al.,\[39\] was shown to be experienced by nearly 46% of depressed patients. Although we focused primarily on PD comorbidity, our findings overlap with the research on anxious MDD, as these patients tend to experience more functional limitations, and impairments in QOL and functioning.\[39\]

While many studies have focused on depressive symptom severity and remission in disorders comorbid with MDD, very few have explored the impact of treatment on QOL and functioning in MDD+PD, as compared to MDDnoPD. This study’s findings highlight the importance of measuring and addressing QOL and functioning during the course of treatment of MDD with and without PD. The relationship between depressive severity and functional measures was explored in previous studies showing that although QOL and functioning are worse with more severe depressive symptoms, the latter accounted for only 48% of the variance.\[8\] These findings support the notion that functional measures are still needed in addition to severity measures in order to assess the full impact of the illness. Novel ways to measure the burden of illness by incorporating depressive symptom severity, functioning, and QOL such as the individual burden of illness index for depression (IBI-D),\[40\] could potentially serve in assessing the impact of interventions in comorbid conditions with MDD such as PD. Future research needs to develop and investigate methods of ameliorating/restoring QOL and functioning during the course of treatment of MDD, PD, and MDD+PD.

**LIMITATIONS AND STRENGTHS**

Limitations of this study include previously described STAR*D study limitations;\[34\] most notably: the absence of a placebo control group, lack of structured interviewing to confirm primary and comorbid diagnoses, and patient attrition as the trial progressed from Level 1 through 4 due to drop-outs as treatments failed. The vast majority of the patients in this data analysis were Caucasian, thus limiting the ability to generalize the results to other ethnic groups. Furthermore, studying the effects of concomitant medications, comorbid substance use and other psychiatric conditions could have provided more information in comparing patients with and without PD. Many patients in both the MDDnoPD and MDD+PD groups had additional comorbid medical conditions that may have impacted outcomes. We were limited by the STAR*D study that did not use measures to detect the clinical severity of PD.
specifically such as the PDSS or the HAM-A; thus missing an opportunity to add more clinical utility to the findings. Another limitation might be the reliance on self-report for measuring entry and exit outcomes. Notwithstanding this limitation, the measures used for QOL, functioning, and depressive symptom severity have very well established validity and reliability, and their utilization is in line with the emerging stress on patient-reported outcomes in medicine with efforts by NIH-PROMIS, FDA, and WHO. Interpretation of the study findings is also limited by the confusion in the functional outcome literature between QOL and functioning. We sought to clearly distinguish them earlier in this manuscript, however one of the limitations of the SF-12 and its parent; SF-36 (both commonly listed as QOL measures) is they continue to mix the operational definitions functioning and QOL in their items.

A major strength of this study is the inclusion of effect size as a measure of assessing the clinical significance of changes in addition to statistical significance. STAR*D recruited a rather large group of treatment-seeking depressed outpatients and then provided treatment both at primary care and psychiatry specialty sites, making generalization of the study findings to clinical practice feasible.

CONCLUSION

This analysis from a large dataset shows that MDD+PD patients experienced lower QOL and functioning at entry compared to individuals with MDDnoPD. Despite the improvements achieved by both groups with treatment, a sizable proportion of patients remained with severe QOL and functioning impairments after treatment. Clinicians and researchers might need to incorporate QOL and functioning measures in assessing and treating patients with MDD in order to identify pre- and posttreatment impairments and design additional interventions aimed at restoring QOL and functioning especially in MDD patients with comorbid PD. Future research should investigate the design and efficacy of innovative interventions to ameliorate QOL and functioning after treatment.

Acknowledgments

Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported “Sequenced Treatment Alternatives to Relieve Depression” (STAR*D). STAR*D focused on nonpsychotic major depressive disorder in adults seen in outpatient settings. The primary purpose of this research study was to determine which treatments worked best if the first treatment with medication does not produce an acceptable response. The study was supported by NIMH Contract # N01MH90003 to the University of Texas Southwestern Medical Center. The ClinicalTrials.gov identifier is NCT00021528. This manuscript reflects the views of the authors and may not reflect the opinions or views of the STAR*D study investigators or the NIH.

Dr. IsHak received research support unrelated to the subject of this manuscript from NARSAD (quality of life in major depression) and Pfizer (ziprasidone as monotherapy for major depression) ended on December 31, 2011.

REFERENCES


Level 1: Citalopram

Level 2: SWITCHING to Bupropion SR, Sertraline, Venlafaxine, or CBT OR AUGMENTING with Bupropion SR, Buspirone, or CBT

Level 3: SWITCHING to Mirtazapine or Nortriptyline OR AUGMENTING with Lithium or T3

Level 4: SWITCHING to Tranylcypromine or Combined Mirtazapine and Venlafaxine XR

Figure 1.
STAR*D interventions
### TABLE 1
Demographic and clinical characteristics of the STAR*D major depressive disorder (MDD) patients with (MDD+PD) and without (MDDnoPD) panic disorder (PD)

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>All</th>
<th>MDD+PD</th>
<th>MDDnoPD</th>
<th>P value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>2,280 (100%)</td>
<td>101 (4.4%)</td>
<td>2,179 (95.6%)</td>
<td>–</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>18.1–75.6</td>
<td>18.8–58.1</td>
<td>18.1–75.6</td>
<td>–</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>42.6 (13.0)</td>
<td>39.8 (11.4)</td>
<td>42.7 (13.1)</td>
<td>.014</td>
</tr>
<tr>
<td>Female</td>
<td>1,432 (62.8%)</td>
<td>72 (71.3%)</td>
<td>1,360 (62.4%)</td>
<td>.089</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,846 (80.9%)</td>
<td>85 (84.2%)</td>
<td>1,761 (80.8%)</td>
<td>.480</td>
</tr>
<tr>
<td>Hispanic</td>
<td>239 (10.5%)</td>
<td>16 (15.8%)</td>
<td>223 (10.2)</td>
<td>.103</td>
</tr>
<tr>
<td>College graduate</td>
<td>686 (30.1%)</td>
<td>20 (19.8%)</td>
<td>666 (30.6%)</td>
<td>.028</td>
</tr>
<tr>
<td>Employed</td>
<td>1,301 (57.1%)</td>
<td>51 (50.5%)</td>
<td>1,250 (57.4%)</td>
<td>.207</td>
</tr>
<tr>
<td>Living with spouse/partner</td>
<td>1,046 (45.9%)</td>
<td>43 (42.6%)</td>
<td>1,003 (46.0%)</td>
<td>.562</td>
</tr>
<tr>
<td>Comorbid anxiety disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific phobia</td>
<td>15 (0.7%)</td>
<td>4 (4.0%)</td>
<td>11 (0.5%)</td>
<td>.003</td>
</tr>
<tr>
<td>Social phobia</td>
<td>82 (3.6%)</td>
<td>21 (20.8%)</td>
<td>61 (2.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OCD</td>
<td>16 (0.7%)</td>
<td>2 (2.0%)</td>
<td>14 (0.6%)</td>
<td>.16</td>
</tr>
<tr>
<td>PTSD</td>
<td>122 (5.4%)</td>
<td>15 (14.9%)</td>
<td>107 (4.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GAD</td>
<td>141 (6.2%)</td>
<td>22 (21.8%)</td>
<td>119 (5.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline scores: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL (Q-LES-Q)</td>
<td>41.5 (14.2)</td>
<td>36.8 (17.0)</td>
<td>41.7 (14)</td>
<td>0.005</td>
</tr>
<tr>
<td>Physical QOL (SF-12–PCS)</td>
<td>49.5 (12.1)</td>
<td>46.9 (12.8)</td>
<td>49.6 (12.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>Mental QOL (SF-12–MCS)</td>
<td>26.1 (8.3)</td>
<td>24.5 (8.6)</td>
<td>26.2 (8.2)</td>
<td>0.048</td>
</tr>
<tr>
<td>Functioning (WSAS)</td>
<td>23.8 (8.9)</td>
<td>26.8 (8.5)</td>
<td>23.7 (8.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression severity (QIDS-SR)</td>
<td>15.4 (5.0)</td>
<td>17.4 (4.8)</td>
<td>15.6 (4.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^{a}\) P values are considered significant at 0.01 or less (Bonferroni-adjusted).

\(^{a}\) P values are obtained from Pearson’s Chi-squared test with Yates’ continuity correction.
### TABLE 2

Mean (SD) of measurements, effect sizes (ES), and comparisons of MDD+PD to MDDnoPD patients

<table>
<thead>
<tr>
<th>QOL: QLESQ</th>
<th>MDD + Panic</th>
<th>MDD no Panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Exit</td>
<td>N</td>
</tr>
<tr>
<td>QLESQ</td>
<td>36.8(17.0)</td>
<td>51.6(23.6)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001 d = 0.71</td>
<td></td>
<td>2,179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QOL (physical): SF12-PCS</th>
<th>MDD + Panic</th>
<th>MDD no Panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Exit</td>
<td>N</td>
</tr>
<tr>
<td>PCS12</td>
<td>46.9(12.8)</td>
<td>45.3(11.7)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>P = .043 d = 0.20</td>
<td></td>
<td>2,179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QOL (mental): SF12-MCS</th>
<th>MDD + Panic</th>
<th>MDD no Panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Exit</td>
<td>N</td>
</tr>
<tr>
<td>MCS12</td>
<td>24.5(8.6)</td>
<td>37.5(12.4)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001 d = 0.89</td>
<td></td>
<td>2,179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functioning: WSAS</th>
<th>MDD + Panic</th>
<th>MDD no Panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Exit</td>
<td>N</td>
</tr>
<tr>
<td>WSAS</td>
<td>26.8(8.5)</td>
<td>18.2(12.7)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001 d = 0.77</td>
<td></td>
<td>2,179</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dep Sev: QIDS-SR</th>
<th>MDD + Panic</th>
<th>MDD no Panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Exit</td>
<td>N</td>
</tr>
<tr>
<td>QIDS-SR</td>
<td>17.4(4.8)</td>
<td>10.6(6.6)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>P &lt; .001 d = 1.02</td>
<td></td>
<td>2,179</td>
</tr>
</tbody>
</table>

P values are considered significant at 0.01 or less (Bonferroni-adjusted).

*d* = Effect size using Cohen’s *d* (statistically significant large/near large values in bold), QIDS-SR, quick inventory of depressive symptomatology-self report; Q-LES-Q, quality of life measure: quality of life, enjoyment, and satisfaction questionnaire—short form; SF-12-PCS, 12-item version of the medical outcomes study—short form, physical component scale, SF-12-MCS, 12-item version of the medical outcomes study—short form, mental component scale, WSAS, work and social adjustment scale.
TABLE 3

N/percentage of patients with severe QOL and functioning impairments by various measures and remission

<table>
<thead>
<tr>
<th>QOL: QLESQ</th>
<th>MDD + Panic</th>
<th>MDD no panic</th>
<th>Between group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Base</td>
<td>Exit</td>
</tr>
<tr>
<td>QLESQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>86.1%</td>
<td>56.4%</td>
</tr>
<tr>
<td>QOL (physical): SF12-PCS</td>
<td>MDD + Panic</td>
<td>MDD no panic</td>
<td></td>
</tr>
<tr>
<td>PCS12</td>
<td>N</td>
<td>Base</td>
<td>Exit</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>13.8%</td>
<td>9.9%</td>
</tr>
<tr>
<td>QOL (mental): SF12-MCS</td>
<td>MDD + Panic</td>
<td>MDD no panic</td>
<td></td>
</tr>
<tr>
<td>MCS12</td>
<td>N</td>
<td>Base</td>
<td>Exit</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>75.2%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Functioning: WSAS</td>
<td>MDD + Panic</td>
<td>MDD no panic</td>
<td></td>
</tr>
<tr>
<td>WSAS</td>
<td>N</td>
<td>Base</td>
<td>Exit</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>77.2%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Dep Sev: QIDS-SR</td>
<td>MDD + Panic</td>
<td>MDD no panic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>MDD remission</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>26.7%</td>
<td></td>
</tr>
</tbody>
</table>

P values are considered significant at .01 or less (Bonferroni-adjusted).

Definitions: Severe Functioning impairment = WSAS > 20, Severe QOL impairments = Q-LES-Q < 55.7, SF-12 PCS < 30, SF-12 MCS < 30, Remission = QIDS-SR = < 5.

QIDS-SR, quick inventory of depressive symptomatology self-report; Q-LES-Q, quality of life measure; quality of life, enjoyment, and satisfaction questionnaire—short form; SF-12 PCS, 12-item version of the medical outcomes study—short form, physical component scale; SF-12 MCS, 12-item version of the medical outcomes study—short form, mental component scale, WSAS, work and social adjustment scale.