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Major Depression Comorbid with Medical Conditions: Analysis of Quality of Life, Functioning, and Depressive Symptom Severity

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ABSTRACT ~ Background: *The presence of Major Depressive Disorder (MDD) is often comorbid in patients with a variety of general medical conditions (GMCs) which could lead to less favorable outcomes.* ***Objective:*** *The goal of this analysis is to examine functional outcomes of QOL and functioning before and after antidepressant treatment among patients with MDD with and without GMCs.* ***Methods:*** *We performed a secondary analysis based on the STAR*D database. The analysis included two patient groups from the STAR*D trial: 1,198 patients comorbid with MDD and GMCs (MDD + GMC) and 1,082 patients with MDD and no GMCs (MDDnoGMC), as defined by the Cumulative Illness Rating Scale. We analyzed depressive symptom severity, functioning and quality of life (QOL) before and after level 1 treatment with citalopram.* ***Results:*** *At baseline, the MDD + GMC group had significantly lower QOL ($p < 0.001$) and functioning ($p = 0.001$) than the MDDnoGMC group, although depressive symptom severity was not significantly different. Following antidepressant treatment, QOL, functioning and depressive symptom severity significantly improved for both MDD + GMC and MDDnoGMC groups. However, patients with MDD + GMC were more likely to experience severe impairments in QOL in (56.8% vs. 43.5% for MDDnoGMC, $p < 0.001$) and functioning (42.5% vs. 29.3% for MDDnoGMC, $p < 0.001$) following treatment. The remission rate was significantly lower for MDD + GMC (30.6% vs. 41.1% for MDDnoGMC, $p < 0.001$).*

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Conclusions: *Our findings suggest that antidepressant treatment had a positive impact on patients with and without GMCs. However, those with GMCs experienced not only a lower remission rate, but also continued to experience more significantly severe impairments in QOL and functioning.* Psychopharmacology Bulletin. *2018;48(1):8–25.*

Introduction

Depression affects more than 350 million people and is the leading global cause of disability and the third leading contributor to disease.[1] As a global health concern, the human toll and economic costs of untreated depression are staggering. Depressed individuals experience substantial impairments in functioning, quality of life (QOL) and an increased risk for physical and mental disorders (i.e., comorbidity). Given the high comorbidity between depression and general medical conditions (GMCs), individuals who do not suffer from depression but have a chronic medical condition, are at a substantial risk of developing depression through a range of biopsychosocial pathways.

Amidst advances in treatments for depression, there is growing recognition that effective interventions must extend beyond symptom reduction, and aim to improve QOL and functioning.[2,3] QOL is defined as the individual's perception and satisfaction of their psychological, social and physical health. Whereas, functioning is considered as an individual's performance of life activities, such as work, relationships, and leisure.[2] QOL and functioning are both patient-reported constructs that are associated with objective markers of health and are useful for quantifying the efficacy of antidepressant therapies.[3] Given the multiple biopsychological pathways that contribute to depression, it is not surprising that QOL and functioning outcomes are influenced by GMCs.[3,4] In addition to the adverse impact on QOL and functioning, comorbidity between Major Depressive Disorder (MDD) and GMCs is associated with greater depression symptom severity and GMC severity, decreased treatment adherence and a higher cost of care, compared to individuals suffering from MDD without GMCs.[5,6]

Despite existing studies investigating QOL and functioning in depression co-morbid with GMCs,[7,8] these associations have not been examined extensively in the context of treatment for depression. To increase the knowledge in this area, we conducted a secondary analysis of the publicly-available Sequenced Treatment Alternatives to Relieve Depression or (STAR*D) data set, characterizing a large group of patients with MDD who participated in a sequenced study to treat their depression. The current analysis sought to compare the effectiveness of first line antidepressant treatment (pre and post-treatment scores) on depressive symptom severity, functioning, and QOL in two groups with

MDD, those with GMCs (MDD + GMC) and those without GMCs (MDDnoGMC).

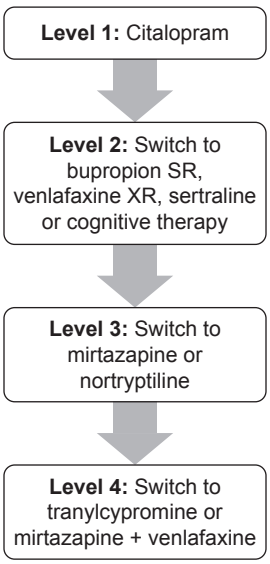
Methods

Study Population and Data Collection

The STAR*D study remains the largest National Institute of Mental Health-funded study on MDD treatment, consisting of sequential treatment trials (see Figure 1). The study methodology has been described in detail elsewhere.[9,10] The STAR*D study enrolled 4,041 outpatients (age range = 18–75). Subjects were recruited from 18 primary care and 23 psychiatric care sites in the United States from 2001–2007. Subjects were eligible to participate if they had a diagnosis of MDD and were seeking treatment at the care sites. Subjects were excluded if they had a history of poor tolerance to the study medication, a substance use disorder requiring detoxification, or an eating disorder or obsessive compulsive disorder. Of the 4,041 subjects, 29% were initially excluded (931 did not meet the study requirement to have at least a "moderate" level of depression, and 234 did not return after the baseline visit) resulting in 2,876 subjects included in Level 1 of the study. In the current analysis, 596 subjects were excluded due to incomplete data, resulting in the analysis of 2,280 subjects. We obtained a data use certificate from the NIMH to analyze the STAR*D Pub Ver3 dataset. Eligibility for data

FIGURE 1

STAR*D Treatment Levels



analyses required all subjects to have complete data values for every outcome measure used in analysis, both at entry and exit from the trial. Treatment was started with Citalopram for 12–14 weeks. Subjects were moved into the next level (switched to an antidepressant class or augmented with a different antidepressant), if they did not achieve remission at exit from their current level. Subjects who became symptom-free or achieved remission during the 12–14 weeks of Citalopram treatment moved to a 12-month follow-up period with continued Citalopram.

Outcome Measures and Definitions

Cumulative Illness Rating Scale (CIRS)

The presence of GMCs was assessed using the 14-item CIRS.[11,12] The CIRS assesses the number, severity and overall morbidity burden of 14 general medical conditions, spanning multiple organ systems. Given this study's focus on physical medical comorbidities, psychiatric conditions (item 14) were excluded from the analysis. The severity of medical illnesses was scored on the CIRS on a scale 0–4, with 0 indicating no impairment and 4 demonstrating extremely severe disability. The presence of GMC was defined by a threshold score of ⩾2 on a CIRS item; the same method was used by the STAR*D investigators.[13]

Quality of Life Enjoyment and Satisfaction Questionnaire—short form (Q-LES-Q)

The scores and interpretation for QOL, functioning and depressive symptom severity are presented in Table 1a. The QOL was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire—short form (Q-LES-Q),[14,15] a 16-item instrument evaluating physical health, mood, work, daily functioning, economic status, and other domains. Each item was scored on a 5-point Likert scale (1 = very poor to 5 = very good). Results were summed from the first 14 items, divided by 70 (the maximum possible score) and multiplied by 100, giving a total score range of 0–100, with a higher score indicating greater satisfaction. Community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3). Scores below 1 SD of community norms (i.e., ⩾67) were considered 'within-normal range,' whereas scores greater than 2 SD below community norms (i.e., ⩽55.7) were considered 'severely impaired,' and scores between 55.7–67 were indicative of 'mild to moderately-impaired' QOL.[15] The Q-LES-Q has demonstrated strong psychometric properties among depressed populations, with a Cronbach's alpha of 0.90, test-retest reliability of r = 0.74,[16] has good construct and criterion validity.[15]

TABLE 1A

Interpretation of QOL, Functioning, Depressive Symptom Severity and Remission

OUTCOME MEASURES	INTERPRETATION	SCORES
Quality of Life (QOL)		
Q-LES-Q = 0–100	Normal QOL	>67
	Moderately impaired QOL	55.7–67
	Severely impaired QOL	<55.7
SF-12-PCS = 0–100 and	Normal QOL	>40
SF-12-MCS = 0–100	Moderately impaired QOL	30–40
	Severely impaired QOL	<30
Functioning		
WSAS = 0–40	Normal functioning	<10
	Significantly impaired functioning	10–20
	Severely impaired functioning	>20
Depression & Remission		
QIDS-SR = 0–27	No depression	0–5
	Mild depression	6–10
	Moderate depression	11–16
	Severe depression	17–20
	Very severe depression	21–27
	Remission	<5

Abbreviations: 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; WSAS, Work and Social Adjustment Scale.

Work and Social Adjustment Scale (WSAS)

Functioning was evaluated using the Work and Social Adjustment Scale (WSAS).[17] The WSAS is a 5-item self-report measure using a 0–8 Likert scale, with 0 indicating no impairment and 8 indicating very severe impairment in functioning in such domains as work, close relationships, social activities, and others. Total range of scores is 0–40, with higher numbers showing greater severity. Scores <10 were considered within-normal, scores between 10–20 are considered significant impairment, and scores >20 were considered severely-impaired. The WSAS demonstrates good test-retest reliability (0.73) and internal consistency (Cronbach's alpha 0.70 to 0.94).[18,19]

Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)

The Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) was used to determine the severity of depressive symptoms.[20] The QIDS-SR rates symptom domains based on the DSM criteria for a major depressive episode, using a scoring system with a range from 0 (not depressed) to 27 (most severely depressed), and remission is defined as a score ⩽5.[21] The QIDS-SR has been shown to be highly correlated

with both the clinician rated Inventory of Depressive Symptomatology (IDS)[21] and the Hamilton rating scale for depression.[22,23] It has a high internal consistency (Cronbach's alpha of 0.86).[22]

Statistical Methods

The variables were confirmed to have a normal distribution (Shapiro–Wilk test) and homogeneity of variance (Levene's test). Summary statistics are presented as means and standard deviations (SD) for continuous variables, and frequencies (%) for categorical variables. Paired t-tests were used for comparisons between entry and exit numerical outcomes, within each patient group. In order to highlight clinical significance, we calculated effect sizes for the measures,[24] in which a Cohen's *d* value of 0.2 is considered small, 0.5 is medium, and 0.8 is considered as a large effect.[25] As we calculated Cohen's *d* values in paired samples pre and post-treatment, effect sizes were corrected for correlated designs as detailed by Dunlap and colleagues in 1996 using Equation 3.[26] Entry to exit comparisons of binary variables within each level and follow-up were assessed using the exact version of the McNemar test for related proportions. The proportions of patients that scored 'within-normal' or 'severely-impaired' on QOL and functioning measures were compared between remitters and non-remitters at exit, using the Chi-square test (or Fisher's exact test for small sample sizes). Given the number of performed tests, we used an adjusted $p < 0.01$ significance level for each test. Analyses were performed using SPSS software, version 20 (Armonk, NY: IBM Corp, USA).

Results

Demographic Characteristics of MDD + GMC and MDDnoGMC

The baseline demographic and clinical characteristics of the analyzed sample (n = 2,280) and comparison between MDD + GMC (n = 1198) and MDDnoGMC (n = 1082) groups are shown in Table 1b. In the overall sample, the majority of patients were Caucasian (81.0%), almost two-thirds were women, and one-third were college graduates. At the time of enrollment, the mean age was 42.6 (SD = 13), more than half of the participants were employed, and almost half lived with a spouse/partner. Compared with the MDDnoGMC group, the MDD + GMC group showed the following statistically significant ($p < 0.001$) differences: they were older (46.9 vs. 37.8), fewer were Caucasian (77.5% vs. 84.9%), were less likely to have graduated from college (21.5% vs. 39.6%), were less likely to be employed (47.9% vs. 67.2%) and were more likely living with a spouse/partner (50.8% vs. 40.4%).

TABLE 1B

Baseline Demographic and Clinical Characteristics of the Star*D Analyzed Sample

	ALL	MDD + GMC	MDDNOGMC	P
Number of subjects	2,280	1198	1082	–
Age range	18.1–75.6	18.3–75.6	18.1–74.4	–
Mean age (SD)	42.6 (13.0)	46.9 (12.3)	37.8 (12.1)	<0.001
Female	1,432 (62.8%)	731 (61.0%)	700 (64.7%)	0.067
Caucasian	1,846 (81.0%)	928 (77.5%)	918 (84.9%)	<0.001
College graduate	686 (30.1%)	257 (21.5%)	428 (39.6%)	<0.001
Employed	1,301 (57.1%)	574 (47.9%)	727 (67.2%)	< 0.001
Living with spouse/partner	1,046 (45.9%)	609 (50.8%)	437 (40.4%)	<0.001
QIDS-SR entry (SD)	15.4 (4.8)	15.8 (4.8)	15.4 (4.9)	0.038
WSAS entry (SD)	23.8 (8.9)	24.4 (9.1)	23.2 (8.5)	0.001
Q-LES-Q entry (SD)	41.5 (14.2)	39.7 (14.8)	43.5 (13.2)	<0.001

Statistical significance = $p < 0.01$ (Bonferroni adjusted).
Abbreviations: QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; WSAS, Work and Social Adjustment Scale at Entry; Q-LES-Q, Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form.

Clinical Characteristics of MDD + GMC and MDDnoGMC Before Treatment

At entry or before treatment, patients with MDD + GMC had worse QOL and functioning compared to MDDnoGMC, as measured by the Q-LES-Q (39.7 vs. 43.5; $p < 0.001$) and WSAS (24.4 vs. 23.2 $p = 0.001$), respectively. However, depressive symptom severity at entry was not significantly different between the MDD + GMC and the MDDnoGMC group.

Impact of SSRI Treatment on QOL, Functioning and Depressive Symptom Severity in MDD + GMC and MDDnoGMC Groups

The change in QOL, functioning and depressive symptom scores before and after treatment (entry and exit scores) for the MDD + GMC and MDDnoGMC groups are presented in Table 2. Both groups showed statistically (*p*-values) and clinically (effect sizes) significant improvements in QOL, functioning and depressive symptom severity with treatment. At the end of Level 1 treatment with Citalopram, MDD + GMC effect sizes were generally medium with $d = 0.66$ on the Q-LES-Q, $d = 0.62$ on the WSAS, and $d = 0.92$ on the QIDS-SR (all p-values <0.001). For MDDnoGMC, the improvement values were generally large with $d = 0.96$ on the Q-LES-Q, $d = 0.97$ on the WSAS, and $d = 1.22$ on the QIDS-SR (all p-values < 0.001).

TABLE 2

Changes in QOL, Functioning and Depressive Symptom Scores at Entry and Exit Measured by Mean, (SD) and Effect Sizes

QOL: Q-LES-Q	*N*	Q-LES-Q ENTRY (SD)	Q-LES-Q EXIT (SD)	MEAN CHANGE (SD)	*P*	EFFECT SIZE*
ALL	2,280	41.5 (14.2)	56.6 (21.9)	15.1 (19.4)	<0.001	0.78
MDD + GMC	1198	39.7 (14.8)	52.7 (22.2)	13.1 (19.4)	<0.001	0.66
MDDnoGMC	1082	43.5 (13.2)	60.8 (20.8)	17.3 (19.3)	<0.001	0.96
Significance	–	<0.001	<0.001	<0.001	–	–
FUNCTIONING: WSAS	*N*	WSAS ENTRY	WSAS EXIT	MEAN CHANGE	*P*	EFFECT SIZE*
ALL	2,280	23.8 (8.9)	15.5 (12.1)	–8.3 (11.2)	<0.001	0.77
MDD + GMC	1198	24.4 (9.1)	17.4 (12.5)	–7.0 (11.0)	<0.001	0.62
MDDnoGMC	1082	23.2 (8.5)	13.4 (11.3)	–9.8 (11.3)	<0.001	0.97
Significance	–	0.001	<0.001	<0.001	–	–
DEPRESSIVE SYMPTOM SEVERITY: QIDS-SR	*N*	QIDS-SR ENTRY	QIDS-SR EXIT	MEAN CHANGE	*P*	EFFECT SIZE*
ALL	2,280	15.6 (4.8)	9.5 (6.5)	–6.1 (6.5)	<0.001	1.05
MDD + GMC	1198	15.8 (4.8)	10.4 (6.7)	–5.4 (6.5)	<0.001	0.92
MDDnoGMC	1082	15.4 (4.9)	8.6 (6.2)	–6.8 (6.4)	<0.001	1.22
Significance	–	0.038	<0.001	<0.001	–	–

*Effect Sizes with Dunlap correction.
P = Within-group significance values from entry to exit. Significance = *p*-values of between-group comparisons.
Statistical significance = $p < 0.01$ (Bonferroni adjusted).
Abbreviations: QOL: Q-LES-Q, Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form; Functioning: WSAS, Work and Social Adjustment Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self Report.

The greatest clinical effect sizes were observed in depressive symptom severity improvements (MDD + GMC = 0.92, MDDnoGMC = 1.22), with the MDD + GMC group showing a smaller effect size. The MDD + GMC group also showed the lowest effect sizes for the other outcome measures including QOL and functioning.

Proportions of Patients Scoring 'Within-normal' on QOL and Functioning

Table 3a shows the proportion of patients scoring 'within-normal' QOL (Q-LES-Q ≥67) and functioning (WSAS <10) at entry and exit for the overall study population, MDD + GMC group, and the MDDnoGMC group. The QOL significantly improved for all patients after treatment. However, at exit, a significantly lower proportion of patients in the MDD + GMC reported 'within-normal' QOL (28.3%) compared to patients in the MDDnoGMC group (40.4%, $p < 0.001$). Both groups had significant increases in the proportion of patients 'within-normal' functioning at exit, yet the MDD + GMC group consisted of a significantly lower proportion of 'within-normal' functioning compared to MDDnoGMC (32.7% vs. 44.9%, $p < 0.001$).

Proportions of Patients with Severe Impairments of QOL and Functioning

The proportions of patients with severely-impaired QOL and functioning at entry and exit are presented in Table 3b. At post-treatment, both groups had statistically significant ($p < 0.001$) decreases in the

TABLE 3A

Proportions of Patients Scoring 'Within-Normal' Quality of Life and Functioning at Entry and Exit

QOL: Q-LES-Q	*N*	WITHIN NORMAL Q-LES-Q ENTRY (%)	WITHIN NORMAL Q-LES-Q EXIT (%)	MCNEMAR TEST *P*-VALUE
ALL	2,280	3.2	34.0	<0.001
MDD + GMC	1198	2.8	28.3	<0.001
MDDnoGMC	1082	3.7	40.4	<0.001
Significance	–	0.203	<0.001	–
FUNCTIONING: WSAS	***N***	**WITHIN NORMAL WSAS ENTRY (%)**	**WITHIN NORMAL WSAS EXIT (%)**	**MCNEMAR TEST *P*-VALUE**
ALL	2,280	6.7	38.5	<0.001
MDD + GMC	1198	6.4	32.7	<0.001
MDDnoGMC	1082	6.9	44.9	<0.001
Significance	–	0.634	<0.001	–

TABLE 3B

Proportions of Patients with Severely Impaired Quality of Life and Functioning at Entry and Exit

QOL: Q-LES-Q	*N*	SEVERELY IMPAIRED Q-LES-Q ENTRY (%)	SEVERELY IMPAIRED Q-LES-Q EXIT (%)	MCNEMAR TEST *P*-VALUE
ALL	2,280	85.6	50.5	<0.001
MDD + GMC	1198	86.6	56.8	<0.001
MDDnoGMC	1082	84.4	43.5	<0.001
Significance	–	0.127	<0.001	–
FUNCTIONING: WSAS	*N*	SEVERELY IMPAIRED WSAS ENTRY (%)	SEVERELY IMPAIRED WSAS EXIT (%)	MCNEMAR TEST *P*-VALUE
ALL	2,280	65.8	36.2	<0.001
MDD + GMC	1198	68.0	42.5	<0.001
MDDnoGMC	1082	63.3	29.3	<0.001
Significance	–	0.016	<0.001	–

Statistical significance = $p < 0.01$ (Bonferroni adjusted),
Abbreviations: QOL: QLESQ, Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form; WSAS, Work and Social Adjustment Scale.
For QOL: QLESQ, within-normal is defined as Q-LES-Q scores within 1 SD of community norms. Since community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3), a Q-LES-Q > = 67 is considered within-normal. Severely-impaired is defined as Q-LES-Q scores greater than 2 SD below the community norms. Since community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3), a Q-LES-Q = < 55.7 is considered severely-impaired.
For functioning, within-normal is defined as WSAS scores of less than 10, severely-impaired is defined as WSAS scores of more than 20.
McNemar Test *p*-value = within-group significance values from entry to exit. Significance = *p*-values of between-group comparisons.

proportions of severely-impaired QOL (ALL = 85.6% to 50.5%, MDD + GMC = 86.6% to 56.8%, MDDnoGMC = 84.4% to 43.5%), and functioning (ALL = 65.8% to 36.2%, MDD + GMC = 68.0% to 42.5%, MDDnoGMC = 63.3% to 29.3%). These results reveal that for both MDD + GMC and MDDnoGMC groups, nearly half remained with severely-impaired QOL, and nearly one-third remained severely-impaired in functioning ($p < 0.001$).

Comparison of Remitters and Non-Remitters in MDD + GMC and MDDnoGMC Groups

After Level 1 treatment, scores for QOL and functioning were analyzed among remitters and non-remitters. Table 4a presents the proportion of remitters and non-remitters in both MDD + GMC and MDDnoGMC groups who had within-normal QOL and functioning at entry and exit. Statistically significant increases at exit in the within-normal proportions for both remitters and non-remitters in both groups were observed. However, more remitters reported within-normal QOL and within-normal functioning than non-remitters ($p < 0.001$). Also, compared to

MDDnoGMC remitters, MDD + GMC remitters were less likely to report within-normal QOL (81.3% vs. 69.5%, $p < 0.001$) and within-normal functioning scores (86.1% vs. 73.8%, $p < 0.001$).

At post-treatment and across all measures, remitters and non-remitters reported less frequent severely-impaired QOL and functioning scores; however, non-remitters were more likely to report severe impairment than remitters ($p < 0.001$; Table 4b). Additionally, compared to MDDnoGMC remitters, MDD + GMC remitters were more likely to report severely-impaired QOL (12.5% vs. 6%, $p < 0.007$); however, no statistically significant differences were detected in the proportions of patients who reported severely-impaired functioning between the two groups.

Discussion

Our analyses of QOL, functioning and depressive symptoms in the STAR*D population with and without comorbid GMCs have led to several important findings. First, at entry, the MDD + GMC group reported lower QOL and functioning than the MDDnoGMC group, despite a lack of difference in depressive symptom severity. Second, QOL, functioning and depressive symptom severity improved after treatment for both MDD + GMC and MDDnoGMC groups, but the improvement was notably reduced for the MDD + GMC group, as evidenced by the lower effect sizes. Third, although QOL and functioning improved in both groups at the end of treatment, a sizable proportion of all patients remained within the severely-impaired range of QOL and functioning. Fourth, in patients who achieved MDD remission, the presence of comorbid GMCs was associated with more frequent reports of severely-impaired QOL and functioning.

The broad context of GMCs allows applicability of these results to many medical specialties and health providers. It is dually recognized that GMCs are associated with an increased risk for developing MDD and that MDD is associated with the development of GMCs.[27–29] The bidirectional relationship between MDD and chronic conditions such as diabetes,[30,31] cardiovascular disease,[32–34] and neurological disorders[35–37] has been particularly well described. As is the case with GMCs, treating MDD is important in reducing QOL and functioning, as confirmed by many studies on QOL and depression.[38–41] The additive effects of MDD and GMCs on QOL and functioning are significant, and may negatively contribute directly or indirectly to impair QOL and functioning. Measurement of symptom severity alone may fail to capture the impact of MDD or other diseases on these patient-centered domains.

Our findings highlight the importance of a global clinical assessment beyond depressive symptom severity, especially for older patients who

TABLE 4A

Proportions of Remitters/Non-Remitters Scoring Within-Normal Quality of Life and Functioning at Entry and Exit

		REMITTERS				NON-REMITTERS			DIFFERENCE AT EXIT
QOL: QLESQ	*N*	WITHIN NORMAL QLESQ ENTRY (%)	WITHIN NORMAL QLESQ EXIT (%)	MCNEMAR TEST *P*-VALUE	*N*	WITHIN NORMAL QLESQ ENTRY (%)	WITHIN NORMAL QLESQ EXIT (%)	MCNEMAR TEST *P*-VALUE	CHI-SQUARE *P*-VALUE
ALL	812	5.7	76.0	<0.001	1,468	1.8	10.8	<0.001	<0.001
MDD + GMC	367	4.9	69.5	<0.001	830	1.8	10.1	<0.001	<0.001
MDDnoGMC	445	6.3	81.3	<0.001	638	1.9	11.8	<0.001	<0.001
Significance	–	0.395	<0.001	–	–	0.915	0.314	–	–
FUNCTIONING: WSAS	*N*	WITHIN NORMAL WSAS ENTRY (%)	WITHIN NORMAL WSAS EXIT (%)	MCNEMAR TEST *P*-VALUE	*N*	WITHIN NORMAL WSAS ENTRY (%)	WITHIN NORMAL WSAS EXIT (%)	MCNEMAR TEST *P*-VALUE	CHI-SQUARE *P*-VALUE
ALL	812	10.2	80.5	<0.001	1,468	4.7	15.2	<0.001	<0.001
MDD + GMC	367	4.9	73.8	<0.001	830	4.5	14.6	<0.001	<0.001
MDDnoGMC	445	5.3	86.1	<0.001	638	5.0	16.1	<0.001	<0.001
Significance	–	0.563	<0.001	–	–	0.613	0.403	–	–

TABLE 4B

Proportions of Remitters/Non-Remitters With Severely Impaired Quality of Life and Functioning at Entry and Exit Functioning at Entry and Exit

		REMITTERS				NON-REMITTERS			DIFFERENCE AT EXIT
QOL: QLESQ	*N*	SEVERELY IMPAIRED QLESQ ENTRY (%)	SEVERELY IMPAIRED QLESQ EXIT (%)	MCNEMAR TEST *P*-VALUE	*N*	SEVERELY IMPAIRED QLESQ ENTRY (%)	SEVERELY IMPAIRED QLESQ EXIT (%)	MCNEMAR TEST *P*-VALUE	CHI-SQUARE *P*-VALUE
ALL	812	79.3	9.0	<0.001	1,468	89.0	73.4	<0.001	<0.001
MDD + GMC	367	79.8	12.0	<0.001	830	89.7	76.5	<0.001	<0.001
MDDnoGMC	445	78.9	6.5	<0.001	638	88.2	69.3	<0.001	<0.001
Significance	–	0.737	0.007	–	–	0.392	0.002	–	–
FUNCTIONING: WSAS	*N*	SEVERELY IMPAIRED WSAS ENTRY (%)	SEVERELY IMPAIRED WSAS EXIT (%)	MCNEMAR TEST *P*-VALUE	*N*	SEVERELY IMPAIRED WSAS ENTRY (%)	SEVERELY IMPAIRED WSAS EXIT (%)	MCNEMAR TEST *P*-VALUE	CHI-SQUARE *P*-VALUE
ALL	812	54.7	3.2	<0.001	1,468	71.9	54.5	<0.001	<0.001
MDD + GMC	367	54.2	3.8	<0.001	830	74.1	59.6	<0.001	<0.001
MDDnoGMC	445	55.1	2.7	<0.001	638	69.0	47.8	<0.001	<0.001
Significance	–	0.812	0.368	–	–	0.029	<0.001	–	–

Statistical significance = $p < 0.01$ (Bonferroni adjusted).

Abbreviations: QOL: QLESQ = Quality of Life, Enjoyment, and Satisfaction Questionnaire – Short Form; WSAS = Work and Social Adjustment Scale.

For QOL: QLESQ, within-normal is defined as Q-LES-Q scores within 1 SD of community norms. Since community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3), a Q-LES-Q > = 67 is considered within-normal. Severely-impaired is defined as Q-LES-Q scores greater than 2 SD below the community norms. Since community norm samples have an average Q-LES-Q of 78.3 (SD = 11.3), a Q-LES-Q = < 55.7 is considered severely-impaired.

For functioning, within-normal is defined as WSAS scores of less than 10, severely-impaired is defined as WSAS scores of more than 20.

McNemar Test *p*-value = within-group significance values from entry to exit. Significance = *p*-values of between-group comparisons.

are more likely to have multiple GMCs.[42,43] In contrast to our findings, Hays et al. found that functioning and well-being in MDD patients was comparable to that of non-depressed patients with chronic GMCs[44], while Bonicatto et al. reported that depressed adults had worse QOL than MDD + GMC patients.[45] Depression may also influence the self-perception of comorbid physical symptoms, such as pain, which may affect how depressed individuals report physical symptoms.[46,47] Nevertheless, our findings highlight the importance of utilizing patient-reported outcomes to ensure that symptomatic reductions for specific conditions lead to demonstrable improvements in patients' lives.

Our findings also suggest that integrating treatment for depression and comorbid GMCs may be a particularly efficient use of health-care resources. Previous studies report that 75% of patients who seek treatment for depression present to a primary care physician rather than a mental health practitioner.[48] There is significant heterogeneity in depression treatment in a primary health care setting.[49] On the other hand, there is abundant evidence which supports that moderate depression can be well managed in the primary care setting.[50] Evolving integrated service delivery models, such as Collaborative Care, show that appropriate treatment of depression in the primary care setting can improve symptoms and QOL, and is also cost-effective.[51,52]

In this study, non-remitters with GMCs reported the least favorable QOL and functioning; others have also observed lower remission rates and higher comorbidities in this population.[53] Therefore, alternative strategies in treating MDD + GMC need to be considered. Future research should evaluate new approaches to comprehensive treatments of comorbid depression with GMCs.

Limitations and Strengths

General limitations pertaining to the STAR*D methodology have been presented in detail in numerous publications.[9,10] Some of these limitations include the lack of placebo-controlled group, reliance on self-report measures, and the lack of clinician and participant blinding. The majority of patients were Caucasian and female; however, those drawbacks are mitigated to some extent by conducting enrollment at a large number of both primary care and specialty mental health settings.

The current analysis has some limitations that warrant consideration. First, our analysis was a post-hoc analysis, such that the hypotheses we evaluated were not specified in advance of the study. Thus, while our findings may help explain variation within subgroups of the study population, our ability to identify causal links is constrained. Second, the analysis did not consider within-group variations in type, severity

or duration of medical conditions among those in the MDD + GMC group. This was not possible within the STAR*D dataset, as the CIRS provides only broad medical categories and does not differentiate between particular conditions.[54] Distinguishing between painful and painless illnesses may have accounted for some variability in patient-centered outcomes. However, a separate STAR*D analysis on painful physical symptoms found that pain was not a predictor of worse treatment outcomes.[54] Thus, the impact of pain symptoms on the current analysis may be negligible.

Although the current analysis does not allow for interpretations for causal pathways of these findings, these results must be considered within a socio-demographic context. For example, two-thirds of the participants in the study were women, who often report greater depression burden in epidemiological studies. Moreover, a mounting body of evidence substantiates the influence of race, ethnicity and socioeconomic status on variations in functioning among individuals with diseases, such that those from lower socioeconomic status having greater impairments than those with higher socioeconomic status.[55–57] While not controlled in the current study, socioeconomic factors appear to influence health outcomes and QOL as a gradient across socioeconomic strata. Because of multiple vulnerabilities, people of lower socioeconomic status tend to have greater stress, and throughout the lifespan, present poorer health behaviors, greater disability and less access to quality care.[58] Future research should aim to replicate the results with a focus on minority populations.

Some of the strengths of STAR*D include a relatively large sample size, valid and reliable measures, and participant recruitment methods that may be more representative of the general population.[59] The strength of our own analysis lies in the strong statistical significance of findings ($p < .001$), as well as the presentation of effect sizes, which offer more clinically relevant findings.

Conclusion

The present analysis showed that subjects with MDD with or without GMCs benefitted across several domains from Citalopram treatment. However, the MDD + GMC patients experienced lower QOL and functioning at entry and exit, compared to MDDnoGMC patients. Furthermore, at exit, the MDD + GMC group had proportionally more patients with severely-impaired QOL and functioning. Despite the improvements achieved by both groups after treatment, a sizable proportion of patients remained with severely-impaired QOL and functioning. These results demonstrate that improvement

in depression symptom severity alone can provide a misleading impression of recovery, and impaired QOL and functioning may continue. Consequently, clinicians and researchers need to move beyond symptom assessment when treating MDD; and incorporating measures of QOL and functioning is critical to track patients' progress. Greater attention and ongoing evaluation of treatment response among individuals with comorbid MDD and GMCs is imperative. New methods and interventions to continuously improve QOL are critically needed to improve MDD prognosis and ensure comprehensive patient care, especially in medically-ill patients. ✤

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