Functional Impairment and Changes in Depression Subtypes for Women in STAR*D: A Latent Transition Analysis

Christine M. Ulbricht, PhD,¹ Anthony J. Rothschild, MD,^{2,3} and Kate L. Lapane, PhD¹

Abstract

Objective: To characterize the association between functional impairment and major depression subtypes at baseline and to characterize changes in subtypes by functional impairment level in women receiving citalopram in level 1 of the Sequenced Treatment Alternatives to Relieve Depression trial.

Method: Women who completed baseline and week 12 study visits were included. Items from the self-reported Quick Inventory of Depressive Symptomatology were used to define the latent depression subtypes. The Work and Social Adjustment Scale was used to classify baseline functional impairment. A latent transition analysis model provided estimates of the prevalence of subtype membership and transition probabilities by functional impairment level.

Results: Of the 755 women included, 69% had major functional impairment at baseline. Regardless of functional impairment level, the subtypes were differentiated by depression severity, appetite changes, psychomotor disturbances, and insomnia. Sixty-seven percent of women with normal/significant functional impairment and 60% of women with major impairment were likely to transition to a symptom resolution subtype at week 12. Women with baseline major impairment who were in the severe with psychomotor agitation subtype at the beginning of the study were least likely to transition to the symptom resolution subtype (4% chance).

Conclusions: Functional impairment level was related to both the baseline depression subtype and the likelihood of moving to a different subtype. These results underscore the need to incorporate not only depression symptoms but also functioning in the assessment and treatment of depression.

Introduction

MAJOR DEPRESSIVE DISORDER (MDD) is one of the most prevalent and burdensome diseases worldwide,^{1,2} producing substantial disability, morbidity, and mortality. In 2013, 15.7 million adults in the United States had experienced major depression in the previous year.³ MDD is the second leading cause of disability worldwide⁴ and is expected to be the leading cause by 2030.⁵ The extent of functional impairment seen with depression often exceeds that which is associated with many other common illnesses.⁶ MDD is a substantial public health issue especially for women, who have twice the odds of men for experiencing lifetime MDD.⁷ The 12-month prevalence of a major depressive episode among adult women in the United States has been estimated at 8%.³

Women and men experience certain aspects of depression differently and these differences appear to extend to func-

tioning. Women with MDD experience greater depression severity than men and have a greater burden of depressive disorders.^{4,8} More women than men experience a major depressive episode with severe functional impairment.¹⁷ When men with depression are affected by functional impairment, the domains in which functioning is impaired appear to differ by gender.⁹ Women with MDD appear to experience more physical limitations, while men report having impaired social relationships.⁹

Given the burden of MDD, effective treatment is necessary but information is limited on how to best treat people so that symptom remission and improved functioning are achieved.¹⁰ Despite a 400% increase in the use of antidepressant medication between 1988–1994 and 2005–2008,¹¹ only 51.7% people with depression receive any treatment.¹² Of the people who do receive treatment, fewer than half experience a clinically meaningful reduction in symptoms.^{10,13} This lack of satisfactory treatment response in depression might be partially explained

¹Department of Quantitative Health Sciences, ²Center for Psychopharmacologic Research and Treatment, Department of Psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts.

³UMass Memorial Healthcare, Worcester, Massachusetts.

by the nonspecific symptomatology and variability in severity and trajectory of the disease. More than 1,400 combinations of criteria symptoms are possible in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)¹⁶ and considerable differences in illness course, prominent symptoms, and treatment response have been observed.¹⁷

Although the presence of heterogeneity in depression is well established, how to best delineate depression subtypes defined by similar features remains debatable.¹⁸ Depression subtypes based on symptom patterns have been proposed but the clinical utility of these categorizations is unclear.¹⁹ Identifying distinct depression subtypes based on clinically observable characteristics could improve the ability to predict who will benefit from which treatments.^{15,20,21} The extent to which proposed subtypes or even individual symptoms^{22,23} and subtypes²⁴ can change throughout depressive episodes, but treatment has rarely been considered in the few longitudinal studies available. Research about the longitudinal stability of subtypes, including transitions between subtypes during treatment, could ultimately inform efforts to address depression heterogeneity in personalizing treatment strategies, a goal of precision medicine and the National Institute of Mental Health's Research Domain Criteria initiative.²⁵

Beyond the issue of syndromal recovery, how to improve functioning in people with MDD is unclear. Despite the profound impact of MDD on functional status, clinical trials of MDD rarely consider improvements in functioning as part of treatment success.²⁶ Remission is usually defined as reaching a specified score as determined by symptom rating scales and response is generally defined as experiencing a certain decrease in symptom rating score. When functioning is incorporated in trial designs, it typically is considered as a secondary outcome and may be underpowered to detect differences. This lack of emphasis of improved functional status in clinical studies of MDD seems paradoxical for several reasons. First, it occurs despite the inclusion of impaired functioning in the diagnostic criteria for major depression.²⁷ Second, depression treatment guidelines recommend assessment of functional impairment.²⁸ Furthermore, treatment guidelines encourage interventions to target improved functioning.²⁸

While it has been seen that the functional impairment associated with MDD is more pronounced in women, there is a dearth of information about how transitions between depression subtypes during treatment may be different as a function of baseline functional impairment. A better understanding of the association between functional impairment and transitions in depression subtypes could influence treatment.^{6,29} Differences in depression subtypes by level of functional impairment, including changes in subtypes after antidepressant treatment, can be explored using latent transition analysis (LTA). Using LTA we sought to examine differences in functional impairment in latent depression subtypes in women participating in level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Specifically, the aims were to (1) characterize the association between functional impairment and MDD subtypes at baseline, and (2) characterize changes in depression subtypes by level of baseline impairment at the end of 12 weeks of citalopram treatment.

Materials and Methods

Study participants

We used the publicly available, limited use, de-identified dataset of participants from level 1 of STAR*D. STAR*D was a large pragmatic clinical trial originally designed to evaluate the effectiveness of different pharmacological and psychosocial treatments for real world patients with moderate to severe non-psychotic major depression.⁴² Eighteen primary care and 23 outpatient psychiatric sites enrolled 4,041 participants who were seeking depression treatment from July 2001–April 2004. Participants in level 1 all received citalopram for up to 14 weeks. Study visits were conducted at 2, 4, 6, 9, and 12 weeks with an optional visit at week 14. Of the evaluable sample of 2,876 participants who had a score greater than or equal to 14 on the Hamilton Rating Scale of Depression (HRSD) and who completed at least one post-baseline visit, 28% achieved remission as defined by an HRSD score ≤ 7 .³⁰ Thirty-three percent achieved remission when it was defined as an observed self-report Quick Inventory of Depressive Symptomatology (QIDS-SR₁₆) score ≤ 5 .³⁰ Approximately 47% achieved response as defined by at least a 50% reduction in baseline QIDS-SR score. STAR*D has been described in detail elsewhere.³¹

Because our overall goal was to examine how functional impairment is related to transitions in depression subgroups over the 12-week treatment period, we excluded men and women from the evaluable sample who were missing all QIDS-SR₁₆ items at baseline and week 12 or the Work and Social Adjustment Scale (WSAS) at baseline ($n = 1,734$). This resulted in a sample of 387 men and 755 women. We ultimately focused on only the women, given our interest in women's experiences with functional impairments and the analytic limitations presented by the small sample of men. STAR*D participants provided written informed consent. The protocol was originally approved and monitored by the institutional review boards at the trial's national coordinating center, the data coordinating center, clinical sites, and the National Institute of Mental Health Data, Safety, and Monitoring Board. The University of Massachusetts Medical School Institutional Review Board determined that this secondary analysis was not human subject research.

Indicators of latent subtype membership

The 16 individual QIDS-SR₁₆ items collected at baseline and week 12 were used as the observed indicators of latent depression subtype. The QIDS-SR₁₆ measures overall depression severity, and the items correspond to the nine DSM-IV criterion symptoms for major depressive disorder.⁴⁶ Although the QIDS-SR₁₆ instructions specify that only one item on appetite increase or decrease and weight increase or decrease should be completed, we included these items as four separate indicator variables to capture the direction of appetite and weight changes. Each item except those pertaining to weight changes reflects the previous 7 days. The increased and decreased weight items inquire about changes in the last 14 days. The score for each item ranges from 0 to 3, with a score ≥ 2 reflecting that the symptom meets the DSM-IV threshold for the presence of a criterion symptom. Accordingly, for this analysis, the items were dichotomized so that a score ≤ 1 indicated the absence of a criterion symptom while a score ≥ 2 indicated the presence of a criterion symptom.³²

Functional impairment measure

Depression-specific functional impairment was measured with the WSAS. The WSAS is a five-item self-report scale assessing work, home management, social activities, private leisure activities, and close relationships.³³ STAR*D participants completed the WSAS via interactive voice response system (IVR) calls at baseline, week 6, and week 12/study exit. Participants were asked to rate how much their depression specifically impaired each of these domains. Each item is scored from 0 (no impairment) to 8 (very severe impairment). WSAS total scores greater than 20 indicate major impairment, scores of 10–20 represent significant functional impairment, and scores less than 10 are considered to be within normal ranges of functioning. Only 5% of women had a baseline WSAS score of 0–9 so WSAS scores were dichotomized as normal/significant functional impairment (WSAS = 0–20) and major functional impairment (WSAS $\geq$ 21).

Statistical analysis

The statistical analysis was conducted in two parts (1) characterizing the sociodemographic and clinical characteristics of the overall sample by level of baseline functional

impairment, and (2) evaluating differences in latent depression subtypes throughout treatment by level of baseline functional impairment. First we calculated descriptive statistics to compare demographic and clinical characteristics of the women categorized as having major functional impairment or normal/significant functional impairment.

In the second part of our analysis, the association of baseline functional impairment and depression subgroup was examined by fitting LTA models with categorical WSAS scores as a grouping variable. Models with all parameters freed to vary and the number of subtypes ranging from two to seven were fit first. The selection of the optimal number of subtypes was informed by the interpretability of each subtype and fit statistics such as Akaike information criterion and Bayesian information criterion.^{34,35} The relative fit and parsimony of the models was emphasized in addition to the formal fit statistics because LTA models can have very large degrees of freedom and extreme sparseness, which can skew the fit statistics.³⁶ Models where measurement invariance was imposed on the item response probabilities between groups and over time were then explored to see if the depression subtypes differed by level of functional impairment. Measurement invariance was formally tested using the G^2

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF WOMEN PARTICIPATING IN STAR*D LEVEL 1 BY BASELINE FUNCTIONAL IMPAIRMENT

Characteristic	Normal/significant functional impairment ^a (n = 231)	Major functional impairment ^b (n = 524)
Age at study entry, mean (SD)	42.5 (14.1)	41.0 (12.7)
Age at depression onset, mean (SD)	27.5 (15.5)	23.6 (14.0)
45 years of age or older at study entry, %	43.3	41.0
Race, %		
White	79.7	75.8
Black or African American	12.1	17.0
Other	8.2	7.3
Hispanic, %	14.3	13.4
Number of depressive episodes before baseline, mean (SD)	4.3 (6.7)	4.6 (6.3)
Depression severity (QIDS-SR ₁₆), mean (SD)	13.6 (3.7)	17.2 (3.6)
SF-12 PCS total score, ^c mean (SD)	52.6 (10.8)	48.4 (12.0)
SF-12 MCS total score, ^d mean (SD)	28.8 (8.7)	24.0 (7.1)
Q-LES-Q total score, ^e mean (SD)	50.8 (11.6)	36.8 (12.3)
Psychiatric comorbidity, %		
Any psychiatric comorbidity	49.8	66.6
Generalized anxiety disorder	13.1	27.2
Post-traumatic stress disorder	7.5	19.1
Bulimia	12.2	18.2
Social phobia	20.0	32.2
Obsessive compulsive disorder	5.7	9.5
Panic disorder	5.7	14.6
Psychosis	7.4	13.5
Agoraphobia	4.0	12.9
Alcohol abuse/dependence	7.9	9.0
Drug abuse/dependence	1.3	6.0
Somatization disorder	1.3	3.1
Hypochondriasis	4.4	4.1

^aNormal/significant functional impairment: Work and Social Adjustment Scale (WSAS) total score $\leq$ 20 at baseline.

^bMajor functional impairment: WSAS total score $\geq$ 21 at baseline.

^cShort Form-12 Health Survey Physical Component Summary (SF-12 PCS): A higher score indicates better functioning.

^dShort Form-12 Health Survey Mental Component Summary (SF-12 MCS): A higher score indicates better functioning.

^eQuality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): A higher score indicates better quality of life.

QIDS-SR₁₆, Quick Inventory of Depressive Symptomatology; SD, standard deviation.

difference likelihood ratio test to compare several nested models (1) models where all parameters were allowed to vary between functional impairment group and from baseline to week 12, (2) models where the parameters were constrained to be equal between the two functional impairment groups but were allowed to vary over time, and (3) models in which the parameters were constrained to be equal between the functional impairment groups and at baseline and week 12.³⁶ Models 2 and 3 were compared with model 1 using separate G^2 difference tests. In this second phase, we used one LTA model to see if the qualitative nature of the latent depression subtypes were different between the baseline impairment level and to see how the transitions in subtype membership were different for each impairment group. As we constructed the LTA model, we were able to constrain some of the item-response probabilities to reduce sources of heterogeneity and improve the interpretability of the model. Analyses were conducted using PROC LTA in SAS 9.3 (SAS Institute, Inc.).^{37,38}

Results

Sixty-nine percent of women had major functional impairment at baseline as measured by the WSAS. Women with major functional impairment at baseline were more likely than women with normal/significant impairment to be younger at depression onset, to have severe depression, to have lower physical and mental functioning scores, and to have lower quality of life (Table 1). Both groups had high rates of having a psychiatric comorbidity, but women with major functional impairment were more likely to have generalized anxiety disorder, posttraumatic stress disorder, bulimia, social phobia, psychosis, agoraphobia, and drug abuse/dependence (p -values all <0.001). At the beginning of STAR*D, the majority of both groups of women were likely to be experiencing sleep-onset insomnia, mid-nocturnal insomnia, sad mood, and fatigue (Table 2). The women with major impairment were more likely to have sleep-onset insomnia, sad mood, decreased appetite, weight changes, impaired concentration, negative self-view, lack of general interest, fatigue, psychomotor retardation, and psychomotor agitation.

When functional impairment was considered as a grouping variable in the LTA models, a four-subtype model fit the data best (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/jwh). Formal G^2 difference tests indicated that measurement invariance for all subtypes across the impairment groups ($G^2_2 - G^2_1 = 171.34$, $df=128$, $p=0.006$) or across groups and time could not be assumed ($G^2_2 - G^2_1 = 355.28$, $df=192$, $p<0.0001$). After careful consideration of the item response probabilities of the indicator variables that produce the description of each subtype, however, measurement invariance was imposed on several latent subtypes due to qualitative similarities: the moderate subtypes at baseline and week 12 for women in the normal/significant and major impairment groups; the severe with increased appetite subtypes at baseline for women in both impairment groups; the symptom resolution subtypes at week 12 for both impairment groups; and the insomnias only subtypes at week 12 for both impairment groups (Tables 3 and 4). Imposing measurement invariance in this way is desirable in aiding model fitting and enhancing the interpretability of the latent subtypes.

TABLE 2. FREQUENCY OF BASELINE QIDS-SR₁₆ INDICATORS BY BASELINE FUNCTIONAL IMPAIRMENT FOR WOMEN PARTICIPATING IN STAR*D LEVEL 1

QIDS-SR ₁₆ item	Percentage	
	Normal/ significant functional impairment ^a (n=231)	Major functional impairment ^b (n=524)
Sleep-onset insomnia	58.0	67.6
Mid-nocturnal insomnia	70.1	72.3
Early morning insomnia	43.3	50.6
Hypersomnia	11.3	16.8
Sad mood	73.2	90.1
Decreased appetite	15.2	24.8
Increased appetite	15.2	21.2
Decreased weight	7.8	13.6
Increased weight	6.5	14.7
Impaired concentration	38.5	69.7
Negative self-view	41.1	61.5
Suicidal ideation	9.1	12.0
Lack of general interest	39.4	67.4
Fatigue	56.7	82.4
Psychomotor retardation	18.6	42.0
Psychomotor agitation	23.4	31.9

^aNormal/significant functional impairment: WSAS total score ≤ 20 at baseline.

^bMajor functional impairment: WSAS total score ≥ 21 at baseline.

For the women in the normal/significant impairment group, the subtypes at baseline were mild depression, moderate depression, severe depression with increased appetite, and severe depression with insomnias (Table 3). The subtypes at week 12 were symptom resolution, mid-nocturnal insomnia only, all insomnias only, and moderate depression. Mid-nocturnal insomnia and sad mood were the only symptoms highly likely to be endorsed in every subtype at baseline whereas only sleep-onset insomnia was likely to be endorsed by women in all the subtypes at week 12 except for those in the symptom resolution subtype.

As shown in Figure 1, the mild, moderate, and severe with insomnias subtypes were almost all equally most prevalent at baseline, with 31%–32% of women likely to belong to these subtypes. With a prevalence of 5%, severe with increased appetite was the least common subtype at baseline. The majority of women (67%) were likely to be in the symptom resolution subtype after treatment. The fewest women (8%) were likely to belong to the moderate subtype. Women in the moderate subtype at baseline moved to the symptom resolution subtype at week 12. The women in the severe with insomnias subtype were the least likely to move to the symptom resolution subtype (32% chance). These women were more likely to transition to the all insomnias only subtype (34% chance).

For the women with major functional impairment, the subtypes at baseline were moderate depression, severe depression with decreased appetite, severe depression with increased appetite, and severe depression with psychomotor agitation (Table 4). The subtypes at week 12 were symptom resolution, depression with all insomnias only, moderate depression, and severe depression with psychomotor disturbances. Women

TABLE 3. ITEM RESPONSE PROBABILITIES FROM A FOUR-SUBTYPE LATENT TRANSITION ANALYSIS OF QIDS-SR₁₆ INDICATORS WITH BASELINE FUNCTIONAL IMPAIRMENT AS A GROUPING VARIABLE

QIDS-SR ₁₆ items	Normal/significant functional impairment at baseline ^a (n = 231)							
	Baseline latent subtypes				Week 12 latent subtypes			
	Mild	Moderate	Severe with	Severe with	Symptom resolution	Mid-nocturnal insomnia Only	All	Moderate
			increased appetite	insomnias			insomnias only	
Sleep onset insomnia	0.41	0.45	0.63	0.81	0.12	0.23	0.59	0.45
Mid-nocturnal insomnia	0.78	0.59	0.69	0.77	0.46	1.00	0.76	0.59
Early morning insomnia	0.39	0.28	0.53	0.65	0.05	0.40	0.50	0.28
Hypersomnia	0.00	0.22	0.27	0.08	0.06	0.00	0.05	0.22
Sad mood	0.53	0.74	0.99	0.89	0.04	0.00	0.26	0.74
Decreased appetite	0.03	0.10	0.00	0.37	0.01	0.05	0.08	0.10
Increased appetite	0.07	0.14	0.85	0.10	0.03	0.02	0.10	0.14
Decreased weight	0.00	0.05	0.00	0.18	0.01	0.08	0.07	0.05
Increased weight	0.05	0.05	0.54	0.01	0.01	0.31	0.07	0.05
Impaired concentration	0.07	0.53	0.78	0.49	0.02	0.00	0.24	0.53
Negative self-view	0.14	0.43	0.73	0.64	0.03	0.05	0.24	0.43
Suicidal ideation	0.05	0.07	0.13	0.17	0.01	0.00	0.07	0.07
Lack of general interest	0.09	0.50	0.83	0.57	0.06	0.00	0.28	0.50
Fatigue	0.28	0.72	0.92	0.62	0.06	0.00	0.31	0.72
Psychomotor retardation	0.00	0.24	0.56	0.30	0.00	0.03	0.18	0.24
Psychomotor agitation	0.09	0.15	0.25	0.45	0.02	0.00	0.30	0.15

Measurement invariance was imposed on the item response probabilities describing the moderate subtypes; the severe with increased appetite subtypes; the symptom resolution subtypes; and the insomnias only subtypes.

^aNormal/significant functional impairment, WSAS total score ≤ 20 at baseline.

in all subtypes were likely to be experiencing mid-nocturnal insomnia, sad mood, and fatigue at baseline. Sleep-onset insomnia and mid-nocturnal insomnia were likely to be endorsed by all subtypes except symptom resolution at week 12.

As seen in Figure 2, the severe with decreased appetite subtype was the most common subtype at baseline for women with major functional impairment, with a prevalence of 36%. At 12% of women, the severe with psychomotor agitation subtype was the least prevalent. These women had the lowest

TABLE 4. ITEM RESPONSE PROBABILITIES FROM A FOUR-SUBTYPE LATENT TRANSITION ANALYSIS OF QIDS-SR₁₆ INDICATORS WITH BASELINE FUNCTIONAL IMPAIRMENT AS A GROUPING VARIABLE

QIDS-SR ₁₆ items	Major functional impairment at baseline ^a (n = 524)							
	Baseline latent subtypes				Week 12 latent subtypes			
	Moderate	Severe with	Severe with	Severe with	Symptom resolution	All	Moderate	Severe with
		decreased appetite	increased appetite	psychomotor agitation		insomnias only		psychomotor disturbances
Sleep onset insomnia	0.45	0.82	0.63	1.00	0.12	0.59	0.45	0.67
Mid-nocturnal insomnia	0.59	0.81	0.69	0.83	0.46	0.76	0.59	0.82
Early morning insomnia	0.28	0.61	0.53	0.72	0.05	0.50	0.28	0.53
Hypersomnia	0.22	0.14	0.27	0.00	0.06	0.05	0.22	0.24
Sad mood	0.74	0.96	0.99	0.95	0.04	0.26	0.74	0.94
Decreased appetite	0.10	0.54	0.00	0.14	0.01	0.08	0.10	0.15
Increased appetite	0.14	0.00	0.85	0.09	0.03	0.10	0.14	0.25
Decreased weight	0.05	0.31	0.00	0.06	0.01	0.07	0.05	0.07
Increased weight	0.05	0.04	0.54	0.12	0.01	0.07	0.05	0.15
Impaired concentration	0.53	0.85	0.78	0.50	0.02	0.24	0.53	0.92
Negative self-view	0.43	0.75	0.73	0.47	0.03	0.24	0.43	1.00
Suicidal ideation	0.07	0.17	0.13	0.09	0.01	0.07	0.07	0.28
Lack of general interest	0.50	0.88	0.83	0.31	0.06	0.28	0.50	0.85
Fatigue	0.72	0.93	0.92	0.65	0.06	0.31	0.72	0.97
Psychomotor retardation	0.24	0.56	0.56	0.23	0.00	0.18	0.24	0.70
Psychomotor agitation	0.15	0.44	0.25	0.55	0.02	0.30	0.15	0.51

Measurement invariance was imposed on the item response probabilities describing the moderate subtypes; the severe with increased appetite subtypes; the symptom resolution subtypes; and the insomnias only subtypes.

^aMajor functional impairment, WSAS total score ≥ 21 at baseline.

FIG. 1. Latent subtype prevalences and probabilities of transitioning in depression subtype membership from baseline to week 12 for women with baseline normal/significant functional impairment. Measurement invariance was imposed on the item response probabilities describing the moderate, severe with increased appetite, symptom resolution, and insomnias only subtypes.

chance of transitioning to the symptom resolution subtype at week 12 (4%) and were most likely to move to the all insomnias only subtype (62% chance). Those in the moderate subtype had the greatest chance (86%) of transitioning to the symptom resolution subtype. The majority of women were likely to belong to the symptom resolution subtype (60%) at

FIG. 2. Latent subtypes prevalences and probabilities of transitioning in depression subtype membership from baseline to week 12 for women with baseline major functional impairment. Measurement invariance was imposed on the item response probabilities describing the moderate, severe with increased appetite, symptom resolution, and insomnias only subtypes.

week 12 while only 5% were likely to be in the severe with psychomotor disturbances subtype. Women in the subtypes distinguished by appetite changes were the only ones with a chance of transitioning to severe with psychomotor disturbances, the only subtype at week 12 that was not distinguished by having fewer prominent symptoms. Women in the severe with decreased appetite subtype had a 13% chance of moving to severe with psychomotor disturbances while those in the severe with increased appetite subtype had a 5% chance of making this transition.

Discussion

The overall goal of this study was to explore how latent depression subtypes differ by baseline functional impairment and to describe how the qualitative nature of these depression subtypes differed by baseline level of functional impairment for women being treated with citalopram. Using baseline level of functional impairment in a multiple-group LTA model demonstrated that depression types for women in STAR*D differed by level of impairment and that baseline impairment influenced changes in depression type during citalopram treatment. Women with major functional impairment at baseline had more severe depression subtypes at both time points when compared to women with normal/significant functional impairment.

The types of depression experienced by women in both functional impairment groups were similar in a few ways but the subtypes for those with major impairment were characterized by more severe depression throughout the study. The moderate, severe with increased appetite, symptom resolution, and all insomnias only subtypes were common to both groups but the women who started level 1 of STAR*D with major functional impairment had more severe depression subtypes at both times. The severe subtypes for these women were marked by prominent symptoms related to decreased and increased appetite and psychomotor disturbances. The women with normal/significant impairment had severe subtypes distinguished by increased appetite and insomnias and these severe subtypes were only present at baseline. Beyond differences in the descriptive nature of the severe subtypes, the prevalences of these subtypes also differed by functional impairment group, with more than three times more women with major impairment than with normal/significant impairment likely to be in the severe with increased appetite group. Women with baseline major impairment also had lower probabilities of transitioning to a subtype differentiated by endorsing fewer symptoms when compared to women with baseline normal/significant impairment.

It is perhaps not surprising that the latent depression subtypes for women with major functional impairment would be characterized by the endorsement of more depression symptoms than those of the women with normal/significant functional impairment since greater depression symptom severity has been seen to be related to reduced quality of life and functioning in all STAR*D participants.^{39,40} Additionally, women with major functional impairment in this analysis had more comorbid anxiety disorders than women with normal/significant impairment and comorbid anxiety disorders appear to increase the risk of low health-related quality of life across numerous domains for women.⁴¹ Rates of improvement in quality of life are lower for people with

chronic major depression and those with comorbid psychiatric disorders. Specific anxiety disorders in particular may differentially impact domains of functioning; for example, social phobia would impair social functioning or the painful physical symptoms that commonly occur with generalized anxiety disorder would affect physical functioning.^{29,42} Understanding the impact of comorbid psychiatric conditions on functioning could aid in developing treatment strategies that produce not just symptomatic recovery but also functional recovery.⁴³

Both groups of women experienced depression subtypes distinguished by combinations of insomnia symptoms at both baseline and week 12. Almost a third of the women with normal/significant impairment were in the severe with insomnias subtype at baseline. These women had the lowest chances of transitioning to the symptom resolution subtype after treatment. While the women with major impairment did not have a depression subtype distinguished by insomnia at baseline, almost a quarter of them had moved into the all insomnias only subtype at week 12. The prominence of these sleep problems is consistent with women generally having a high risk of experiencing insomnia and is in line with the associations between insomnia, sleepiness, fatigue and functioning in depression.^{6,44–46} Insomnia also increases risk of depression recurrence^{47,48} and lack of treatment response.⁴⁹ These insomnia symptoms likely warrant further attention in treatment approaches for depression since they are common residual symptoms³² and antidepressant side effects.⁵⁰ Future efforts should examine both pretreatment insomnia and treatment-emergent insomnia and strategies to address sleep problems in people with depression. One area for exploration is the role of γ -aminobutyric acid and glutamate systems, which may support the development of highly tolerable hypnotics with low potential for abuse that could be used in augmenting selective serotonin reuptake inhibitors.⁵¹

Our results should be interpreted in the context of several limitations. This was a post hoc analysis of clinical trial data that were not originally collected for such subgroup analyses. These LTA models were unable to address all of the known correlates of functional impairment in depression because of issues of model convergence when trying to fit complex latent variable models. Age, race, education, marital status, employment status, medical comorbidities, and health insurance coverage have been observed to be related to baseline functioning in a separate subsample of STAR*D participants.⁵² This analysis also only examined functioning as captured by the self-reported WSAS, which does not cover all aspects of functional impairment including cognition, self-care and mobility. Furthermore, 21 women were excluded from this analysis because they did not complete the IVR call during which the functioning assessments were completed and these women might differ on level of functioning compared to the women who were able to complete the call. New research should assess additional functional domains and objective measures of functioning should also be examined. For example, the poor concentration ability and memory challenges commonly experienced in depression, which would appear to impede a number of functional domains, suggests cognitive impairment remediation as a potential treatment. Exploring how cognitive impairment mediates the relationship between depression symptoms and functional

impairment could be beneficial for developing pharmacological and psychosocial treatment strategies.⁵³ This might be an area of interest, especially for women with depression given the role of estrogen in regulating mood and cognition.⁵⁴

This analysis focused only on functional impairment observed at baseline. It is important to consider functioning longitudinally since improvements in functioning have been demonstrated with antidepressant treatment and such improvements can lag behind symptom improvements.⁵⁵ This is particularly concerning because most people who achieve remission when treated for depression still experience residual symptoms.³² In one study of people who were being treated for major depression, half of those with residual depression symptoms but who reported normal functioning considered themselves to be in remission from their depression.⁵⁶ Discordance also often exists between patients' symptoms and their level of functioning.^{26,56} This discordance is not unidirectional, with some people with mild/moderate depression symptoms having major functional deficits while others with severe symptoms are able to function normally.⁴⁴ This is particularly concerning because most people who achieve remission when treated for depression still experience residual symptoms.³²

Despite these limitations, our analysis is noteworthy for several reasons. This is one of the first analyses to use LTA to examine how functional impairment is related to depression subtypes and changes in these subtypes following antidepressant treatment. LTA allowed us to efficiently discern depression subtypes among women during a clinical trial and to examine the association between functional impairment and changes in depression symptoms following treatment with citalopram. Although data sparseness limited our ability to examine some factors of potential interest, this is still one of the largest samples to which LTA has been applied. While methods for power calculations in LTA are still being developed, it has been suggested that sample sizes of 300 people or more are sufficient.⁵⁷ Although STAR*D enrolled treatment-seeking outpatients and thus our results have limited generalizability, it is still the largest and longest depression treatment study and is considered more representative of people with depression who are seen outside of idealized research setting than most trials.⁵⁸

Conclusions

For women in STAR*D, level of functional impairment was related to the likelihood of moving to a depression subtype differentiated by endorsing fewer depression symptoms and thus treatment strategies may want to consider not only symptom severity but also degree of functional impairment. Our results highlight the importance of looking beyond summary rating scores of depression symptoms when studying depression heterogeneity during treatment. Relying on cutoff scores from symptom rating scales to define treatment success obscures changes in functioning, making it difficult to know when patients are experiencing satisfactory relief from their depression and improved quality of life. Future research on the assessment and treatment of major depression should not focus exclusively on symptoms but also incorporate domains of functioning. Doing so could reduce the substantial disability and burden associated with depression.

Author Disclosure Statement

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Address correspondence to:

Christine M. Ulbricht, PhD

Department of Quantitative Health Sciences

University of Massachusetts Medical School

368 Plantation Street

Worcester, MA 01605

E-mail: Christine.Ulbricht@umassmed.edu