Residual Symptoms in Depressed Outpatients Who Respond by 50% But Do Not Remit to Antidepressant Medication

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Abstract: Little is known about the quantity or quality of residual depressive symptoms in patients with major depressive disorder (MDD) who have responded but not remitted with antidepressant treatment. This report describes the residual symptom domains and individual depressive symptoms in a large representative sample of outpatients with nonpsychotic MDD who responded without remitting after up to 12 weeks of citalopram treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Response was defined as 50% or greater reduction in baseline 16-item Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR_{16}) by treatment exit, and remission as a final QIDS-SR_{16} of less than 6. Residual symptom domains and individual symptoms were based on the QIDS-SR_{16} and classified as either persisting from baseline or emerging during treatment. Most responders who did not remit endorsed approximately 5 residual symptom domains and 6 to 7 residual depressive symptoms. The most common domains were insomnia (94.6%), sad mood (70.8%), and decreased concentration (69.6%). The most common individual symptoms were midnocturnal insomnia (79.0%), sad mood (70.8%), and decreased concentration/decision making (69.6%). The most common treatment-emergent symptoms were midnocturnal insomnia (51.4%) and decreased general interest (40.0%). The most common persistent symptoms were midnocturnal insomnia (81.6%), sad mood (70.8%), and decreased concentration/decision making (70.6%). Suicidal ideation was the least common treatment-emergent symptom (0.7%) and the least common persistent residual symptom (17.1%). These findings suggest that depressed outpatients who respond by 50% without remitting to citalopram treatment have a broad range of residual symptoms. Individualized treatments are warranted to specifically address each patient's residual depressive symptoms.

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Major depressive disorder (MDD) is a debilitating disease that is difficult to treat, even when using systematic antidepressant strategies.[1,2] Although approximately 50% of patients with MDD reach a response, many of these responders experience residual depressive symptoms (ie, symptoms that persist in the context of adequate short-term treatment). Commonly reported residual symptoms found in clinical investigations of patients who responded to antidepressant treatment have included insomnia, anxiety, and anhedonia.[3–6] Residual symptoms increase the probability for depressive relapse and are associated with poorer functional and psychosocial outcomes.[7,8]

Paykel et al[7] identified lack of remission as a key factor in subsequent relapse, a finding that has been widely replicated.[9–12] The nature of symptoms that remain in those who have responded but not remitted has not been widely evaluated. Such information could guide treatment options to target specific residual symptoms such as anxiety and insomnia.[13] This information could also help individualize treatment for adult and geriatric populations.[14] By further understanding the nature of residual symptoms in responders, one might identify and treat specific symptoms to optimize clinical and functional outcomes.[15] Also, a better understanding of the residual symptoms at the point of response would help differentiate those symptoms that are present at baseline and persist throughout treatment from those that emerge during treatment.

Since the earlier reports on residual depressive symptoms by Paykel et al,[7] most research has focused on identifying individual symptoms that remain in patients who have achieved remission.[16] This focus leaves a considerable gap in our knowledge about the residual symptoms that remain in patients who reach response (ie, 50% decrease in depressive severity) without reaching remission. Knowledge of which residual symptoms are common would assist physicians in early implementation of counteractive treatments, more quickly converting responders into remitters, and thereby possibly reducing the higher likelihood of the relapse and functional impairment associated with response that is short of remission.

This report characterizes residual depressive symptoms in a large sample of representative outpatients with nonpsychotic MDD who responded but did not remit to the first step antidepressant treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[17,18] Specifically, we sought to (1) describe the residual depressive domains and symptoms that remain after antidepressant treatment, (2) determine which residual symptoms are most likely to emerge during antidepressant treatment, and (3) identify which initial symptoms are most likely to persist over the course of antidepressant treatment.

MATERIALS AND METHODS

Study Overview

The STAR*D study was aimed to define prospectively the effectiveness of several antidepressant treatments when used in an augmenting or switching strategy in individuals with nonpsychotic MDD who have an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s).[17,18]

Fourteen regional centers oversaw the study, which was conducted at 18 primary and 23 nonresearch psychiatric care settings across the United States. The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki and was approved and monitored by the study's national coordinating center (Dallas, Tex) and data coordinating center (Pittsburgh, Pa), the institutional review boards at each clinical site and regional center, and the data safety and monitoring board of the National Institute of Mental Health (NIMH, Bethesda, Md). Before enrollment, all potential risks, benefits, and adverse events associated with STAR*D participation were explained and a written informed consent was obtained from each participant.

Study Population

The STAR*D study enrolled 4041 outpatients, 18 to 75 years of age, with a condition diagnosed as nonpsychotic MDD (established by treating physicians and confirmed by a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*] checklist). A baseline 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[19] score of 14 or higher (moderate severity) was required for enrollment. The patients were excluded if they had schizophrenia, schizoaffective disorder, bipolar disorder, anorexia nervosa, a current primary diagnosis of bulimia nervosa or obsessive-compulsive disorder, or a well-documented history of nonresponse or intolerance (in the current major depressive episode) to one or more of the protocol treatments in the first 2 treatment steps.

Additional exclusions included the presence of psychiatric disorders or substance abuse that required immediate hospitalization, general medical conditions, or concomitant medications that contraindicated the use of protocol treatments in the first 2 steps, or the use of a targeted psychotherapy for depression. The study also excluded patients who were breastfeeding, pregnant, or trying to become pregnant. For the purposes of this analysis, we excluded patients who remitted with citalopram, as Nierenberg et al[20] previously reported those data.

Assessment Measures

Sociodemographic and clinical data were collected at the screening/baseline visit. The participants completed the self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ)[21] to identify the following concurrent anxiety disorders: generalized anxiety disorder, panic disorder, post-traumatic stress disorder, social phobia, obsessive-compulsive disorder, and agoraphobia.[21,22] The presence of each disorder was determined based on a prior established threshold of 90% specificity for the number of positive items in each anxiety domain.[23] Within 72 hours of the screening/baseline visit and exit visit, trained research outcome assessors masked to the treatment conducted telephone interviews to complete the 17-item Hamilton Rating Scale for Depression and the 30-item Inventory of Depressive Symptomatology—Clinician-rated.[24] Within 72 hours of each clinic visit, a telephone-based interactive voice response system[25] gathered the 16-item Quick Inventory of Depressive Symptomatology—Self-report ($QIDS\text{-}SR_{16}$).[26]

TABLE 1. Baseline Characteristics of Responders But Not Remitters to Antidepressant Treatment (n = 428)

Baseline Characteristic	n (%)
Race	
White	313 (73.1)
Black or African American	78 (18.2)
Others	37 (8.6)
Ethnicity: Hispanic	54 (12.6)
Sex: Female	284 (66.4)
Marital Status	
Never married	129 (30.1)
Married	163 (38.1)
Divorced	122 (28.5)
Widowed	14 (3.3)
Employment Status	
Unemployed	160 (37.4)
Employed	239 (55.8)
Retired	29 (6.8)
Insurance Status	
Private insurance	196 (48.9)
Public insurance*	68 (17.0)
No insurance	137 (34.2)
Family History of Depression	238 (55.6)
No. Axis I Disorders	
0	161 (38.2)
1	115 (27.3)
2	72 (17.1)
3	32 (7.6)
4	42 (10.0)
No. General Medical Conditions	
0	39 (9.1)
1	62 (14.5)
2	86 (20.1)
3	71 (16.6)
4	170 (39.7)
Depressive Subtype	
Melancholic	
No	311 (72.7)
Yes	117 (27.3)
Atypical	
No	327 (76.4)
Yes	101 (23.6)
Anxious	
No	204 (47.7)
Yes	224 (52.3)
	Mean (SD)
Age, y	40.2 (13.5)
Years of Schooling	13.7 (3.3)
Depression Severity	
$HRSD_{17}$ (ROA)	22.5 (5.0)
$IDS\text{-}C_{30}$ (ROA)	40.6 (8.7)
$QIDS\text{-}SR_{16}$	18.0 (3.2)

*Public insurance includes both Medicare and Medicaid.

$HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; $IDS\text{-}C_{30}$: 30-item Inventory of Depressive Symptomatology—Clinician-rated; $QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology—Self-Report; ROA, research outcome assessor.

Treatment

Citalopram was to begin at 20 mg/d and could be raised to 40 mg/d by weeks 2 to 4 and to 60 mg/d by weeks 4 to 6 using a measurement-based care approach.[27] Dose adjustments were guided by recommendations in a treatment manual (www.star-d.org). Individualized starting doses and dose adjustments were used to minimize adverse effects, maximize safety, and optimize the chances of therapeutic benefit for each participant.

The protocol recommended treatment clinic visits at weeks 0, 2, 4, 6, 9, and 12. Extra visits could be held if needed. For a participant with a response or remission only at week 12, treatment could be extended for up to 2 additional weeks (14 weeks total) to determine whether that status would be sustained. Treatment response was defined as a 50% or greater reduction in the baseline QIDS-SR_{16} by the end of citalopram treatment, and remission was defined as a QIDS-SR_{16} score of 5 or less at treatment exit.[26]

Definition of Residual Symptoms

The presence of domain or individual residual depressive symptoms was categorized at baseline and at exit from the citalopram treatment using items of the QIDS-SR_{16}. We chose the QIDS-SR_{16}, as it had the most complete data available for depressive symptoms. Residual *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* symptom domains were obtained from the QIDS-SR_{16} (sleep, sad mood, appetite/weight, concentration, outlook, suicidal ideation, involvement, energy/fatigue, and psychomotor). An item score of 1 or greater or 2 or greater defined the minimal and moderate boundaries, respectively, between the presence or absence of residual symptoms.

Statistical Analysis

Summary statistics were used to describe the baseline sociodemographic and clinical characteristics of the population. Means and SDs are presented for continuous variables; percentages are presented for discrete variables.

RESULTS

Sociodemographic and Clinical Characteristics

Of the evaluable sample (n = 2876) of participants who completed step 1 of the STAR*D trial, approximately 15% (n = 428) responded but did not remit (hereafter referred to as "responders"). Table 1 shows the sociodemographic and clinical characteristics of the study sample of responders.

Residual Depressive Domains and Symptoms That Remained in Responders

All responders endorsed from 2 to 9 residual depressive symptom domains on the QIDS-SR_{16}, and approximately 75% reported 5 or more. Of the 9 symptom domains that responders rated as mild (score ≥1), insomnia (94.6%), sad mood (70.8%), decreased concentration (69.6%), and psychomotor disturbance (67.3%) were the most common. Of the domains rated by responders as at least moderately severe (score, ≥2), insomnia (75.5%), and appetite/weight change (20.1%) were the most common (Table 2).

Of the possible 14 individual residual depressive symptoms captured on the QIDS-SR_{16}, responders reported ratings of 1 or greater on 3 to 13 such symptoms. Approximately 75% of responders endorsed the presence of 5 or more residual depressive symptoms to at least a mild degree. The most frequently reported mild residual symptoms were midnocturnal insomnia (79.0%), sad mood (70.8%), decreased concentration/decision making (69.6%), and low energy (63.3%). Of the symptoms that were rated as moderately severe, the most frequent symptom reported was midnocturnal insomnia (59.6%), which was reported to at least a moderate degree more than twice as frequently as any other symptom (Table 3).

Residual Depressive Symptoms That Emerged During Citalopram Treatment

The most common depressive symptoms to emerge during the citalopram treatment were midnocturnal insomnia (51.4% of the participants without the symptom at baseline) and decreased general interest (40.0%). Four symptoms emerged very infrequently after starting treatment: sad mood (0.0%; note: 100% of the responders had this symptom at baseline, so emergence was not possible in this sample), suicidal ideation (0.7%), negative self-view (3.3%), and feeling slowed down (6.1%; Table 4).

Residual Depressive Symptoms That Persisted From Baseline to Exit

The depressive symptoms that most frequently persisted throughout the course of treatment included midnocturnal insomnia (81.6%), sad mood (70.8%), and decreased concentration/decision making (70.6%). Equally important, the symptoms of negative self-view, suicidal ideation, and feeling slowed down all decreased by more than 50% in reported frequency from baseline to exit in responders (Table 4).

DISCUSSION

This was one of the first studies to systematically examine residual depressive symptoms in a cohort of patients with MDD who had responded but not remitted to a first-line antidepressant agent (citalopram). We found that most nonremitting responders endorsed multiple residual symptom domains and symptoms. The most common treatment-emergent residual symptoms were midnocturnal insomnia and decreased general interest. Most residual symptoms that were present at baseline simply persisted.

TABLE 2. Proportion of Responders With at Least Mild or Moderate Levels of Residual Symptom Domains (n = 428)

Proportions	Insomnia	Sad Mood	Appetite/ Weight	Concentration	Outlook	Suicidal Ideation	Involvement	Energy/ Fatigability	Psychomotor
Percent with at least mild domain score*	94.6	70.8	60.3	69.6	36.5	11.5	54.7	63.3	67.3
Percent with at least moderate domain score†	75.5	10.1	20.1	8.8	7.5	2.3	15.0	11.7	13.3

*Any QIDS-SR_{16} item ≥1.

†Any QIDS-SR_{16} item ≥2.

TABLE 3. Proportion of Responders With at Least Mild or Moderate Levels of Residual Symptoms (N = 428)

Proportions	Sleep-Onset Insomnia	Midnocturnal Insomnia	Early-Morning Insomnia	Hypersomnia	Sad Mood	Decreased Appetite	Increased Appetite	Weight Decrease	Weight Increase	Concentration/ Decision Making	Negative Self-View	Suicidal Ideation	Involvement	Energy	Slowed Down	Restless
Percent with at least mild symptoms*	52.1	79.0	38.3	33.4	70.8	24.3	19.9	19.6	25.9	69.6	36.5	11.5	54.7	63.3	31.1	53.5
Percent with at least moderate symptoms†	25.9	59.6	22.2	10.3	10.1	2.6	5.1	6.8	10.1	8.9	7.5	2.3	15.0	11.7	4.2	9.8

*Any QIDS-SR_{16} item ≥1.
†Any QIDS-SR_{16} item ≥2.

They were of mild intensity, except for insomnia, which was rated as moderately severe.

Interestingly, suicidality very rarely emerged over the course of treatment and was a rarely endorsed persistent residual depressive symptom. Furthermore, suicidality was rarely endorsed even in the presence of other residual depressive symptoms. With conflicting research findings regarding the link between antidepressant usage and suicidality,[28,29] this study provides new evidence to suggest little to no relation between use of a selective serotonin reuptake inhibitor and self-reported suicidal ideation.

Most research on residual depressive symptoms has focused on patients who have remitted with antidepressant treatment.[12,20] Nonetheless, our findings of residual insomnia, decreased concentration, and sad mood are similar to other reports.[12,13] Furthermore, insomnia is a criterion symptom of MDD that is highly related to subsequent depressive relapse in adults.[30,31] Studies suggest that physicians should determine whether insomnia is a treatment-emergent or persisting symptom, inasmuch as this distinction may help determine therapeutic options.[8,32] The current study found that midnocturnal insomnia is the most frequent persistent and the most frequent treatment-emergent insomnia item.

Cognitive impairment can lead to incomplete remission, increased propensity for depressive relapse, and increased functional impairment in activities of daily living (ie, balancing checkbook).[33,34] If cognitive disruption persists from baseline or emerges during treatment, then treatment options to consider could include changing the dose of the current medication or using pharmacological agents that may specifically address the cognitive complaints.[35,36]

Our study findings could have resulted from the pharmacotherapeutic agent (citalopram), the participant cohort, or the use of the QIDS-SR_{16} to measure residual depressive symptoms. The treatment-emergent residual depressive symptoms could have been related to the adverse effects of citalopram.[32] Alternatively, they could have resulted from fluctuating illness or extraneous factors. Common side effects of citalopram include sleep disturbance, decreased libido, diarrhea, decreased appetite, and decreased energy. However, except for frequent reports of mid-nocturnal insomnia and decreased interest, and infrequent reports of feeling slowed down, these adverse effects were not reported as residual depressive symptoms. Another explanation for our findings may be related to the participant cohort. This cohort included patients with nonpsychotic MDD, of whom approximately half had anxious features and most of whom had at least one *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* Axis I comorbidity and general medical comorbidity. The persistent residual symptoms could have been due in part to the presence of anxiety and/or general medical comorbidities. However, these persistent symptoms have been found in other studies of patients with depression who responded but did not remit with antidepressant treatment.[37]

Study limitations include the use of the QIDS-SR_{16} to determine the presence of residual symptoms. Relying on a self-report precludes an evaluation of observable symptoms rated by a physician. In addition, the QIDS-SR_{16} does not rate anxiety, an often-reported residual symptom after effective antidepressant treatment.[7,13,38] The use of a specific residual symptom instrument such as the Depression Residual Symptom Scale, might also have identified the presence of residual symptoms[38] not captured by the QIDS-SR_{16}. Another limitation is that all participants were treated only with citalopram. Residual depressive symptoms after response with other pharmacotherapeutic or psychotherapeutic interventions might well be different. For instance, Taylor et al[39] found that decreased libido,

TABLE 4. Proportion of Responders With Persistent Baseline Symptoms and Treatment-Emergent Symptoms (n = 428)

QIDS-SR16 Item	Percent With Symptoms at Baseline	Percent With Persistent Baseline Symptoms	Percent With Treatment-Emergent Symptoms*
Sleep onset insomnia	82.9	57.5	26.0
Midnocturnal insomnia	91.4	81.6	51.4
Early-morning insomnia	69.6	49.0	13.9
Hypersomnia	33.6	60.4	19.7
Sad mood	100.0	70.8	0.0
Decreased appetite	53.5	31.0	16.6
Increased appetite	31.1	27.8	16.3
Decreased weight	42.8	25.1	15.5
Increased weight	32.9	35.5	21.3
Concentration/decision making	97.7	70.6	30.0
Negative self-view	93.0	38.9	3.3
Suicidal ideation	65.7	17.1	0.7
General interest	97.7	55.0	40.0
Energy	97.0	64.6	23.1
Slowed down	84.6	35.6	6.1
Restlessness	77.1	63.0	21.4

*These patients did not have the symptom at baseline, they only had the symptom at exit.

For example, 82.9% of the participants had sleep-onset insomnia at baseline. Of these, 57.5% continued to have sleep-onset insomnia at exit; 26.0% of those who had sleep-onset insomnia at exit did not have it at baseline.

Presence of symptom indicated by a QIDS-SR_{16} domain score of ≥1.

somatic anxiety, and guilt remained after patients responded to acute cognitive behavior therapy, although they also found residual symptoms of insomnia, sad mood, and decreased energy. Whether the present findings apply to other antidepressant therapies is an open question.

In summary, patients with nonpsychotic MDD who achieved response but not remission with citalopram experienced substantial residual depressive symptoms. The current study characterized the frequency and quality of this cohort's depressive residual domains and symptoms. It seems important to differentiate symptoms that emerge during treatment from those that persist from baseline to exit, as this distinction may well have implications for guiding treatment.

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