Does the Duration of Index Episode Affect the Treatment Outcome of Major Depressive Disorder? A STAR*D Report

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Objective: This article aims to identify baseline sociodemographic and clinical characteristics associated with the duration of the index major depressive episode (MDE) and to assess the effect of the current MDE duration on response and remission rates with up to 14 weeks of citalopram.

Method: Eligible participants met DSM-IV criteria for nonpsychotic major depressive disorder, scored ≥ 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), and were not resistant to adequate antidepressant treatment in the current episode. The first patient was enrolled in July 2001 and the last visit for the last patient in follow-up was in March 2006. The evaluable sample (N = 2851) was divided into 4 groups based on the index MDE duration at study entry: acute (≤ 6 months, N = 1324), subchronic (7–23 months, N = 807), chronic (24–41 months, N = 326), and ultrachronic (≥ 42 months, N = 394). These 4 groups were compared in terms of baseline sociodemographic and clinical characteristics and treatment outcomes. Citalopram was generally begun at 20 mg/day and raised to 40 mg/day by weeks 2 through 4 and to 60 mg/day (final dose) by weeks 4 through 6. Logistic regression models with adjusted post hoc analyses were used to control for associated baseline characteristics. Response was defined as ≥ 50% reduction in baseline 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) scores at exit. Remission was defined as ≤ 7 on the HAM-D-17 or ≤ 5 on the QIDS-SR-16.

Results: MDE duration was longer in primary care settings, blacks, Hispanics, single or widowed, unemployed, publicly insured or uninsured, older, and less educated participants and in those with lower income, less recurrence, or greater concurrent general medical or Axis I comorbidities. HAM-D-17 remission rates ranged from 31.0% (acute group) to 24.1% (ultrachronic group). HAM-D-17 remission rates were significantly related to MDE duration (p = .0010), but after adjustments for baseline differences among the 4 groups, remission rates were not different. QIDS-SR-16 response rates were lower for the subacute and chronic groups but not different for the acute and ultrachronic groups after adjustment.

Conclusion: Longer MDE duration is associated with socioeconomic disadvantage and greater Axis I and medical comorbidity. Episode duration per se does not significantly affect the likelihood of remission.

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Despite improved recognition of mood disorders, persistent depressive episodes are common,[1] and they are associated with significant morbidity and psychosocial and functional impairments.[2–5] It has been suggested that the duration of the index major depressive episode (MDE) may explain individual differences in clinical outcome.[6–9] If true, efforts are necessary to understand the means by which this may occur.

Several studies have demonstrated the efficacy of pharmacotherapy for chronic depression (chronic episodes of major depressive disorder [MDD] or dysthymic disorder),[10–15] albeit with modest outcome. However, some reports suggest that the longer the current episode, the lower the chances of recovery.[16,17]

Notably, approximately 1 in 4 participants in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[18,19] (www.star-d.org) reported a chronic (> 24 months) index MDE at study entry.[9] These participants were less likely to remit during the first treatment step (optimized dosing of citalopram) than those not in a chronic episode at entry.[9] Lack of remission was also associated with less education, less monthly income, unemployment, comorbid anxiety, and greater general medical burden. These baseline characteristics were more common among those with a chronic index MDE in the first 1500 STAR*D participants.[5]

The present analyses were designed to investigate the relationship between index episode duration and outcome with citalopram treatment independent of confounding characteristics using the STAR*D data. To generate greater specificity, index MDE duration was divided into 4 time periods: acute (≤ 6 months), subchronic (7–23 months), chronic (24–41 months), and ultrachronic (≥ 42 months). This report aims to identify baseline sociodemographic and clinical characteristics associated with persistent depressions, particularly ultrachronic status, and to investigate response and remission rates with citalopram treatment as a function of index MDE duration.

METHOD

Study Description

The rationale and design for the STAR*D trial are detailed elsewhere.[18,19] This National Institute of Mental Health (NIMH)–sponsored, multisite study investigated the comparative efficacy and tolerability of several state-of-the-art treatments for adult outpatients with nonpsychotic MDD who had an unsatisfactory outcome to initial and, if necessary, subsequent treatment steps. The initial treatment entailed an optimized trial of the selective serotonin reuptake inhibitor (SSRI) citalopram.

Study Organization and Setting

The study protocol was approved and monitored by the institutional review boards at the National Coordinating Center in Dallas, Tex.; the Data Coordinating Center in Pittsburgh, Pa.; each clinical site and regional center; and the Data Safety and Monitoring Board of the NIMH. Fourteen regional centers each coordinated 2 to 4 primary and/or psychiatric (specialty) care clinical sites serving either public or private sector patients. Study sites included 18 primary care and 23 psychiatric care settings throughout the United States.

Study Population

Only treatment-seeking outpatients, 18 to 75 years of age, with a diagnosis of nonpsychotic MDD were approached for study participation. Advertising for symptomatic volunteers was proscribed. All risks, benefits, and adverse events associated with the study were explained to participants, who provided written informed consent prior to enrollment. The first patient was enrolled in July 2001 and the last visit for the last patient in follow-up was in March 2006.

Broadly inclusive selection criteria were used to enhance generalizability.[18,19] Eligible participants met DSM-IV criteria for nonpsychotic MDD, scored greater than or equal to 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[20] and were not resistant to adequate antidepressant treatment in the current episode. Most concurrent general medical conditions were permissible, unless contraindicated by any protocol medication in the first 2 treatment steps. Concomitant medications for general medical conditions and for anxiety, insomnia, and sexual dysfunction were permitted. Exclusion criteria included intended or current pregnancy, postpartum breastfeeding, participation in other depression-targeted psychotherapies, and primary psychiatric disorders requiring other treatment approaches.

Baseline Assessments

At the initial evaluation, trained and certified clinical research coordinators located at the clinical sites collected baseline sociodemographic and clinical information. Determination of episode duration was made to the best of the abilities of the clinical research coordinators, who were all experienced mental health clinicians. Patients were asked to identify the age at which they first experienced depression, the total number of depressive episodes since that time, and the duration of the current episode. In doing so, patients were educated that they were not being asked how long since they first became depressed, but rather how long the current period of depression had lasted. When necessary, patients were asked when they last felt they were not depressed, and attempts were made to have patients identify landmarks to assist in timing the onset of the current episode. Duration was estimated to the nearest month.

The clinical research coordinators completed the HAM-D-17 and the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated[21,22] (QIDS-C-16), as well as the 14-item Cumulative Illness Rating Scale[23] (CIRS) to assess current general medical conditions. Participants completed the 16-item Quick Inventory of Depressive Symptomatology–Self-Report[21,22,24] (QIDS-SR-16) to assess depression severity and the Psychiatric Diagnostic Screening Questionnaire[25] (PDSQ) for assessment of concurrent psychiatric comorbidities.

Centrally located research outcome assessors contacted participants for a telephone interview within 72 hours of

the initial visit to complete the HAM-D-17, the 30-item Inventory of Depressive Symptomatology–Clinician Rated[26,27] (IDS-C-30), and the 5-item Income and Public Assistance Questionnaire (IPAQ). Also within 72 hours of the initial visit, a telephone-based interactive voice response system[28] was used to gather the QIDS-C-16, the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire[29] (Q-LES-Q), and functional measures including the 12-item Short-Form Health Survey[30] (SF-12), the 6-item Work Productivity and Activity Impairment (WPAI) questionnaire,[31] and the 5-item Work and Social Adjustment Scale[32] (WSAS) from participants.

Intervention and Safety Assessment

The treatment goal in STAR*D was remission defined at each clinic visit by the QIDS-C-16. Vigorous dose adjustments were guided by treatment manual recommendations. Citalopram was generally begun at 20 mg/day and raised to 40 mg/day by weeks 2 through 4 and to 60 mg/day (final dose) by weeks 4 through 6. Flexibility in dosing was permitted to account for individual differences in side effect burden. Clinicians used clinically relevant information, QIDS-C-16 scores, and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale[33] obtained at each visit to monitor progress and inform the dosage schedule. The study used intensive, manualized, measurement-based care and centralized monitoring to ensure high-quality care across all clinical sites.[9]

Treatment visits were recommended at weeks 2, 4, 6, 9, and 12, with an optional visit at week 14 if needed. After a 12- to 14-week optimized trial of citalopram, participants who reached remission or response could enter the naturalistic 12-month follow-up; however, all participants with a QIDS-C-16 score greater than 5 were encouraged to move on to level 2 treatment randomization. Participants could move to the second step prior to 12 weeks if they experienced intolerable side effects or if significant symptoms (QIDS-C-16 score ≥ 9) persisted after 9 weeks at maximally tolerated doses. Side effects and serious adverse events were monitored across multiple levels, including the clinical research coordinators, study clinicians, interactive voice response, regional center directors, and the NIMH Data Safety and Monitoring Board.[34] The use of psychostimulants, antipsychotics, alprazolam, anticonvulsants, and nonprotocol antidepressants (with the exception of trazodone less than or equal to 200 mg at bedtime for insomnia) was not allowed. Anxiolytics (except alprazolam) or hypnotics were permitted during the acute phase based on clinical necessity. Treatments for SSRI-related sexual side effects were allowed.

Treatment Outcome Measures

The HAM-D-17 and the IDS-C-30 were collected by research outcome assessors using telephone-based structured interviews at entry and exit from citalopram treatment. The QIDS-SR-16, QIDS-C-16, and the FIBSER were obtained at each clinic visit. For research outcomes, remission was a score less than or equal to 7 on the HAM-D-17 (primary outcome) or less than or equal to 5 on the QIDS-SR-16 (secondary outcome) at treatment exit. When exit HAM-D-17 scores were missing, participants were designated as not remitted. Response was defined as a reduction of greater than or equal to 50% in baseline QIDS-SR-16 score at the last assessment.

Statistical Analysis

All analyses were based on the evaluable sample of 2851 participants. Participants were a priori divided into 4 groups based on the length of their index depressive episode at the time of study enrollment: acute (≤ 6 months), subchronic (7–23 months), chronic (24–41 months), and ultrachronic (≥ 42 months). The thresholds were selected with consideration of the 24-month threshold required for the chronicity definition in the DSM-IV,[35] previous observations suggesting a median MDE duration of less than 6 months,[36–39] and the creation of parallel groups of 18-month duration on either side of the 24-month cut-off. This method approximates that of Savino et al.[40] with our addition of an ultrachronic group. Although somewhat arbitrary, this categorical approach avoids the inherent limitation of having to precisely define episode duration retrospectively and enhances clinical interpretation of findings.

Descriptive statistics (mean percentages) of the sociodemographic and clinical characteristics are presented by duration group status. Chi-square and 2-sample t tests compared the discrete and continuous baseline characteristics, respectively, by duration status. A logistic regression model tested the association of duration group with clinical outcome, controlling for baseline characteristics not equally distributed between groups. Statistical significance was defined as a 2-sided p value less than .05. Kaplan-Meier curves were generated to display the time to first response and first remission by duration status. Cox proportional hazards models were used to estimate the effect of duration status on time to first response and remission, controlling for baseline characteristics not equally distributed between groups. For all adjusted outcome analyses that were statistically significant at p less than .05, post hoc pairwise comparisons were conducted. Pairwise comparisons were corrected for multiple comparisons using a Bonferroni correction; thus, statistical significance was defined as a 2-sided p value less than .0083.

RESULTS

Sociodemographic and Clinical Characteristics

Table 1 summarizes the sociodemographic characteristics based on index episode duration. The overall

Table 1. Baseline Sociodemographic Characteristics by Major Depressive Episode Duration[a]

Characteristic	Acute (N = 1324)	Subchronic (N = 807)	Chronic (N = 326)	Ultrachronic (N = 394)	p Value
Setting, %[b,c,d]					< **.0001**
Primary care	31.3	42.5	45.1	44.7	
Specialty care	68.7	57.5	54.9	55.3	
Race, %[d]					**.0002**
White	77.7	77.3	72.1	69.3	
Black	15.2	17.4	20.6	23.6	
Other	7.1	5.3	7.4	7.1	
Ethnicity, Hispanic, %[d]					**.0001**
No	89.5	86.6	85.6	81.0	
Yes	10.5	13.4	14.4	19.0	
Sex, %					.7668
Male	35.8	36.8	34.7	38.1	
Female	64.2	63.2	65.3	61.9	
Marital status, %[c,d]					**.0002**
Never married	30.7	29.1	23.6	41.4	
Married	41.0	43.3	40.8	25.4	
Divorced	26.6	24.0	31.0	27.4	
Widowed	1.7	3.6	4.6	5.8	
Employment status, %[b,c,d,e]					< **.0001**
Employed	62.2	54.5	49.7	44.4	
Unemployed	33.3	39.4	45.7	46.7	
Retired	4.5	6.1	4.6	8.9	
Insurance status, %[b,c,d,e]					< **.0001**
Private	57.7	49.4	43.9	38.4	
Public	10.4	14.9	18.6	21.2	
None	31.9	35.7	37.5	40.5	
Age, mean (SD), y[b,c,d,e]	39.1 (12.5)	40.8 (13.4)	42.6 (13.4)	44.6 (12.4)	< **.0001**
Education, mean (SD), y[b,c,d]	13.9 (3.1)	13.2 (3.2)	12.8 (3.3)	12.8 (3.4)	< **.0001**
Income, mean (SD), $/mo[b,c,d,e]	2577 (2952)	2361 (3164)	2078 (3697)	1842 (2314)	< **.0001**

[a]Post hoc comparisons based on a Bonferroni correction for multiple comparisons ($p < .0083$). All bolded p values indicate statistical significance.
[b]Acute vs. subchronic.
[c]Acute vs. chronic.
[d]Acute vs. ultrachronic.
[e]Subchronic vs. ultrachronic.

racial and ethnic composition of the study sample was representative of the U.S. Census.[41] Consistent with most previous clinical studies of MDD, approximately two thirds of the participants were women. Most participants were treated in psychiatric outpatient treatment clinics, although participants with longer MDEs were more likely to be treated in outpatient primary care clinics. Participants with longer episode duration were significantly more likely to be older, black, Hispanic, unemployed or retired, and less educated and to have public or no insurance and have less monthly income. Participants in the ultrachronic group were least likely to be married and most likely to be widowed.

Table 2 summarizes baseline clinical characteristics by index MDE duration. Participants with longer episode durations reported greater general medical comorbidity as measured by the CIRS. Specifically, longer episode duration was associated with a significantly higher CIRS total score, more general medical conditions, and greater general medical condition severity. Participants with longer episodes had poorer physical functioning by the SF-12 and worse quality of life by the Q-LES-Q and the WSAS. Although depressive symptom severity was not different among groups, participants with longer episode durations reported fewer depressive episodes and a greater length of illness.

Table 3 summarizes course of illness, suicide risk, and presence of concurrent psychiatric comorbidities by episode duration. Chronic participants showed a significantly greater rate of family history of suicide, but there were no significant differences between groups regarding family history of mood or substance use disorders. Participants with longer episodes showed less recurrent depression and greater rates of concurrent anxiety, obsessive-compulsive, and panic disorders; social phobia; posttraumatic stress disorder; agoraphobia; and hypochondriasis and more concomitant psychiatric Axis I comorbidities overall (assessed by the PDSQ).

We found no significant differences among the 4 groups regarding serious psychiatric adverse events or intolerance to citalopram. Similarly, there were no differences among groups in maximum dose of citalopram, time in treatment, or number of treatment visits.

Table 4 summarizes remission and response outcomes by episode duration. Participants with shorter episodes showed significantly higher remission rates by the HAM-D-17 and the QIDS-SR-16 and higher QIDS-SR-16 response rates. Those with longer index episodes had

Table 2. Baseline Clinical Features by Major Depressive Episode (MDE) Duration[a]

Clinical Feature	Acute (N = 1324)	Subchronic (N = 807)	Chronic (N = 326)	Ultrachronic (N = 394)	p Value
CIRS count, %[b,c,d,e]					< **.0001**
0	12.5	9.3	8.3	4.6	
1	18.4	14.6	13.2	8.6	
2	18.9	17.2	13.5	19.0	
3	15.4	14.4	13.2	14.0	
≥ 4	34.9	44.5	51.8	53.8	
CIRS, mean (SD)					
Categories endorsed[b,c,d,e]	2.7 (2.1)	3.2 (2.3)	3.6 (2.5)	3.9 (2.4)	< **.0001**
Total score[b,c,d,e]	3.8 (3.4)	4.6 (3.7)	5.2 (4.1)	5.8 (4.0)	< **.0001**
Severity index[b,d,e,f]	1.2 (0.6)	1.2 (0.6)	1.3 (0.6)	1.4 (0.5)	< **.0001**
Symptom severity, mean (SD)					
HAM-D-17 score	21.7 (5.0)	21.8 (5.3)	21.8 (5.4)	22.3 (5.5)	.2820
IDS-C-30 score	38.2 (9.1)	38.5 (9.8)	38.7 (10.0)	39.8 (10.4)	.0720
QIDS-SR-16 score	16.1 (3.9)	16.1 (4.1)	16.4 (3.9)	16.5 (4.0)	.3178
SF-12 score, mean (SD)					
Physical[b,c,d,e]	50.7 (11.5)	48.4 (12.1)	46.6 (12.3)	44.6 (12.3)	< **.0001**
Mental[b,d]	24.8 (7.8)	26.4 (8.3)	25.5 (8.1)	26.7 (8.6)	< **.0001**
Quality of life, mean (SD)					
Q-LES-Q score[d,e]	40.1 (13.9)	39.6 (14.8)	38.0 (14.3)	36.8 (14.4)	**.0003**
WSAS score[d,e]	24.6 (8.5)	24.5 (8.9)	25.6 (9.1)	26.4 (8.5)	**.0011**
Age at onset of first MDE, median (IQR)	21 (19)	21 (21)	22 (23)	22 (21)	.6647
No. of episodes, median (IQR)[b,c,d,e,f]	3 (4)	3 (3)	2 (3)	1 (2)	< **.0001**
Length of current episode, median (IQR), mo	3 (3)	12 (7)	31 (8)	78 (79)	…
Length of illness, median (IQR)[c,d,e,f]	12 (18)	12 (22)	14 (23)	13 (22)	< **.0001**

[a]Post hoc comparisons based on a Bonferroni correction for multiple comparisons (p < .0083). All bolded p values indicate statistical significance.
[b]Acute vs. subchronic.
[c]Acute vs. chronic.
[d]Acute vs. ultrachronic.
[e]Subchronic vs. ultrachronic.
[f]Chronic vs. ultrachronic.
Abbreviations: CIRS = Cumulative Illness Rating Scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician Rated, IQR = interquartile range, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SF-12 = 12-item Short-Form Health Survey, WSAS = Work and Social Adjustment Scale.
Symbol:… = no data.

significantly higher mean exit scores on the QIDS-SR-16. The acute group had the greatest improvement from baseline QIDS-SR-16 score and the largest percent reduction in the baseline QIDS-SR-16 score.

Further post hoc comparisons between groups were conducted. Significant between-group differences are noted in the footnotes in Tables 1 through 4.

Table 5 presents the unadjusted and adjusted logistic regression findings. The unadjusted results revealed a significant impact of index episode duration on both response and remission rates. The adjusted analyses revealed no statistically significant differences in remission rates. Response rates were related to duration, but the ultrachronic group was no more or less likely to respond than the acute group.

Figures 1 and 2 present the time to first remission and first response, respectively; patients with a longer duration of MDEs demonstrated longer time to first remission (p < .0001) or response (p < .0001). Consistent with the above outcome findings, however, after adjusting for baseline factors, the time to first remission was not statistically significant (p = .0704), although those with a longer duration did show a longer time to first remission (hazard ratio: 7–23 months vs. 0–6 months = .842, 24–41 months vs. 0–6 months = .748, and ≥ 42 months vs. 0–6 months = .857) as well as time to first response (p = .1167) (hazard ratio: 7–23 months vs. 0–6 months = .859, 24–41 months vs. 0–6 months = .769, and ≥ 42 months vs. 0–6 months = .911).

DISCUSSION

Overall, we found that progressively longer depressive episodes were associated with older age, greater general medical and psychiatric illness burden, worse quality of life, socioeconomic disadvantage, and greater racial/ethnic minority and primary care treatment representation. These results are consistent with previous studies that compared the characteristics of individuals with chronic (≥ 24 months) versus nonchronic depression (< 24 months).[5,16] The present results provide a more finely delineated characterization of these relationships given the 4 groups examined.

We also found that longer duration MDEs were associated with lower likelihood of remission with treatment, as expected given our prior report.[9] However, this asso-

Table 3. Course of Illness, Suicide Risk, and Presence of Psychiatric Comorbidities by Major Depressive Episode Duration[a]

Clinical Feature, %	Acute (N = 1324)	Subchronic (N = 807)	Chronic (N = 326)	Ultrachronic (N = 394)	p Value
Family history of depression	55.6	55.2	58.1	53.4	.6541
Family history of alcohol abuse	40.7	42.1	43.8	40.8	.7359
Family history of drug abuse	23.6	25.0	25.2	25.3	.8325
Family history of suicide[b]	3.4	3.4	6.2	2.1	**.0271**
Family history of mood disorder	57.2	58.1	60.0	56.3	.7429
Attempted suicide	18.5	16.7	16.0	20.0	.3765
Present suicide risk	3.4	2.5	2.8	3.3	.6593
Age at onset, y					.7450
≤ 18	42.7	42.1	40.7	39.9	
> 18	57.3	57.9	59.3	60.1	
Atypical features	17.5	18.3	20.2	23.1	.0824
Melancholic features	23.9	22.6	22.4	25.1	.7242
Recurrent features[b,c,d,e,f]	83.1	76.6	71.5	51.8	< **.0001**
Psychiatric comorbidities (PDSQ)					
Generalized anxiety disorder[c,d,e]	18.1	27.1	27.8	31.8	< **.0001**
Obsessive-compulsive disorder[b,c,e]	11.6	16.4	12.2	20.6	< **.0001**
Panic disorder[e]	11.8	13.2	11.6	18.3	**.0084**
Social phobia[e]	28.4	32.5	31.6	38.0	**.0035**
Posttraumatic stress disorder	18.8	20.0	24.6	24.5	**.0227**
Agoraphobia[b,e]	9.6	13.1	8.7	17.8	< **.0001**
Alcohol abuse	11.0	14.3	11.2	11.6	.1387
Drug abuse	7.8	7.5	5.0	8.0	.3674
Somatoform disorder	2.3	2.5	1.9	3.1	.7359
Hypochondriasis[e]	3.1	5.0	5.6	7.0	**.0064**
Bulimia	12.3	13.3	14.1	13.1	.8114
Axis I disorder count[c,e]					< **.0001**
0	46.5	40.1	38.6	34.5	
1	27.1	26.4	29.3	25.0	
2	12.8	15.8	15.3	16.2	
3	6.3	7.7	8.4	9.5	
≥ 4	7.3	10.1	8.4	14.7	

[a]Post hoc comparisons based on a Bonferroni correction for multiple comparisons (p < .0083). All bolded p values indicate statistical significance.
[b]Chronic vs. ultrachronic.
[c]Acute vs. subchronic.
[d]Acute vs. chronic.
[e]Acute vs. ultrachronic.
[f]Subchronic vs. ultrachronic.
Abbreviation: PDSQ = Psychiatric Diagnostic Screening Questionnaire.

Table 4. Remission and Response Status by Major Depressive Episode Duration

Outcome	Acute (N = 1324)	Subchronic (N = 807)	Chronic (N = 326)	Ultrachronic (N = 394)	Total (N = 2851)	p Value[a]
HAM-D-17 remission, %[b,c]						
No	69.0	75.8	75.2	75.9	72.6	**.0010**
Yes	31.0	24.2	24.8	24.1	27.4	
QIDS-SR-16 remission, %[b,c]						
No	63.4	69.6	70.9	72.6	67.3	**.0005**
Yes	36.6	30.4	29.1	27.4	32.7	
QIDS-SR-16 response, %[b,c,d]						
No	48.7	56.6	59.6	56.7	53.3	< **.0001**
Yes	51.3	43.4	40.4	43.3	46.7	
Exit QIDS-SR-16 score, mean (SD)[b,c,d]	8.7 (5.9)	9.4 (5.8)	9.6 (5.9)	9.8 (5.9)	9.1 (5.9)	**.0002**
QIDS-SR-16 score change, mean (SD)[b]	–7.4 (6.0)	–6.7 (5.9)	–6.8 (5.9)	–6.7 (5.8)	–7.0 (5.9)	**.0042**
QIDS-SR-16 score percent change, mean (SD)[b,c]	–45.5 (35.7)	–40.2 (35.4)	–40.8 (34.4)	–40.2 (33.7)	–42.7 (35.2)	**.0003**

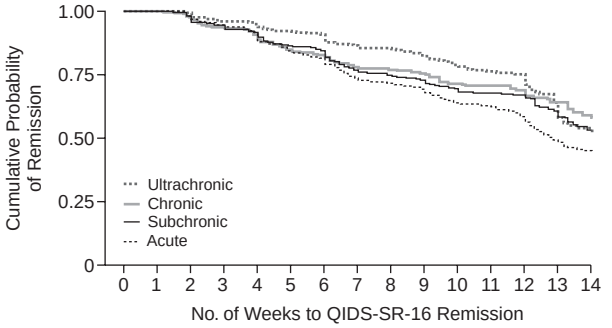
[a]All bolded p values indicate statistical significance.
[b]Acute vs. subchronic.
[c]Acute vs. ultrachronic.
[d]Acute vs. chronic.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

Table 5. Remission and Response Outcomes by Major Depressive Episode Duration (adjusted analysis)[a]

	Unadjusted		Adjusted[b]	
Outcome Variable	Odds Ratio	p Value	Odds Ratio	p Value
HAM-D-17 remission		**.0010**		.1942
Acute	1.0		1.0	
Subchronic	0.71		0.78	
Chronic	0.73		0.87	
Ultrachronic	0.71		0.92	
QIDS-SR-16 remission		**.0005**		.3033
Acute	1.0		1.0	
Subchronic	0.76		0.86	
Chronic	0.71		0.77	
Ultrachronic	0.66		0.96	
QIDS-SR-16 response		**< .0001**		**.0337**[c]
Acute	1.0		1.0	
Subchronic	0.73		0.81	
Chronic	0.64		0.69	
Ultrachronic	0.73		1.0	

[a]All bolded p values indicate statistical significance.
[b]Adjusted for setting, race, ethnicity, marital status, employment status, insurance, age, education, income, number of episodes, family history of suicide, Cumulative Illness Rating Scale total score, and any anxiety disorder (obsessive-compulsive disorder, panic disorder, social phobia, posttraumatic stress disorder, agoraphobia, hypochondriasis).
[c]After adjustment for multiple comparisons, there were no pairwise differences (all p > .0083).
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

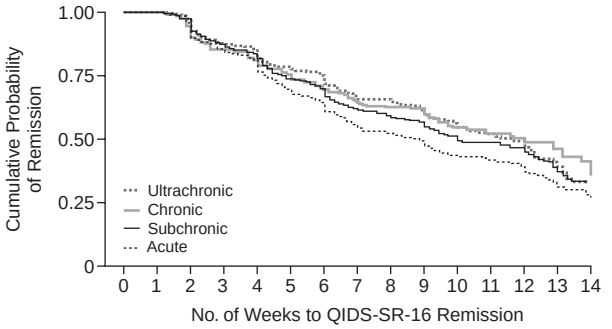
Figure 1. Time to First Remission Among Patients With Major Depressive Episodes (unadjusted)



N at Risk								
Acute	1322	1242	1040	807	604	417	308	113
Subchronic	805	747	620	496	372	259	192	79
Chronic	325	305	254	198	158	113	92	38
Ultrachronic	390	374	329	280	226	161	124	43
Total	2842	2668	2243	1781	1360	950	716	273

Abbreviation: QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

Figure 2. Time to First Response Among Patients With Major Depressive Episodes (unadjusted)



N at Risk								
Acute	1320	1217	904	616	424	263	190	73
Subchronic	804	735	559	399	278	175	116	40
Chronic	325	292	224	163	120	72	54	21
Ultrachronic	390	367	291	225	166	108	72	19
Total	2839	2611	1978	1403	988	618	432	153

Abbreviation: QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

ciation did not remain after controlling for multiple clinical and demographic characteristics associated with longer episodes. The absence of a direct effect of index episode duration on symptomatic outcomes is truly notable as it indicates that longer episodes, in and of themselves, do not necessarily portend poorer outcomes with adequate treatment. Rather, our results suggest that the actual causes for poorer outcomes among patients with longer episodes are most likely the multiple underlying factors that are linked to or are represented by the covariates.

Remarkably, after controlling for the various confounds, the ultrachronic group was no more or less likely to remit or respond to treatment than the acute group. It thus appears that the effect of confounding characteristics in treatment outcome is especially great for unusually long depressions. One interpretation is that various confounds might be highly associated with onset of depression but less so with persistence of depression except in a subset of patients with heightened vulnerabilities. Theoretically, such vulnerabilities might include exaggerated physiologic stress-reactivity or personality traits such as neuroticism or rejection sensitivity.

Our data suggest that longer MDE duration is primarily related to specific clinical and sociodemographic characteristics (e.g., greater medical burden, unpartnered status, or socioeconomic disadvantage), which may incur depressogenic effects. However, the apparent cause and effect relationship between episode length and characteristics, such as educational, occupational, financial, or marital status, is likely to be bidirectional.

Several of the associated characteristics tend to cluster together, and we are not able to discern the relative contribution of these characteristics from our present analyses. Although some characteristics associated with longer depressive episodes are fixed (e.g., race, gender), other characteristics are more fluid and ultimately could be influenced by effective treatment, although the effect may

occur substantially later in time. For example, symptomatic improvement and sense of well-being might enhance a patient's ability to achieve higher levels of education, employment, and income, all of which are likely to be interrelated. Also, better treatment outcomes for depression might facilitate more effective disease management of other medical illnesses, thereby decreasing overall disease burden. Further research will be required to parse out how these clustered characteristics individually affect treatment outcomes.

Previous reports have suggested that chronic episodes may simply reflect inadequate or incorrect treatment.[11,16,42–44] This suggestion may be applicable to our current finding that participants in primary care settings had longer index episodes prior to enrollment into the study, as well as to our earlier finding of more chronic episodes in primary care,[5] especially since a preliminary analysis of data from the STAR*D study did not find substantial differences in the presentation of major depression in primary care versus specialty care settings.[45] It is possible that the recognition of depression is obscured in primary care settings by a greater somatic focus or by the presence of other medical illnesses in these settings and thus leads to a lesser prioritization of depression treatment. Socioeconomic status, access to mental health treatment options, cultural factors, and stigmatization of mental illness could also be contributing to the higher rate of longer episodes seen in primary care.

Further, when depression treatment occurs in primary care settings, nonpsychiatric clinicians may not be accustomed to utilizing higher antidepressant doses to ensure complete efficacy and therefore may not provide optimal treatment of the depression. Notably, treatment outcomes in STAR*D did not differ for primary care and psychiatric settings,[9] likely due to similar treatment methods, procedures, and visit frequencies in both settings to optimize dosing with measurement-based care. Unfortunately, we do not have specific data to determine whether prior treatment inadequacy explains the higher rate of chronicity in primary care settings.

Broadly, our findings suggest that positive outcomes with adequate treatment are possible in persistently depressed patients and argue for a differential consideration of the confounding characteristics associated with longer depressive episodes. Identification of specific factors that contribute to longer depressive episodes could potentially lead to the modification of existing treatments or the development of novel interventions that target such characteristics and improve treatment outcome. The potential for such strategies is supported by the superior outcomes previously found for patients with chronic depression who receive depression-targeted psychotherapy combined with pharmacotherapy[12,14] and by the finding that patients nonresponsive to one treatment may have a differential response to another treatment.[46]

Strengths and Limitations

Our study has several strengths. Specifically, our analytic approach uses a careful examination of the strength of relationship between patient characteristics and clinical outcome, has a rigorous control of covariates, and has a large and naturalistic data set that facilitates generalizable results. Notably, the generalizability of our findings is enhanced by the broadly inclusive selection criteria and the fact that our overall racial and ethnic composition was representative of the U.S. population.

From these analyses, we are unable to determine the degree that physiologic and psychological vulnerabilities directly operate to increase episode persistence. For example, we did not include data regarding early life adversity, which is associated with poorer pharmacotherapy response in individuals with chronic depression.[47] Furthermore, while psychotherapy—both with and without citalopram—was included in a later step of the STAR*D protocol, the current analysis did not consider the potential benefit of psychotherapy in the initial level of treatment. Keller et al.[12] demonstrated an additive effect of combination treatment with nefazodone and psychotherapy in individuals with chronic depression. The degree to which the addition of psychotherapy enhances outcomes for those who report greater medical burden, unpartnered status, or socioeconomic disadvantage is open for further investigation. Additionally, it is possible that pharmacotherapy and psychotherapy, individually and together, may have differential effectiveness at different stages of episode length.

We also did not evaluate the role of depressive cognitive styles or premorbid neuroticism,[48,49] which have been suggested by some to be associated with chronicity and, possibly, poorer treatment outcome.[50] Though data suggest that premorbid personality and cognitive style do not influence treatment response for individuals with chronic depression,[11,51] our analyses incorporated a significant breadth of variables that may have inadvertently controlled the effect of cognitive and behavioral patterns.

Multiple factors might have prevented us from finding an association of episode duration and treatment outcome after controlling for covariates. For example, we may have biased our findings through the exclusion of patients who were already treatment resistant in the current episode. The exclusion of preexisting treatment resistance, however, was consistent with STAR*D's primary goal of assessing treatment effectiveness in the context of prospectively determined treatment resistance.

A major limitation of this secondary analysis is the difficulty in retrospectively defining MDE duration and the specific time frames we used to categorize participants. This is a limitation inherent in any retrospectively collected data, whether of a research or clinical nature. The delineation of insidious onsets and the defining of boundaries in chronic major depression and double de-

pression (i.e., major depression with underlying dysthymia)[52] are especially challenging. Yet, few meaningful differences have been found in the clinical features[53] or treatment outcomes[42] of chronic major depression and double depression.

While it is possible that the lack of predictive power of episode duration with outcome, when controlling for covariates, is due to our imprecision in defining the onset of a fully syndromal depressive episode (and similarly the patient's inability to do so), we are reassured by our finding, before controlling for covariates, of an association of increasing duration and lack of remission. A strength of our naturalistic approach in STAR*D is that it reflects how patients actually present and report their course of illness.

As any clinician can attest, it is not unusual for patients to present with reports of depressive episodes lasting several years. Even with further probing to identify less symptomatic periods, a subgroup of patients will persist in their reporting of unusually chronic depressive episodes. What makes our findings especially intriguing is that we specifically carved out the "ultrachronic" subjects. Clearly, the characteristics of the "ultrachronic" group require further evaluation.

Since episode duration was defined by the patients' retrospective recall, it is possible that other factors such as highly recurrent depressive patterns, overinterpretation of intervening subsyndromal symptoms, or more pessimistic cognitive styles may produce an exaggerated reporting of episode length. In the future, identifying such perceptions will be critical to further study and to the formulation of effective interventions for these patients.

CONCLUSION

A range of factors may be associated with more chronic index depressive episodes. However, the duration of the index MDE is not in and of itself a predictor of the likelihood of remission. Thus, medication treatment is of value for depressed patients independent of the duration of the index MDE. Earlier intervention may be especially useful as it could engage patients before some of the potential consequences of sustained depression such as poorer function and comorbid conditions take hold.

Drug names: alprazolam (Niravam, Xanax, and others), citalopram (Celexa and others).

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