The Impact of Chronic Depression on Acute and Long-Term Outcomes in a Randomized Trial Comparing Selective Serotonin Reuptake Inhibitor Monotherapy Versus Each of 2 Different Antidepressant Medication Combinations

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ABSTRACT

Objective: To compare sociodemographic and clinical features, acute and continuation treatment outcomes, and adverse events/side effect burden between outpatients with chronic (current episode > 2 years) versus nonchronic major depressive disorder (MDD) who were treated with combination antidepressant therapy or selective serotonin reuptake inhibitor (SSRI) monotherapy.

Method: 663 outpatients with chronic (n = 368) or nonchronic (n = 295) moderate to severe *DSM-IV-TR* MDD (17-item Hamilton Depression Rating Scale score ≥ 16) were enrolled from March 2008 through September 2009 in a single-blind 7-month prospective randomized trial conducted at 6 primary and 9 psychiatric care sites across the United States. Participants were treated with escitalopram monotherapy plus placebo or 1 of 2 combination treatments (bupropion sustained-release [SR] + escitalopram or venlafaxine extended-release [XR] + mirtazapine). Analyses compared baseline sociodemographic and clinical characteristics, rates of remission (at least 1 of the last 2 consecutive scores on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report [QIDS-SR_{16}] < 6, with the other < 8), and adverse events/side effect burden (Frequency, Intensity, and Burden of Side Effects Ratings) obtained at 12 and 28 weeks.

Results: Participants with chronic MDD were at greater socioeconomic disadvantage and had greater medical and psychiatric disease burden. The chronic and nonchronic groups did not differ in rates of remission at 12 weeks (35.9% vs 42.0%, respectively; odds ratio [OR] = 0.778, *P* = .1500; adjusted OR [AOR] = 0.956, *P* = .8130) or at 28 weeks (41.0% vs 49.8%, respectively; OR = 0.706, *P* = .0416; AOR = 0.837, *P* = .3448). Participants with chronic MDD had higher final QIDS-SR_{16} scores and smaller overall percent changes in QIDS-SR_{16} from baseline to exit, but these differences did not remain after adjusting for covariates. There were no significant differences in adverse events or side effect burden. No significant interactions were found between chronicity and type of treatment at 12 or 28 weeks.

Conclusion: Chronicity of illness does not appear to differentially impact acute or longer-term outcomes with SSRI monotherapy or combination antidepressant medication treatment in patients with moderate to severe nonpsychotic MDD.

Trial Registration: ClinicalTrials.gov identifier: NCT00590863

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Major depressive disorder (MDD) affects 6%–7% of adults in the United States each year.[1] Overall, 10%–25% of patients with MDD experience a chronic course of illness,[2,3] defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[4] as depressive illness in which the criteria for a major depressive episode have been met continuously for ≥ 2 years.

Chronic MDD has been associated with a number of comorbid psychiatric conditions including higher rates of personality, anxiety, and substance-use disorders, as well as other features associated with increased psychiatric disease burden: earlier age at MDD onset, longer duration of depressive episodes, greater family psychiatric history, and increased rates of suicide. On average, patients with chronic MDD also have significantly more medical comorbidities and report a greater physical illness burden, as well as poorer quality of life.[2,5–9] This population of patients has been found to be at greater socioeconomic disadvantage and are more frequent users of health care services.[2,6,10]

Patients with chronic MDD may also have poorer treatment outcomes. Longer episodes have been associated with a lower likelihood of remission with selective serotonin reuptake inhibitor (SSRI) treatment.[11] However, there is some emerging evidence that chronicity alone cannot fully account for these differences. For example, Gilmer et al[7] compared response and remission with up to 14 weeks of citalopram in 2,851 patients with acute (index episode lasting ≤ 6 months), subchronic (index episode lasting 7–23 months), chronic (index episode lasting 24–41 months), or ultrachronic (index episode lasting ≥ 42 months) MDD. Initial results were consistent with previous reports of lower response and remission in those with chronic forms of MDD, but this association did not remain after adjusting for pretreatment sociodemographic and clinical characteristics. In a trial focused solely on patients with chronic MDD, Kocsis et al[12] also failed to show superiority for a combination of antidepressant medications plus cognitive therapy when compared to antidepressant medications alone during second-step treatment for patients with chronic depression.

The low remission rates with any initial monotherapy and the modest additional remissions achieved with a subsequent switch or augmentation step suggest the

Clinical Points

- Evidence suggests that first-step combined antidepressant treatment does not provide a significant advantage over selective serotonin reuptake inhibitor monotherapy for patients with chronic major depressive disorder (MDD).
- Clinicians should closely monitor patients with a history of chronic MDD to prevent early discontinuation of antidepressant treatment.
- Patients with chronic MDD may need additional support to address the poorer treatment outcomes associated with comorbid medical and psychiatric conditions, low education and employment, and poor quality of life.

potential need for medication combinations at the outset of treatment of MDD. At least 1 form of combination treatment (antidepressant treatment plus psychotherapy) appears to perform better as a first step than either therapy alone among patients with chronic MDD.[13] Recent data also support the notion that the combination of 2 antidepressants may produce additive pharmacologic effects by affecting a broader range of neurotransmitters and/or by the creation of a broader spectrum of action (ie, treating a broader range of patients) than can be achieved with monotherapy,[14] but the extent to which first-step medication combinations are more effective than traditional SSRI monotherapy for patients with chronic MDD remains unclear.

This study compares 3 different initial medication treatments (escitalopram + placebo, escitalopram + bupropion sustained-release [SR], and venlafaxine extended-release [XR] + mirtazapine) in short-term (12 weeks) and continuation (7 months) phases of treatment. Data from a cohort of 665 treatment-seeking outpatients with chronic and nonchronic MDD enrolled in the Combining Medications to Enhance Depression Outcomes (CO-MED) study[15] were used to address the following questions:

1. What baseline sociodemographic and clinical features are associated with chronic versus nonchronic MDD?
2. Do patients with chronic MDD have poorer acute- and continuation-phase antidepressant treatment outcomes (efficacy and tolerability)?
3. Do combination medications provide better treatment outcomes (efficacy and tolerability) for patients with chronic MDD than traditional SSRI monotherapy?

METHOD

Study Overview

The multicenter CO-MED study[15] was a 7-month prospective, single-blind, placebo-controlled randomized trial that examined the efficacy of each of 2 different antidepressant medication combinations versus escitalopram + placebo (1:1:1 ratio) as a first-step MDD treatment, including acute (12 weeks) and long-term continuation treatment (total 28 weeks). The study enrolled outpatients with nonpsychotic MDD from 6 primary care and 9 psychiatric care sites across the United States. Study details and methodology are available elsewhere.[15] The CO-MED study is registered at ClinicalTrials.gov (identifier: NCT00590863).

Participants

CO-MED enrolled participants from March 2008 through September 2009. Potential participants were treatment-seeking adult outpatients, 18–75 years of age, who met *DSM-IV-TR* criteria for either chronic (current major depressive episode for ≥ 2 years) or recurrent (≥ 1 prior major depressive episode) MDD on the basis of clinical interview by the treating clinician and confirmed using a *DSM-IV* MDD symptom checklist completed by the clinical research coordinator. Eligible participants were required to have at least moderate depression (baseline 17-item Hamilton Depression Rating Scale [$HDRS_{17}$][16] score of ≥ 16) and had to have been in the index episode for ≥ 2 months. Exclusion criteria included lifetime history of bipolar disorder, any psychotic disorder, or the immediate need for hospitalization (see http://www.co-med.org for a complete list of exclusion criteria).

The CO-MED protocol was developed in accordance with the principles of the Declaration of Helsinki. All consent and study procedures were approved by the National Coordinating Center (University of Texas Southwestern Medical Center at Dallas), the Data Coordinating Center (University of Pittsburgh, Pennsylvania), and the institutional review boards at each participating Regional Center and clinical site. A full description of the protocol was given to each participant prior to obtaining written informed consent.

Baseline Characteristics

Sociodemographic and clinical characteristics were gathered at baseline. Concurrent Axis I disorders were assessed using the Psychiatric Diagnostic Screening Questionnaire (PDSQ),[17,18] and comorbid general medical conditions were assessed using the Self-Administered Comorbidity Questionnaire (SCQ).[19] Severity of depressive symptoms was assessed using the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated ($QIDS\text{-}SR_{16}$).[20,21] The presence of anxious features was assessed on the basis of responses to the HDRS.[22] The presence of atypical and melancholic features was assessed on the basis of responses to the 30-item Inventory of Depressive Symptomatology–Clinician-Rated ($IDS\text{-}C_{30}$).[21] Risk of suicidal thoughts or plans was measured using the Concise Health Risk Tracking Scale–Self-Rated (CHRT-SR),[23] while possible manic symptoms were evaluated using the Altman Self-Rated Mania Scale (ASRMS).[24] Functioning and quality of life were evaluated using the Work and Social Adjustment Scale (WSAS)[25] and Quality of Life Inventory (QOLI),[26] respectively.

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Summary of Treatment Protocol

Antidepressant treatment was provided during an initial 12-week acute study period in order to maximize likelihood of response and remission while minimizing risk of attrition. Participants were started on 1 of 3 study medications at week 1 (ie, bupropion SR, venlafaxine XR, or escitalopram), and a second medication was added at week 2 (ie, escitalopram, mirtazapine, and placebo, respectively). Participants were blind to the second study medication throughout acute and continuation treatment. Physicians and clinical research coordinators were not blind to either medication in order to manage flexible dosing and address safety concerns.

Measurement-based care was implemented following guidelines set forth in the CO-MED Operations Manual (available at http://www.co-med.org). During the acute treatment period, dosage adjustments were made at each clinic visit on the basis of participant adherence to the current regimen, clinician-rated depressive symptom severity, and participant report of side effects (see Rush et al[15] for a detailed description of dosing in each group). Treatment visits were planned for baseline and weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 and 28. Per the study protocol, participants who did not respond by week 8 had the option to exit the study if they had received a maximally tolerated dose of the study medication(s) for at least 4 weeks without obtaining a 30% reduction in clinician-rated depressive symptoms. As in routine clinical practice, the decision to exit or continue was made jointly by the clinician and patient. Those who received an acceptable treatment benefit by week 12 (≥ 40% reduction in depressive symptoms) were eligible to enter the continuation phase. In keeping with ethical principles, all participants were free to withdraw from the study at any time.

Participants were allowed to remain on medications for comorbid general medical conditions, but treatment with other antidepressant medications or those with possible antidepressant effects (eg, anxiolytics, sedative hypnotics) were prohibited during the study period. Medications to treat side effects of the study medications were allowed on the basis of clinician judgment. Concurrent treatment with cognitive-behavioral therapy or any other empirically validated psychotherapy designed specifically for depression was also prohibited. Other therapies, such as supportive counseling and couples therapy, were allowed.

Treatment Measures

The QIDS-SR_{16} score was collected at baseline and at each clinic visit, along with the WSAS, the QOLI, and the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER).[27] Additional measures included medication dosing, presence of serious adverse events, and the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI).[28] These same measures were collected throughout the continuation phase with the addition of number of weeks in treatment, number of postbaseline visits, maximum medication dose, final medication dose, and whether the participant discontinued the trial.

Outcome Measures

The primary treatment outcome, symptom remission, was based on the change in QIDS-SR_{16} scores from baseline to either the 12-week or 28-week endpoint. Remission was ascertained on the basis of the final 2 consecutive QIDS-SR_{16} scores during the 12-week acute trial to ensure that remission was not falsely assigned due to a single week of symptom improvement. One of these ratings had to be < 8, and the other had to be < 6. For participants who exited prior to 12 weeks, the scores from their last 2 consecutive visits were used to assign remission. Participants who exited before completing 2 postbaseline visits were deemed not remitted for the purposes of all analyses. Treatment response was indicated by an improvement in QIDS-SR_{16} score ≥ 50% over baseline.

Secondary outcomes included early termination, side effect burden as measured by the FIBSER, detailed side effects as measured by the SAFTEE-SI, functioning as measured by the WSAS, anxiety as measured by the anxiety subscale of the IDS-C_{30}, and quality of life as measured by the QOLI.

Statistical Analyses

All analyses were computed using the full intention-to-treat sample (N = 663). Group differences in baseline characteristics, course of treatment, and outcome measures were examined using χ^2 or Fisher exact test for categorical variables and *t* tests and Kruskal-Wallis tests for continuous variables. Bivariate logistic regression was used to examine binary outcomes such as response, remission, and side effect burden. A treatment × chronic depression interaction term was computed to examine differences in outcome between the 3 treatment conditions for those with chronic versus nonchronic MDD. Polytomous logistic regression was used for discrete outcomes with more than 2 levels. Outcome analyses were first computed without adjustment for baseline characteristics. Potential covariates were identified using a stepwise logistic regression model with an indicator of chronic depression as the outcome and all other baseline characteristics as independent variables. The stepwise approach was used to minimize the number of parameters in the model by excluding highly correlated baseline characteristics (eg, income and education) unless both variables had an independent association with the outcome. Those variables that remained in the final stepwise model (treatment, gender, race, education, psychiatric comorbidity, quality of life) were considered as potential covariates in a second set of adjusted models. Overall type I error rate was controlled for by using a *P* value of < .025 to determine statistical significance. There were no missing data for the primary outcome measure. For secondary outcomes, only observed data were analyzed.

RESULTS

Baseline Characteristics

CO-MED enrolled 665 participants, of which 663 were analyzable for this report (see Supplementary eFigure 1,

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Table 1. Sociodemographic and Clinical Characteristics by Chronic Depression Status

Characteristic	Chronic Depression		Analyses		
	Yes (N = 368), n (%)	No (N = 295), n (%)	Statistic	*df*	*P* Value[a]
Age, y			$\chi^2 = 7.550$	2	**.0229**
18–29	65 (17.7)	70 (23.7)			
30–54	211 (57.3)	174 (59.0)			
55–75	92 (25.0)	51 (17.3)			
Sex			$\chi^2 = 17.18$	1	**<.0001**
Male	143 (38.9)	70 (23.7)			
Female	225 (61.1)	225 (76.3)			
Race			$\chi^2 = 6.006$	2	.0496
White	223 (63.0)	207 (72.1)			
Black	107 (30.2)	66 (23.0)			
Other	24 (6.8)	14 (4.9)			
Ethnicity			$\chi^2 = 2.011$	1	.1561
Hispanic	62 (16.8)	38 (12.9)			
Not Hispanic	306 (83.2)	257 (87.1)			
Employed	164 (44.6)	166 (56.3)	$\chi^2 = 8.975$	1	**.0027**
Body mass index (kg/m^2)			$\chi^2 = 0.214$	3	.9753
Normal/underweight (< 25.0)	91 (24.9)	77 (26.2)			
Overweight (25.0–29.9)	104 (28.4)	83 (28.2)			
Obese I (30.0–34.9)	75 (20.5)	57 (19.4)			
Obese II and III (35.0+)	96 (26.2)	77 (26.2)			
Menopausal	85 (39.4)	54 (24.8)	$\chi^2 = 10.59$	1	**.0011**
Menopausal status			$\chi^2 = 10.62$	2	**.0049**
Premenopausal	131 (60.6)	164 (75.2)			
Postmenopausal (with HRT)	7 (3.2)	4 (1.8)			
Postmenopausal (without HRT)	78 (36.1)	50 (22.9)			
At least 1 prior episode	222 (60.3)	295 (100)	$P < .001$[b]	NA	**<.0001**
Ever attempted suicide	37 (10.3)	22 (7.8)	$\chi^2 = 1.240$	1	.2653
Neglected before age 18	143 (38.9)	95 (32.3)	$\chi^2 = 3.041$	1	.0812
Emotionally abused before age 18	157 (42.7)	102 (34.7)	$\chi^2 = 4.357$	1	.0368
Physically abused before age 18	80 (21.7)	50 (17.0)	$\chi^2 = 2.319$	1	.1278
Sexually abused before age 18	81 (22.1)	63 (21.4)	$\chi^2 = 0.039$	1	.8424
Abused before age 18	182 (49.6)	126 (42.9)	$\chi^2 = 2.974$	1	.0846
	Mean ± SD	Mean ± SD			
Age, y	44.3 ± 13.0	40.8 ± 12.8	$t = 3.4$	661	**.0006**
Education, y	13.3 ± 2.9	14.3 ± 3.0	$t = 4.1$	637	**<.0001**
Monthly household income, $	2,490 ± 6,254	2,926 ± 3,899	$H = 16.7$	1	**<.0001**
Body mass index (kg/m^2)	30.8 ± 8.3	31.3 ± 9.4	$H = 0.011$	1	.9138
Systolic blood pressure, mm Hg	127 ± 18	122 ± 16	$t = 3.5$	650	**.0005**
Diastolic blood pressure, mm Hg	80.1 ± 11.8	77.7 ± 11.0	$t = 2.7$	654	**.0074**
Pulse, beats/min	73.9 ± 12.1	72.9 ± 10.7	$t = 1.1$	648	.2720
Age at first episode, y	25.1 ± 15.3	22.6 ± 12.3	$H = 1.7$	1	.1948
Years since first episode	19.1 ± 14.3	18.2 ± 12.7	$H = 0.012$	1	.9124
No. of prior episodes	7.5 ± 19.7	11.0 ± 20.1	$H = 73.1$	1	**<.0001**

[a]Bolded *P* values reflect statistical significance at $P < .025$.
[b]*P* value refers to the Fisher exact test.
Abbreviation: HRT = hormone replacement therapy, NA = not applicable.

available at PSYCHIATRIST.COM). Descriptives from the overall sample have been reported in detail elsewhere.[15] More than half (55.5%) of the participants were in a chronic index episode, and these participants were more likely to be socioeconomically disadvantaged (ie, less education, less employment, lower household income), older, and male. They were more likely to have had fewer prior episodes of depression than patients with nonchronic depression. The groups did not significantly differ regarding suicidality. Women with a chronic index episode were more likely to have completed menopause, and most were not receiving hormone replacement therapy (Table 1).

Participants with chronic depression were more likely to seek treatment in a psychiatric care setting, while those with nonchronic depression tended to seek treatment in primary care. Those with chronic depression were more likely to endorse psychiatric comorbidities (particularly obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), more health problems (particularly back pain and diabetes), more concomitant medications, greater impairment of socio-occupational functioning, lower quality of life, and more self-reported manic symptoms (Table 2).

Treatment Measures

At the end of the acute phase (week 12), participants with chronic depression did not significantly differ from those without chronic depression regarding number of weeks in treatment, number of postbaseline visits, maximum medication dose, final medication dose, or number of weeks on last medication dose. Those with chronic depression were less likely to complete at least 4 weeks of treatment than those with nonchronic depression (Table 3).

At 7 months, participants with chronic depression had slightly fewer weeks in treatment. However, the small

Table 2. Comorbidity, Symptomatology, and Function Measures by Chronic Depression Status

Variable	Chronic Depression		Analyses		
	Yes (N = 368), n (%)	No (N = 295), n (%)	Statistic	*df*	*P* Value[a]
Clinical setting			$\chi^2 = 5.873$	1	**.0154**
Primary care	176 (47.8)	169 (57.3)			
Psychiatric care	192 (52.2)	126 (42.7)			
PDSQ agoraphobia	45 (12.2)	24 (8.1)	$\chi^2 = 2.941$	1	.0863
PDSQ alcohol abuse	39 (10.6)	28 (9.5)	$\chi^2 = 0.207$	1	.6489
PDSQ bulimia	43 (11.7)	35 (11.9)	$\chi^2 = 0.005$	1	.9431
PDSQ drug abuse	20 (5.4)	15 (5.1)	$\chi^2 = 0.040$	1	.8412
PDSQ generalized anxiety	79 (21.5)	52 (17.6)	$\chi^2 = 1.523$	1	.2172
PDSQ hypochondriasis	19 (5.2)	10 (3.4)	$\chi^2 = 1.230$	1	.2672
PDSQ obssessive-compulsive	55 (14.9)	24 (8.1)	$\chi^2 = 7.235$	1	**.0071**
PDSQ panic	43 (11.7)	22 (7.5)	$\chi^2 = 3.308$	1	.0689
PDSQ posttraumatic stress	57 (15.5)	24 (8.1)	$\chi^2 = 8.256$	1	**.0041**
PDSQ social phobia	115 (31.3)	63 (21.4)	$\chi^2 = 8.161$	1	**.0043**
PDSQ somatoform	12 (3.3)	9 (3.1)	$\chi^2 = 0.023$	1	.8780
No. of PDSQ psychiatric disorders			$\chi^2 = 12.54$	4	**.0137**
0	149 (40.5)	145 (49.3)			
1	87 (23.6)	72 (24.5)			
2	51 (13.9)	41 (13.9)			
3	37 (10.1)	13 (4.4)			
4+	44 (12.0)	23 (7.8)			
No. of treated SCQ health problems			$\chi^2 = 19.14$	3	**.0003**
0	160 (43.6)	166 (56.5)			
1	85 (23.2)	73 (24.8)			
2	65 (17.7)	33 (11.2)			
3+	57 (15.5)	22 (7.5)			
SCQ back pain	224 (60.9)	143 (48.5)	$\chi^2 = 10.17$	1	**.0014**
SCQ diabetes	52 (14.1)	22 (7.5)	$\chi^2 = 7.352$	1	**.0067**
SCQ heart	26 (7.1)	14 (4.7)	$\chi^2 = 1.553$	1	.2126
SCQ neuropsychological	14 (3.8)	4 (1.4)	$\chi^2 = 3.716$	1	.0539
SCQ thyroid	23 (6.3)	14 (4.7)	$\chi^2 = 0.703$	1	.4017
Chronic/recurrent depression			$P < .001$[b]	NA	**< .001**
Chronic only	146 (39.7)	0 (0.0)			
Recurrent only	0 (0.0)	295 (100)			
Both	222 (60.3)	0 (0.0)			
$QIDS\text{-}SR_{16}$			$\chi^2 = 5.352$	3	.1477
0–10, None/mild	38 (10.5)	43 (15.3)			
11–15, Moderate	145 (39.9)	92 (32.7)			
16–20, Severe	143 (39.4)	116 (41.3)			
21–27, Very severe	37 (10.2)	30 (10.7)			
Anxious features	279 (75.8)	218 (73.9)	$\chi^2 = 0.320$	1	.5713
Atypical features	58 (15.8)	45 (15.3)	$\chi^2 = 0.032$	1	.8580
Melancholic features	71 (21.6)	53 (19.3)	$\chi^2 = 0.458$	1	.4985
$IDS\text{-}C_{30}$ sleep disturbance	319 (86.7)	266 (90.2)	$\chi^2 = 1.915$	1	.1664
CHRT-SR suicidal thoughts/plans	63 (17.1)	47 (15.9)	$\chi^2 = 0.166$	1	.6830
	Mean ± SD	Mean ± SD			
No. of prior antidepressants	1.6 ± 1.8	1.5 ± 1.6	$H = 0.113$	1	.7359
No. of concomitant medications	3.3 ± 3.1	2.6 ± 2.4	$H = 6.3$	1	**.0122**
$QIDS\text{-}SR_{16}$	15.6 ± 4.2	15.4 ± 4.4	$t = 0.640$	642	.5223
ASRMS	1.7 ± 2.4	1.3 ± 2.1	$H = 6.3$	1	**.0124**
QOLI	−1.4 ± 1.9	−0.9 ± 1.8	$t = 3.0$	657	**.0026**
WSAS	27.7 ± 8.7	25.9 ± 8.9	$t = 2.6$	660	**.0102**

[a]Bolded *P* values reflect statistical significance at $P < .025$.
[b]*P* value refers to the Fisher exact test.
Abbreviations: ASRMS = Altman Self-Rated Mania Scale, CHRT-SR = Concise Health Risk Tracking Scale–Self-Rated, $IDS\text{-}C_{30}$ = 30-item Inventory of Depressive Symptomatology–Clinician-Rated, NA = not applicable, PDSQ = Psychiatric Diagnostic Screening Questionnaire, $QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated, QOLI = Quality of Life Inventory, SCQ = Self-Administered Comorbidity Questionnaire, WSAS = Work and Social Adjustment Scale.

magnitude of this difference suggests that it may not be clinically significant (see Table 3).

Outcome Measures

At 12 weeks, the primary outcome of remission (based on the final 2 $QIDS\text{-}SR_{16}$ scores) did not differ significantly between groups (35.9% for chronic depression and 42.0% for nonchronic depression). Participants with chronic depression had a smaller percent change in $QIDS\text{-}SR_{16}$ scores from baseline to exit or 12 weeks, higher last $QIDS\text{-}SR_{16}$ scores, lower last quality-of-life ratings, and worse last WSAS scores. However, after adjusting for potential covariates (ie, type of treatment, gender, race, education, comorbid general medical conditions, quality-of-life domains), only the last WSAS score remained significant. Those with chronic depression were more likely to experience anxious features ($IDS\text{-}C_{30}$)

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Table 3. Treatment Measures by Study Phase and Chronic Depression Status

	Acute Phase					Continuation Phase				
	Chronic Depression		Analyses			Chronic Depression		Analyses		
Measure	Yes (N = 368), n (%)	No (N = 295), n (%)	Statistic	*df*	*P* Value[a]	Yes (N = 368), n (%)	No (N = 295), n (%)	Statistic	*df*	*P* Value[a]
No. of weeks in treatment[b]										
< 4	62 (16.9)	30 (10.2)	$\chi^2 = 6.179$	1	**.0129**					
< 8	86 (23.4)	57 (19.3)	$\chi^2 = 1.632$	1	.2014					
< 12	110 (30.0)	74 (25.1)	$\chi^2 = 1.947$	1	.1629					
	Mean ± SD	Mean ± SD				Mean ± SD	Mean ± SD			
No. of weeks in treatment	9.6 ± 4.1	10.2 ± 3.5	$H = 2.9$	1	.0906	19.2 ± 10.8	20.8 ± 10.0	$H = 5.4$	1	**.0204**
No. of postbaseline visits	5.2 ± 2.3	5.5 ± 2.0	$H = 1.5$	1	.2195	7.5 ± 3.8	8.0 ± 3.5	$H = 3.9$	1	.0473
Maximum bupropion dose, mg/d	324 ± 80	324 ± 81	$H = 0.008$	1	.9257	331 ± 82	325 ± 82	$H = 0.470$	1	.4927
Last bupropion dose, mg/d	284 ± 124	292 ± 117	$H = 0.117$	1	.7317	259 ± 148	286 ± 120	$H = 0.710$	1	.3993
Maximum escitalopram dose, mg/d	14.3 ± 7.3	13.7 ± 7.2	$H = 0.471$	1	.4925	14.5 ± 7.3	13.7 ± 7.2	$H = 1.1$	1	.2936
Last escitalopram dose, mg/d	12.5 ± 8.3	12.4 ± 8.3	$H = 0.017$	1	.8938	11.4 ± 8.9	11.6 ± 8.4	$H = 0.017$	1	.8960
Maximum escitalopram dose, mg/d[c]	17.4 ± 4.6	17.8 ± 4.4	$H = 0.503$	1	.4779	17.6 ± 4.7	18.3 ± 4.0	$H = 1.7$	1	.1880
Last escitalopram dose, mg/d[c]	16.5 ± 5.6	17.3 ± 4.9	$H = 0.603$	1	.4374	15.5 ± 7.0	15.9 ± 6.9	$H = 0.269$	1	.6034
Maximum venlafaxine dose, mg/d	210 ± 74	204 ± 62	$H = 0.697$	1	.4035	218 ± 79	216 ± 66	$H = 0.179$	1	.6720
Last venlafaxine dose, mg/d	196 ± 86	187 ± 77	$H = 0.848$	1	.3569	171 ± 100	186 ± 85	$H = 0.927$	1	.3355
Maximum mirtazapine dose, mg/d	24.2 ± 14.5	26.8 ± 46.2	$H = 0.870$	1	.3509	25.2 ± 14.8	28.7 ± 46.3	$H = 0.186$	1	.6658
Last mirtazapine dose, mg/d	20.8 ± 16.4	19.0 ± 14.7	$H = 0.465$	1	.4953	17.0 ± 16.8	19.2 ± 16.0	$H = 1.2$	1	.2673

[a]Bolded *P* values reflect statistical significance at $P < .025$.
[b]Not applicable to continuation phase.
[c]Reflects dose for single-agent escitalopram group.

than those with nonchronic depression, and this difference remained significant after adjustment (Table 4).

At 7 months, remission did not differ significantly between groups (41% for chronic depression, and 49.8% for nonchronic depression). Participants with chronic depression had a smaller percent change in QIDS-SR_{16} scores from baseline to exit or 7 months, higher last QIDS-SR_{16} scores, lower last quality-of-life ratings, and worse WSAS scores, and they were more likely to experience anxious features compared to those with nonchronic depression. However, these differences were not significant after adjustment for covariates (see Table 4).

Participants with and without chronic depression did not differ with respect to reported adverse events or side effect burden during acute or continuation treatment. Early termination, maximum FIBSER scores, and QIDS-SR_{16} scores did not significantly differ at 12 or 28 weeks (see Table 4).

Combination Treatments

Treatment outcomes were not significantly different between the treatments (escitalopram + placebo, bupropion SR + escitalopram, venfaxine XR + mirtazapine) for participants in the chronic MDD or nonchronic MDD groups. Early termination, tolerability, and reductions in depressive symptom severity were comparable between the chronic and nonchronic groups and between treatments within each group (Table 5).

DISCUSSION

Consistent with previous studies, we found chronic MDD to be associated with greater socioeconomic disadvantage, higher rates of comorbid anxiety disorders and medical illnesses, lower levels of social and occupational functioning, and reduced quality of life.[2,7,8,10] Treatment outcomes provided evidence of poor functioning and greater anxiety in patients with chronic depression than in those with nonchronic depression, with worse WSAS and IDS-C_{30} anxiety scores after adjustment at 12 and 28 weeks for patients with chronic depression. We found several differences between participants with and without chronic depression with regard to QIDS-SR_{16} scores at 12 and 28 weeks, but these effects were small and none remained significant after adjustment. These last findings are similar to those reported by Gilmer et al,[7] who found that duration of index episode was no longer associated with remission status among patients with chronic forms of MDD after controlling for potential confounding factors. It is therefore possible that the poorer outcomes reported in prior studies of patients with chronic MDD were more closely related to socioeconomic disadvantage and the presence of comorbid medical and/or psychiatric conditions than to chronicity of depression per se.

There were no significant interactions between chronicity and type of treatment at 12 or 28 weeks. All 3 treatments worked equally well in reducing depressive symptoms, both within and between the chronic and nonchronic groups. Although it has been suggested that patients with chronic MDD will have a less satisfactory experience with antidepressant treatment, our results indicate that these participants were not more likely to report serious adverse events or to have an increased side effect burden compared to those with nonchronic MDD. However, patients with chronic depression were less likely to complete 4 or more weeks of antidepressant treatment; this patient category should be closely monitored early in the acute phase to prevent premature discontinuation of antidepressant treatment.

Taken together, results from this study and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Table 4. Outcome Measures by Study Phase and Chronic Depression Status

	Acute Phase						Continuation Phase					
	Chronic Depression		Analyses				Chronic Depression		Analyses			
			Unadjusted		Adjusted[a]				Unadjusted		Adjusted[a]	
Measure	Yes (N = 368), n (%)	No (N = 295), n (%)	OR, β	*P* Value[b]	OR, β	*P* Value[b]	Yes (N = 368), n (%)	No (N = 295), n (%)	OR, β	*P* Value[b]	OR, β	*P* Value[b]
Early termination	111 (30.2)	69 (23.4)	1.422	.0695	1.181	.4436	147 (39.9)	95 (32.2)	1.307	.1327	1.123	.5539
Last FIBSER frequency rating			1.129	.4548	1.282	.1609			1.256	.1720	1.434	.0477
No side effects	144 (41.9)	118 (41.5)					166 (48.1)	146 (51.2)				
10%–25% of the time	125 (36.3)	121 (42.6)					115 (33.3)	104 (36.5)				
50%–75% of the time	56 (16.3)	35 (12.3)					46 (13.3)	24 (8.4)				
90%–100% of the time	19 (5.5)	10 (3.5)					18 (5.2)	11 (3.9)				
Last FIBSER intensity rating			1.062	.7128	1.161	.3979			1.170	.3447	1.219	.2739
No side effects	148 (43.0)	115 (40.5)					169 (49.0)	142 (49.8)				
Minimal/mild	114 (33.1)	127 (44.7)					104 (30.1)	108 (37.9)				
Moderate/marked	71 (20.6)	29 (10.2)					61 (17.7)	24 (8.4)				
Severe/intolerable	11 (3.2)	13 (4.6)					11 (3.2)	11 (3.9)				
Last FIBSER burden rating			1.171	.3565	1.225	.2763			1.335	.1021	1.349	.1217
No impairment	186 (54.1)	158 (55.6)					198 (57.4)	176 (61.8)				
Minimal/mild	113 (32.8)	101 (35.6)					97 (28.1)	86 (30.2)				
Moderate/marked	35 (10.2)	18 (6.3)					41 (11.9)	18 (6.3)				
Severe/intolerable	10 (2.9)	7 (2.5)					9 (2.6)	5 (1.8)				
At least 1 SAE[c]	19 (5.2)	8 (2.7)	…	…	…	…	30 (8.2)	16 (5.4)	1.489	.2663	1.936	.1112
At least 1 psychiatric SAE[c]	6 (1.6)	1 (0.3)	…	…	…	…	10 (2.7)	5 (1.7)	…	…	…	…
Remission[d]	132 (35.9)	124 (42.0)	0.778	.1500	0.956	.8130	151 (41.0)	147 (49.8)	0.706	.0416	0.837	.3448
Response[e]	178 (49.2)	156 (55.9)	0.799	.1886	0.949	.7790	191 (53.2)	183 (65.6)	0.644	**.0119**	0.736	.1075
Last WSAS score[f]			1.906	**<.0001**	1.439	.0313			1.839	**.0001**	1.466	**.0231**
0	47 (13.7)	59 (20.8)					61 (17.7)	78 (27.5)				
1–10	84 (24.4)	88 (31.1)					89 (25.9)	81 (28.5)				
11–20	73 (21.2)	68 (24.0)					66 (19.2)	68 (23.9)				
21–30	77 (22.4)	43 (15.2)					64 (18.6)	32 (11.3)				
31–40	63 (18.3)	25 (8.8)					64 (18.6)	25 (8.8)				
	Mean ± SD	Mean ± SD					Mean ± SD	Mean ± SD				
Last SAFTEE-SI score, no. of worsenings	5.4 ± 5.3	4.8 ± 4.7	0.109	.1898	0.054	.5429	5.4 ± 5.8	4.4 ± 4.5	0.205	.0268	0.154	.1184
Last QIDS-SR_{16} score	8.8 ± 5.6	7.3 ± 5.0	1.351	**.0032**	0.649	.1615	8.3 ± 5.9	6.7 ± 5.0	1.186	**.0231**	1.111	.1771
Percent QIDS-SR_{16} score change	−43.0 ± 34.2	−50.0 ± 33.7	6.829	**.0190**	3.308	.2815	−46.0 ± 36.7	−55.0 ± 31.9	8.168	**.0062**	5.873	.0636
IDS-C_{30} anxiety score	2.8 ± 2.1	2.3 ± 2.1	0.197	**.0078**	0.171	**.0248**	2.7 ± 2.2	2.2 ± 2.0	0.216	**.0067**	0.186	.0257
Last QOLI score	−0.13 ± 2.40	0.53 ± 2.18	−0.621	**.0021**	−0.253	.1725	0.20 ± 2.40	0.79 ± 2.33	−0.557	**.0068**	−0.219	.2458

[a]Adjusted for treatment, gender, race, education, baseline SCQ, and QOLI.
[b]Bolded *P* values reflect statistical significance at $P < .025$.
[c]Models that were inestimable are represented by ellipses (…).
[d]At least 1 of the last 2 consecutive QIDS-SR_{16} scores < 6, with the other < 8.
[e]50% or greater reduction in QIDS-SR_{16} score from baseline.
[f]An extremely non-normal distribution required binning.
Abbreviations: FIBSER = Frequency, Intensity, and Burden of Side Effects Ratings; IDS-C_{30} = 30-item Inventory of Depressive Symptomatology–Clinician-Rated; QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated; QOLI = Quality of Life Inventory; SAE = serious adverse event; SAFTEE-SI = Systematic Assessment for Treatment-Emergent Events–Systematic Inquiry; SCQ = Self-Administered Comorbidity Questionnaire; WSAS = Work and Social Adjustment Scale.

trial suggest that, when treated at high enough doses and over a sufficient period of time, the majority of patients with chronic depression are no less likely to reach remission than those with nonchronic depression. These patients show a distinct pattern of social disadvantage (eg, comorbid medical and psychiatric conditions, low education and employment, and poor quality of life), which underscores the notion that a number of interrelated factors are likely to play a role in the persistence of MDD. Each of these factors, independently and in combination, may have an impact on duration of illness and treatment response, so it may be particularly important to attend to the types of problems associated with chronic depression when managing these patients in clinical practice. Support for the efficacy of such approaches comes from recent studies showing that combining antidepressant medications with cognitive-behavioral therapy that is specifically tailored to chronic depression results in better acute and continuation treatment outcomes for a substantial number of patients with chronic MDD.[13,29–31]

Limitations

Broad inclusion criteria were used to increase the generalizability of results to the population of patients typically treated in primary and psychiatric clinics throughout the United States. However, because this study was smaller than some other investigations of chronic depression (eg, the STAR*D trial and the Research Evaluating the Value of Augmenting Medications with Psychotherapy [REVAMP] trial) and included only patients with the most persistent forms of MDD (chronic and/or recurrent), we may not have been able to detect some meaningful differences between the 2 groups. For example, the effect of chronicity on remission was relatively small (about a 20% reduction in the odds in the chronic group, with relatively low odds of remission to start

Table 5. Selected Outcome Measures by Chronic Depression, Treatment, and Study Phase

Measure	Chronic Depression, Yes			Chronic Depression, No			*P* Value[a]
	Bupropion SR + Escitalopram (n = 121)	Escitalopram + Placebo (n = 121)	Venlafaxine XR + Mirtazapine (n = 126)	Bupropion SR + Escitalopram (n = 100)	Escitalopram + Placebo (n = 102)	Venlafaxine XR + Mirtazapine (n = 93)	
Acute phase							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Early termination	39 (32.2)	38 (31.4)	34 (27.0)	31 (31.0)	16 (15.7)	22 (23.7)	.1348
Last FIBSER burden rating							.8771
No impairment	64 (56.1)	61 (55.5)	61 (50.8)	54 (56.8)	56 (56.0)	48 (53.9)	
Minimal/mild	37 (32.5)	37 (33.6)	39 (32.5)	32 (33.7)	36 (36.0)	33 (37.1)	
Moderate/marked	9 (7.9)	9 (8.2)	17 (14.2)	5 (5.3)	7 (7.0)	6 (6.7)	
Severe/intolerable	4 (3.5)	3 (2.7)	3 (2.5)	4 (4.2)	1 (1.0)	2 (2.2)	
Remission[b]	37 (30.8)	39 (32.2)	41 (32.5)	45 (45.5)	42 (41.2)	38 (41.8)	.7949
Response[c]	56 (47.1)	59 (49.2)	63 (51.2)	55 (57.3)	54 (55.7)	47 (54.7)	.7853
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Last QIDS-SR_{16} score	8.8 ± 5.4	8.6 ± 5.6	8.9 ± 5.9	7.2 ± 5.0	7.0 ± 4.6	7.7 ± 5.4	.8855
Percent QIDS-SR_{16} score change	−41.2 ± 33.4	−44.4 ± 33.0	−42.1 ± 36.4	−48.9 ± 35.9	−50.6 ± 32.5	−52.0 ± 32.7	.8578
Continuation phase							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Early termination	49 (40.5)	47 (38.8)	51 (40.5)	35 (35.0)	30 (29.4)	30 (32.3)	.8929
Last FIBSER burden rating							.9271
No impairment	66 (57.9)	69 (62.2)	63 (52.5)	62 (64.6)	66 (66.0)	48 (53.9)	
Minimal/mild	33 (28.9)	30 (27.0)	34 (28.3)	27 (28.1)	29 (29.0)	30 (33.7)	
Moderate/marked	12 (10.5)	9 (8.1)	20 (16.7)	3 (3.1)	4 (4.0)	11 (12.4)	
Severe/intolerable	3 (2.6)	3 (2.7)	3 (2.5)	4 (4.2)	1 (1.0)	NA	
Remission[b]	46 (38.7)	50 (41.7)	47 (37.6)	55 (55.6)	51 (50.0)	43 (47.3)	.6323
Response[c]	62 (52.5)	67 (56.3)	62 (50.8)	63 (65.6)	62 (63.9)	58 (67.4)	.6437
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Last QIDS-SR_{16} score	8.2 ± 5.7	8.0 ± 5.7	8.6 ± 6.1	6.2 ± 4.7	6.4 ± 4.7	7.4 ± 5.5	.7112
Percent QIDS-SR_{16} score change	−45.0 ± 38.1	−48.4 ± 34.9	−44.1 ± 37.3	−56.0 ± 33.5	−55.5 ± 29.2	−53.9 ± 33.3	.8440

[a]Probability associated with the "treatment × chronic depression" interaction term.
[b]At least 1 of the last 2 consecutive QIDS-SR_{16} scores < 6, with the other < 8.
[c]50% or greater reduction in QIDS-SR_{16} score from baseline.
Abbreviations: FIBSER = Frequency, Intensity, and Burden of Side Effects Ratings; NA = not applicable; QIDS-SR_{16} = 16-Item Quick Inventory of Depressive Symptomatology–Self-Rated; SR = sustained release; XR = extended release.

with in the nonchronic group), suggesting that we did not have enough power to detect small effect size differences.

The CO-MED study was intended to be conducted in a real-world setting, and, thus, we relied on clinician interviews and rating scales to assess *DSM-IV* MDD. Although this approach increases the generalizability of findings to routine clinical care settings, a potential drawback is that the duration of index episode was necessarily based on participant self-report. This method closely matches the procedures used in routine care, but self-report is variable, and it is possible that participants were not accurate reporters of current episode onset. This limitation notwithstanding, the median duration of the index episode was 49.5 months (range, 24.0–720.0 months) in the chronic group, suggesting that these participants had been depressed for significantly longer than the 24 months required by *DSM-IV*. It has also been noted that some patients with recurrent depression may go on to develop a more chronic course of illness.

CONCLUSION

Patients with chronic MDD are no less likely to reach remission with antidepressant treatment, although they may experience fewer improvements in anxiety and work functioning. After adjustment for pretreatment differences, patients with chronic MDD do not appear to have worse outcomes than those with nonchronic MDD during acute or continuation treatment with escitalopram alone, escitalopram + bupropion SR, or venlafaxine XR + mirtazapine. When taken together, chronicity, socioeconomic disadvantage, and comorbid medical and psychiatric illness do appear to be associated with poorer treatment outcomes. Patients who present with these features may be in need of closer monitoring during the acute phase of treatment to prevent early dropout.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), escitalopram (Lexapro and others), mirtazapine (Remeron and others), venlafaxine (Effexor and others).

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has a patent application for a combination of azapirones and bupropion in major depressive disorder; and has received copyright royalties for the MGH Cognitive and Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs and Symptoms scale, and SAFER Criteria Interview diagnostic instruments. **Dr Nierenberg** has consulted for Appliance Computing (Mindsite), Brandeis University, and, through the MGH Clinical Trials Network and Institute, AstraZeneca, BrainCells, Dainippon Sumitomo/Sepracor, Johnson & Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda-Lundbeck; has received grant/research support through MGH from NIMH, PamLabs, Pfizer, and Shire; has received honoraria from Belvior Publishing, Hillside Hospital, American Professional Society of ADHD and Related Disorders, American Society for Clinical Psychopharmacology, Columbia University, Imedex, International Society for Bipolar Disorders, MJ Consulting, New York State, MBL Publishing, Physicians Postgraduate Press, SciMed, State University of New York at Buffalo, University of Wisconsin, and the University of Pisa; 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Supplementary material: Supplementary eFigure 1 is available at PSYCHIATRIST.COM.

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003; 289(23):3095–3105.
2. Gilmer WS, Trivedi MH, Rush AJ, et al. Factors associated with chronic depressive episodes: a preliminary report from the STAR-D project. *Acta Psychiatr Scand*. 2005;112(6):425–433.
3. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry*. 1992;49(10):809–816.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
5. Angst J, Gamma A, Rössler W, et al. Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. *J Affect Disord*. 2009;115(1–2):112–121.
6. Blanco C, Okuda M, Markowitz JC, et al. The epidemiology of chronic major depressive disorder and dysthymic disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2010;71(12):1645–1656.
7. Gilmer WS, Gollan JK, Wisniewski SR, et al. Does the duration of index episode affect the treatment outcome of major depressive disorder? a STAR*D report. *J Clin Psychiatry*. 2008;69(8):1246–1256.
8. Hölzel L, Härter M, Reese C, et al. Risk factors for chronic depression: a systematic review [published online ahead of print May 21, 2010]. *J Affect Disord*. 2011;129(1–3):1–13.
9. Klein DN, Shankman SA, Lewinsohn PM, et al. Family study of chronic

depression in a community sample of young adults. *Am J Psychiatry*. 2004;161(4):646–653.
10. Satyanarayana S, Enns MW, Cox BJ, et al. Prevalence and correlates of chronic depression in the Canadian Community Health Survey: Mental Health and Well-Being. *Can J Psychiatry*. 2009;54(6):389–398.
11. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
12. Kocsis JH, Gelenberg AJ, Rothbaum BO, et al; REVAMP Investigators. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. *Arch Gen Psychiatry*. 2009;66(11):1178–1188.
13. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. 2000;342(20):1462–1470.
14. Blier P, Ward HE, Tremblay P, et al. Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. *Am J Psychiatry*. 2010;167(3):281–288.
15. Rush AJ, Trivedi MH, Stewart JW, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry*. 2011; 168(7):689–701.
16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
17. Zimmerman M, Mattia JI. A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. *Arch Gen Psychiatry*. 2001;58(8):787–794.
18. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. *Compr Psychiatry*. 2001;42(3):175–189.
19. Sangha O, Stucki G, Liang MH, et al. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum*. 2003;49(2):156–163.
20. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
21. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med*. 2004;34(1):73–82.
22. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008;165(3):342–351.
23. Trivedi MH, Wisniewski SR, Morris DW, et al. Concise Health Risk Tracking (CHRT) scale: a brief self-report and clinician-rating of suicidal risk. *J Clin Psychiatry*. 2011;72(6):765–774.
24. Altman EG, Hedeker D, Peterson JL, et al. The Altman Self-Rating Mania Scale. *Biol Psychiatry*. 1997;42(10):948–955.
25. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry*. 2002;180(5):461–464.
26. Frisch MB, Clark MP, Rouse SV, et al. Predictive and treatment validity of life satisfaction and the Quality of Life Inventory. *Assessment*. 2005; 12(1):66–78.
27. Wisniewski SR, Rush AJ, Balasubramani GK, et al; for the STAR*D Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. *J Psychiatr Pract*. 2006;12(2):71–79.
28. Levine J, Schooler NR. General versus specific inquiry with SAFTEE [letter]. *J Clin Psychopharmacol*. 1992;12(6):448.
29. Arnow BA, Constantino MJ. Effectiveness of psychotherapy and combination treatment for chronic depression. *J Clin Psychol*. 2003;59(8):893–905.
30. Kocsis JH, Rush AJ, Markowitz JC, et al. Continuation treatment of chronic depression: a comparison of nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination. *Psychopharmacol Bull*. 2003;37(4):73–87.
31. Stulz N, Thase ME, Klein DN, et al. Differential effects of treatments for chronic depression: a latent growth model reanalysis. *J Consult Clin Psychol*. 2010;78(3):409–419.

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Supplementary Material

Article Title: The Impact of Chronic Depression on Acute and Long-Term Outcomes in a Randomized Trial Comparing Selective Serotonin Reuptake Inhibitor Monotherapy Versus Each of 2 Different Antidepressant Medication Combinations

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List of Supplementary Material for the article

1. eFigure 1 Flow of Participants Through the Study

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eFigure 1. Flow of Participants Through the Study