Effects of Race and Ethnicity on Depression Treatment Outcomes: The CO-MED Trial

Ira M. Lesser, M.D.
Sidney Zisook, M.D.
Bradley N. Gaynes, M.D., M.P.H.
Stephen R. Wisniewski, Ph.D.
James F. Luther, M.A.
Maurizio Fava, M.D.
Ahsan Khan, M.D.
Patrick McGrath, M.D.
Diane Warden, Ph.D.
A. John Rush, M.D.
Madhukar Trivedi, M.D.

Objective: **The investigators examined whether outcomes differ by race-ethnicity for patients with major depressive disorder in acute- (12 weeks) and continuation-phase (weeks 12–28) treatment with one of two antidepressant combinations or one selective serotonin reuptake inhibitor.** ***Methods:*** **This single-blind, seven-month prospective, randomized trial enrolled 352 non-Hispanic white (59%), 169 black (28%), and 79 white Hispanic (13%) participants from six primary and nine psychiatric care U.S. sites. Patients had nonpsychotic chronic or recurrent major depressive disorder (or both) of at least moderate severity. Escitalopram plus placebo, bupropion sustained-release plus escitalopram, or venlafaxine extended-release plus mirtazapine were delivered according to measurement-based care. The primary outcome was remission (last two consecutive 16-item Quick Inventory of Depressive Symptomatology–Self-Report ratings <8 and <6); secondary outcomes included side effects, adverse events, quality of life, function, and attrition.** ***Results:*** **Black participants had greater baseline psychiatric and medical comorbidity. Baseline depression severity did not significantly differ between groups. In both phases more blacks than those in other groups exited the trial early. There were only minor differences in side effects, no significant differences in remission rates, and no significant differences between groups in other outcomes for each treatment.** ***Conclusions:*** **Despite differences in sociodemographic characteristics and comorbidities, when measurement-based care was used, members of different minority groups had similar outcomes when treated with one antidepressant or a combination of two antidepressants. Black participants had the highest attrition rate, an important issue to address in clinical care. (*Psychiatric Services* 62:1167–1179, 2011)**

Dr. Lesser is affiliated with the Department of Psychiatry and the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Box 8, 1000 West Carson St., M/C 176847, Torrance, CA 90509 (e-mail: ilesser@labiomed.org). Dr. Zisook is with the Department of Psychiatry, University of California, San Diego, in La Jolla. Dr. Gaynes is with the Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill. Dr. Wisniewski and Mr. Luther are with the Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania. Dr. Fava is with the Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston. Dr. Khan is with the Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine, Wichita. Dr. McGrath is with the Depression Evaluation Service, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York City. Dr. Warden is with the Department of Psychiatry and Dr. Trivedi is with the Departments of Psychiatry and Clinical Sciences, both at the University of Texas Southwestern Medical Center, Dallas. Dr. Rush is with the Office of Clinical Sciences, Duke–National University of Singapore.

Despite a similar lifetime prevalence of major depressive disorder across racial and ethnic groups in the United States, patients from minority groups typically have poorer access to mental health care and are less likely than whites to receive either pharmacological or nonpharmacological treatment (1–7). Many, but not all, studies of depression treatment in naturalistic settings have shown poorer outcomes for patients of minority backgrounds compared with whites (3,4,6,8,9). On the other hand, treatment outcomes are similar between minority and white groups in clinical trials using protocol-driven and measurement-based care, particularly after adjustment for baseline sociodemographic and clinical variables (10–15).

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, blacks (particularly young men) had the highest attrition rates and the least robust response to initial treatment with citalopram; however, most outcome differences were not significant after adjustment for baseline sociodemographic and clinical variables (14,16). Approximately 30% of participants achieved remission with citalopram; an additional 35% achieved remission after adding another antidepressant or buspirone, a finding suggesting that two antidepressants might be more effective than one (13), which has been supported by recent reports (17–19). These studies raise the question of whether initiating treatment with two antidepressants would lead

to a quicker or more robust outcome for patients with depression and whether outcomes would be affected by race or ethnicity.

The Combining Medications to Enhance Depression Outcomes (CO-MED; www.co-med.org) study used a patient cohort different from the cohort for STAR*D to compare outcomes from use of two different antidepressant combinations with outcomes from use of a single antidepressant in a 12-week acute phase and subsequent continuation phase (20). This article reports the findings from a secondary analysis of the data, which examined associations between race-ethnicity and outcome in a manner similar to that done in STAR*D.

Methods

Study overview

CO-MED was a seven-month single-blind, randomized trial that compared the efficacy of two antidepressant medication combinations with the selective serotonin reuptake inhibitor (SSRI) escitalopram plus a placebo (1:1:1 ratio). Outpatients with nonpsychotic major depressive disorder were recruited from six primary and nine psychiatric care sites. Sites were selected to ensure adequate patient flow and minority representation and to represent primary and psychiatric care. A sample size of 660 outpatients was chosen to allow detection of roughly a 15% difference in remission rate between each antidepressant combination and escitalopram plus placebo (with an expected remission rate of 35%). This difference was viewed as sufficiently large to affect practice, because it approximates the benefit of a single antidepressant over placebo in successful antidepressant registration trials.

Recruitment

Treatment-seeking patients were enrolled from March 2008 through September 2009. Potential participants were screened with each site's standard procedure (variable across sites), which could include using questions from the Patient Health Questionnaire (21,22) or physician and nurse queries during routine clinical visits. Patients meeting screening criteria were identified to their study clinicians and met with the site's clinical research coordinator, who explained the protocol and obtained written informed consent before proceeding.

Participants

Broad inclusion and minimal exclusion criteria were used to ensure a reasonably representative sample. Outpatient enrollees, 18–75 years of age, met *DSM-IV-TR* (23) criteria for either recurrent (one or more prior major depressive episodes) or chronic major depressive disorder (current major depressive episode for two or more years) based on a clinical interview and confirmed with a *DSM-IV* major depressive disorder symptom checklist. Eligible participants had to be in the index episode for a minimum of two months to reduce the likelihood of placebo response and had to have a score ≥16 on the 17-Item Hamilton Rating Scale for Depression (HRSD-17) (24). A list of exclusion criteria is available at www.co-med.org.

The study protocol was developed according to the principles of the Declaration of Helsinki. The protocol and all consent and study procedures were approved by the institutional review boards at the National Coordinating Center (University of Texas Southwestern Medical Center), the University of Pittsburgh Data Coordinating Center, each participating regional center, and all clinical sites.

Baseline data

Sociodemographic and illness features were gathered at baseline. The anxiety subscales of the baseline HRSD-17 and the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C-30) (25–29) established the presence of anxious features. The self-report Psychiatric Diagnostic Screening Questionnaire (PDSQ) (30,31) established the presence of current axis I disorders with 90% specificity (32). The Concise Health Risk Tracking–self-report scale (33) established degree of suicidal ideation, the Altman Self-Rating Mania Scale (ASRMS) (34) established the presence of manic symptoms, and the Cognitive and Physical Functioning Questionnaire (35) measured functioning. The Self-Administered Comorbidity Questionnaire (SCQ) (36) established the presence, severity, and functional impact of a range of general medical comorbidities.

Data on race and ethnicity were collected by self-report. Participants could select one or more of the following choices: Asian American, black, Native American, Pacific Islander, white, or other; in addition they could identify whether they were Hispanic.

Antidepressant treatment

We chose a 12-week study period (acute phase) so that maximal doses (if needed) could be delivered for at least four weeks, most participants whose depression could remit would do so without an excessively long trial, and attrition might be minimized. Treatment visits were planned at baseline and weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28, with weeks 12–28 designated as the continuation phase of the study. Measurement-based care provided rigorous dosing at each visit (37–39); dosage adjustments were based on the 16-item Quick Inventory of Depressive Symptomatology–Clinician-rated (QIDS-C-16) (26,27,40), which was extracted from the IDS-C-30 (27), and the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) (41) and was guided by the CO-MED Operations Manual (available at www.co-med.org).

Treatment was randomly assigned and stratified by clinical site with a Web-based randomization system (42). Random block sizes of three and six minimized the probability of identifying the next treatment assignment. Dosing schedules were based on prior reports (43–45), and doses were increased only in the context of acceptable side effects. Dose changes were made by the treating physician in collaboration with the clinical research coordinator after review of the data collected at the visit. Participants could exit the study if unacceptable or intolerable side effects occurred that could not be resolved with dose reduction or medication treatment of side effects.

The dosing protocols are described below.

Table 1

Baseline sociodemographic and clinical characteristics of 600 patients with depression, by race-ethnicity

Characteristic	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Test statistic[a]	df	p	Pairwise comparison		
	N	%	N	%	N	%				White and black	White and Hispanic	Black and Hispanic
Age							χ^2=2.71	4	.61			
18–29	71	20	27	16	18	23						
30–54	203	58	108	64	45	57						
55–75	78	22	34	20	16	20						
Sex							χ^2=5.62	2	.06			
Male	127	36	47	28	20	25						
Female	225	64	122	72	59	75						
Employed	177	50	70	41	53	67	χ^2=14.20	2	<.01	.06	<.01[b]	<.01[b]
Age at first depressive episode <18	169	48	64	38	32	41	χ^2=4.92	2	.08			
At least 1 prior depressive episode	287	86	124	74	58	74	χ^2=4.89	2	.09			
Ever attempted suicide	29	9	19	11	6	8	χ^2=1.27	2	.53			
Lifetime severity of suicidality							FET[c]<.01		.37			
None	93	28	53	32	31	40						
Thoughts of dying	94	28	51	31	20	26						
Suicidal thoughts	55	16	23	14	10	13						
Specific method	39	12	11	7	5	7						
Plan or gesture	22	7	5	3	3	4						
Preparation	6	2	5	3	2	3						
Attempt	29	9	19	11	6	8						
Neglected before age 18	131	37	62	37	29	37	χ^2=.02	2	.99			
Abused before age 18	167	48	76	45	34	43	χ^2=.74	2	.69			
Emotionally	149	43	60	36	28	35	χ^2=2.95	2	.23			
Physically	71	20	31	18	17	22	χ^2=.41	2	.81			
Sexually	67	19	44	26	19	24	χ^2=3.47	2	.18			
Age (M±SD)	43.0±13.3		43.5±12.0		41.5±12.5		F=.64	2, 597	.53			
Education (M±SD years)	14.2±3.0		13.2±2.5		12.1±2.9		F=20.3	2, 577	<.01	<.01[b]	<.01[b]	<.01[b]
Monthly household income (M±SD $)	3,159±6,606		1,751±1,587		2,898±5,928		χ^2=6.03	2	<.05	.02	.99	.06
Body mass index (M±SD)[d]	30.7±8.8		31.8±8.9		30.8±8.0		χ^2=2.49	2	.29			
Age at first depressive episode (M±SD)	22.8±13.7		26.5±14.1		24.8±14.3		χ^2=8.54	2	.01	.01[b]	.22	.35
Years since first depressive episode (M±SD)	20.2±14.0		16.9±12.4		16.9±13.6		χ^2=8.40	2	.01	.01[b]	.04	.78
N prior depressive episodes (M±SD)	11.5±23.8		6.6±14.7		4.7±7.5		χ^2=6.63	2	.04	<.05	.04	.60
N suicide attempts (M±SD)	.26±1.65		.23±.78		.17±.68		χ^2=1.32	2	.52			

[a] Chi square statistic for continuous measures indicates Kruskal-Wallis test.
[b] Significant after Bonferroni correction (p<.0166)
[c] Fisher's exact test
[d] Body mass indices >30 indicate obesity.

Ecitalopram plus placebo. Escitalopram began at one tablet (10 mg per day) and increased to two tablets (20 mg per day) at week 4 (if QIDS-C-16 score was >5). Pill placebo (one pill) was started at week 2, with the option to increase to two pills at week 4 if the QIDS-C-16 score was >5 and side effects were tolerable.

Bupropion–sustained release (SR) plus escitalopram. Bupropion-SR (150 mg per day) was started at baseline and increased to 300 mg per day at week 1. Escitalopram began at 10 mg per day at week 2. At week 4, bupropion-SR could be raised to 400 mg per day and escitalopram could be increased to 20 mg per day if the QIDS-C-16 score was >5 and side effects were tolerable. At week 6 and beyond, if not already done, the bupropion-SR dose was increased to a maximum of 400 mg per day (200 mg per day b.i.d.) and escitalopram to 20 mg per day if the QIDS-C-16 score was >5 and side effects were tolerable to the patient.

Venlafaxine–extended release (XR) plus mirtazapine. Venlafaxine-XR was begun at 37.5 mg per day for three days and then raised to 75 mg per day. At week 1, venlafaxine-XR was raised to 150 mg per day. At week 2 if the QIDS-C-16 score was >5, mirtazapine was added (15 mg per day). At week 4, if the QIDS-C-16 score was >5, venlafaxine-XR could be raised to 225 mg per day and mirtaza-

Table 2

Baseline axis I, axis III, and symptomatology characteristics of 600 patients with depression, by race or ethnicity

Characteristic	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Test statistic[b]	df	p	Pairwise comparison		
	N	%[a]	N	%[a]	N	%[a]				White and black	White and Hispanic	Black and Hispanic
Clinical setting							χ^2=41.90	2	<.01	.74	<.01[c]	<.01[c]
Primary	172	49	80	47	69	87						
Specialty	180	51	89	53	10	13						
Chronic depression[d]	176	50	103	61	47	60	χ^2=7.06	2	.03	.01[c]	.10	.87
Chronic or recurrent depression							χ^2=8.20	4	.08			
Chronic only[d]	65	19	44	26	20	26						
Recurrent only	176	50	65	39	31	40						
Both	111	32	59	35	27	35						
QIDS-SR-16 score level[e]							χ^2=8.26	6	.22			
0–10, none to mild	42	12	21	13	12	15						
11–15, moderate	116	34	68	41	27	35						
16–20, severe	150	44	54	33	33	42						
21–27, very severe	33	10	23	14	6	8						
Lethargic depression[f]	242	69	112	66	59	75	χ^2=1.78	2	.41			
Anxious features	262	74	129	76	54	68	χ^2=1.82	2	.4			
Atypical features	62	18	24	14	10	13	χ^2=1.75	2	.42			
Melancholic features	64	20	34	23	18	24	χ^2=.96	2	.62			
Sleep disturbance[g]	301	86	160	95	67	85	χ^2=9.96	2	<.01	<.01[c]	.87	<.01[c]
Suicidal thoughts or plans[h]	62	18	27	16	9	11	χ^2=1.85	2	.39			
Axis I comorbidity[i]												
Agoraphobia	24	7	32	19	7	9	χ^2=18.10	2	<.01	<.01[c]	.52	.04
Alcohol abuse or dependence	34	10	21	12	5	6	χ^2=2.32	2	.31			
Bulimia	39	11	24	14	9	11	χ^2=1.09	2	.58			
Drug abuse or dependence	20	6	11	7	2	3	χ^2=1.69	2	.43			
Generalized anxiety	64	18	47	28	9	11	χ^2=10.80	2	<.01	.01[c]	.15	<.01[c]
Hypochondriasis	9	3	14	8	5	6	χ^2=8.98	2	.01	<.01[c]	.15	.59
Obsessive-compulsive	26	7	38	23	5	6	χ^2=27.90	2	<.01	<.01[c]	.74	<.01[c]
Panic	19	5	34	20	8	10	χ^2=27.10	2	<.01	<.01[c]	.12	.05
Posttraumatic stress	36	10	35	21	3	4	χ^2=17.70	2	<.01	<.01[c]	.07	<.01[c]
Social anxiety	80	23	57	34	19	24	χ^2=7.36	2	.02	<.01[c]	.80	.12
Somatoform	7	2	7	4	4	5	χ^2=3.15	2	.21			
Substance abuse or dependence	46	13	26	15	6	8	χ^2=2.89	2	.23			
N axis I comorbidities							χ^2=47.50	8	<.01	<.01[c]	.02	<.01[c]
0	162	46	56	33	49	62						
1	99	28	36	21	10	13						
2	52	15	24	14	8	10						
3	16	5	19	11	5	6						
≥4	22	6	34	20	7	9						
Axis III comorbidity[j]												
Back pain	61	17	32	19	8	10	χ^2=3.18	2	.2			
Diabetes	32	9	25	15	11	14	χ^2=4.30	2	.12			
Heart problems	24	7	11	7	4	5	χ^2=.33	2	.85			
Thyroid problems	25	7	6	4	3	4	χ^2=3.29	2	.19			
N axis III comorbidities							χ^2=17.10	6	<.01	<.01[c]	.34	.02
0	187	53	62	37	42	53						
1	79	23	48	29	20	25						
2	45	13	29	17	13	17						
≥3	40	11	29	17	4	5						
N prior antidepressants (M±SD)	1.9±1.8		1.3±1.7		.9±1.2		χ^2=39.80	2	<.01	<.01[c]	<.01[c]	.23
N concomitant medications (M±SD)	3.0±2.9		3.3±3.1		2.4±1.8		χ^2=3.71	2	.16			
Current episode duration (M±SD months)	57.3±103		72.3±116		56.1±96.5		χ^2=4.25	2	.12			
HRSD-17 score (M±SD)[k]	23.5±4.9		24.7±4.9		23.6±4.4		F=3.74	2, 595	.02	<.01[c]	.85	.09
IDS-C-30 score (M±SD)[l]	37.7±9.0		39.1±9.6		38.0±8.8		F=1.38	2, 597	.25			

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Table 2

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Characteristic	Whites (N=352) N	%[a]	Blacks (N=169) N	%[a]	Hispanics (N=79) N	%[a]	Test statistic[b]	df	p	Pairwise comparison: White and black	White and Hispanic	Black and Hispanic
IDS-C-30[l] anxiety subscale score (M±SD)[m]	4.9±2.4		5.2±2.2		4.8±2.0		F=.94	2, 597	.39			
QIDS-C-16 score (M±SD)[n]	15.8±3.4		16.3±3.6		15.5±3.3		F=1.81	2, 597	.16			
QIDS-SR-16 (M±SD score)[e]	15.6±4.2		15.5±4.6		15.1±4.2		F=.39	2, 582	.68			
ASRMS score (M±SD)[o]	1.2±1.6		2.5±3.0		1.1±2.1		χ^2=33.60	2	<.01	<.01[c]	.09	<.01[c]
CPFQ score (M±SD)[p]	28.0±5.5		26.8±6.5		28.0±6.0		F=2.75	2, 597	.06			
QOLI score (M±SD)[q]	–1.4±1.8		–1.0±2.0		–.4±2.1		F=10.60	2, 593	<.01	<.01[c]	<.01[c]	.04
WSAS score (M±SD)[r]	26.6±8.8		27.1±9.5		27.9±8.1		χ^2=1.66	2	.44			
SCQ score (M±SD)[s]	3.2±3.4		4.3±4.0		2.6±2.5		χ^2=12.90	2	<.01	<.01[c]	.38	<.01[c]
Treated SCQ health problems score (M±SD)[s]	.91±1.28		1.27±1.37		.73±.92		χ^2=13.90	2	<.01	<.01[c]	.68	<.01[c]

[a] Percentages are based on available data for each characteristic.
[b] Chi square statistic for continuous measures was by Kruskal-Wallis test.
[c] Significant after Bonferroni correction (p<.0166)
[d] Current episode duration ≥2 years
[e] 16-item Quick Inventory of Depressive Symptomatology–Self-Rated. Possible scores range from 0 to 27, with higher scores indicating greater depressive symptom severity.
[f] A score of 2 or 3 on any two of the following 30-item Inventory of Depressive Symptomatology (IDS-C-30) items: general interest, energy level, capacity for pleasure or enjoyment, interest in sex, or leaden paralysis or physical energy
[g] A score of 2 or 3 on any one of the following items from the 30-item clinician-rated Inventory of Depressive Symptomatology: falling asleep, sleep during the night, or waking up too early.
[h] A score of 3, 4, or 5 on any one of the following self-rated concise health risk tracking items: thinks of killing self, thinks of how to kill self, or has a plan to kill self
[i] From the Psychiatric Diagnostic Screening Questionnaire
[j] From the Self-Administered Comorbidity Questionnaire
[k] 17-item Hamilton Rating Scale for Depression. Possible scores range from 0 to 52, with higher scores indicating greater depressive symptom severity.
[l] 30-item Inventory of Depressive Symptomatology–Clinician-Rated. Possible scores range from 0 to 84, with higher scores indicating greater depressive symptom severity.
[m] Sum of the following items: mood (anxious), somatic complaints, sympathetic arousal, panic or phobic symptoms, and gastrointestinal problems. Possible scores range from 0 to 18, with a score ≥7 indicating presence of anxiety.
[n] 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated. Possible scores range from 0 to 27, with higher scores indicating greater depressive symptom severity.
[o] Altman Self-Rating Mania Scale. Possible scores range from 0 to 20, with a cutoff score of ≥6 indicating a high probability of a manic or hypomanic condition.
[p] Cognitive and Physical Functioning Questionnaire. Possible scores range from 7 to 42, with higher scores indicating worse cognitive and physical functioning.
[q] Quality of Life Inventory. Possible scores range from –6 to 6, with higher scores indicating higher overall quality of life.
[r] Work and Social Adjustment Scale. Possible scores range from 0 to 40, with higher scores indicating greater impairment.
[s] Self-Administered Comorbidity Questionnaire. Possible scores range from 0 to 45, with higher scores indicating greater comorbidity.

pine could be increased to 30 mg per day. At week 6, if the QIDS-C-16 score was >5, mirtazapine could be raised to 45 mg per day (maximum dose). At week 8, if the QIDS-C-16 score was >5, venlafaxine-XR could be raised to 300 mg per day (maximum dose).

Concurrent treatments. Only protocol antidepressant medications were allowed. Other treatments with possible antidepressant effects were proscribed, including depression-targeted, empirically validated psychotherapies for depression. Other therapies (such as supportive therapy and couples therapy) were allowed, as were medications for general medical conditions. Given the bupropion-SR inhibition of the 2D6 isoenzyme, clinicians were alerted to recognize nonprotocol medications (such as type 1C antiarrythmics and beta blockers) for which serum levels or dose adjustments might be needed. Medications to treat antidepressant side effects were allowed to mimic practice and enhance retention.

Research outcomes

Assessments were collected at baseline and at all subsequent visits. The primary outcome, symptom remission, was based on the self-report version of the 16-item QIDS (QIDS-SR-16) (26,27,40). Remission was determined on the basis of the last two consecutive measurements obtained during the acute trial to ensure that a single "good week" was not falsely signaling remission. At least one of these ratings had to be <8, and the other had to be <6. If participants exited before 12 weeks, their last two consecutive QIDS-SR-16 scores were used to assess remission. Those exiting before having two postbaseline measures were considered as not reaching remission.

Participants could exit the study if they had received a maximally tolerat-

Table 3

Acute-phase (12-week) outcomes of 600 patients treated for depression, by race and ethnicity

Outcome	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Unadjusted OR			Adjusted OR[a]		
	N	%[b]	N	%[b]	N	%[b]	Black and white	Hispanic and white	p	Black and white	Hispanic and white	p
Early termination	77	22	71	42	17	22	2.59	.94	<.01	2.49[c]	.75	<.01
FIBSER maximum rating[d]												
Frequency							.79	1.20	.25	.76	1.52	.06
No side effects	55	16	19	12	8	10						
10%–25% of the time	99	29	57	37	29	37						
50%–75% of the time	107	32	53	35	20	26						
90%–100% of the time	78	23	24	16	21	27						
Intensity							.92	1.66	.07	.89	2.28[c]	<.01
No side effects	46	14	23	15	6	8						
Minimal to mild	115	34	45	29	30	39						
Moderate to marked	128	38	63	41	21	27						
Severe to intolerable	50	15	22	14	21	27						
Burden							1.20	1.55	.17	1.05	2.02[c]	.04
No impairment	78	23	28	18	13	17						
Minimal to mild	148	44	65	43	36	46						
Moderate to marked	81	24	47	31	17	22						
Severe to intolerable	32	9	13	9	12	15						
FIBSER last rating[d]												
Frequency							1.08	1.06	.92	1.08	1.43	.45
No side effects	143	42	63	41	32	42						
10%–25% of the time	133	40	55	36	32	42						
50%–75% of the time	45	13	30	20	7	9						
90%–100% of the time	16	5	5	3	5	7						
Intensity							1.00	.96	.99	1.01	1.34	.57
No side effects	139	41	65	43	32	42						
Minimal to mild	135	40	52	34	33	43						
Moderate to marked	50	15	31	20	8	11						
Severe to intolerable	13	4	5	3	3	4						
Burden							1.19	.88	.55	1.07	1.13	.91
No impairment	190	56	80	52	46	61						
Minimal to mild	113	34	52	34	24	32						
Moderate to marked	24	7	17	11	5	7						
Severe to intolerable	10	3	4	3	1	1						
≥1 serious adverse event	6	2	13	8	5	6	4.99	5.63	.02	4.47	3.31	.09
≥1 psychiatric serious adverse event[e]	1	0	4	2	1	1						

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ed dose for at least four weeks by week 8 without receiving a ≥30% reduction from baseline QIDS-C-16. They could enter continuation treatment if they had received an acceptable benefit (QIDS-C-16 score ≤9 by week 12) or if they reached a QIDS-C-16 score of 10–13 with the clinician and participant judging the benefit to be substantial enough to indicate treatment continuation.

Secondary outcomes included attrition; response (QIDS-SR-16 score reduction of ≥50%); anxiety, measured by the anxiety subscale of IDS-C-30 (26–29); function, measured by the Work Productivity and Activity Impairment scale (46) and the Work and Social Adjustment Scale (WSAS) (47); quality of life, measured by the Quality of Life Inventory (QOLI) (48,49); side-effect burden, measured by the FIBSER (41); and specific side effects, measured by the Systematic Assessment of Treatment Emergent Events–Systematic Inquiry (SAFTEE-SI) (50,51).

Statistical analyses

Descriptive statistics, including measures of central tendency and dispersion, were computed for continuous data. Frequency distributions were estimated for categorical data. The appropriate parametric (t test) or nonparametric (chi square and Wilcoxon tests) test was used to ensure a balanced distribution of the sociodemographic, psychiatric, and medical characteristics among the groups.

At weeks 12 and 28, unadjusted and adjusted outcomes among the racial-ethnic groups were compared via regression models. The type of regression models varied by outcome and included linear regression, logistic regression, ordinal logistic regression, and negative binomial regression models. Potential confounders were identified with a stepwise logistic regression model with race-ethnicity as the outcome and all other baseline characteristics as independent vari-

Table 3

Continued from previous page

Outcome	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Unadjusted OR			Adjusted OR[a]		
	N	%[b]	N	%[b]	N	%[b]	Black and white	Hispanic and white	p	Black and white	Hispanic and white	p
Remission[f]	144	41	47	28	40	51	.61	1.62	<.01	.77	1.42	.19
QIDS-SR-16 score[g]												
Last score <6	138	39	42	25	37	47	.54	1.41	<.01	.67	1.34	.10
Score reduction by ≥50%	188	56	68	41	47	60	.55	1.31	<.01	.6	1.06	.06
Last Work and Social Adjustment Scale score[h]							1.58	.97	.04	1.48	1.09	.18
0	55	16	22	15	18	23						
1–10	104	31	33	22	21	27						
11–20	81	24	34	23	9	12						
21–30	57	17	33	22	18	23						
31–40	40	12	29	19	11	14						
SAFTEE score[i]												
Maximum (M±SD)	9.2±6.1		10.0±6.6		9.6±5.5		1.06	1.07	.56	1.00	1.04	.89
Last (M±SD)	4.9±4.8		5.6±5.0		4.7±5.3		.16	–.05	.19	.06	.01	.86
QIDS-SR-16 score[g,j]												
Last (M±SD)	7.9±5.2		9.3±5.3		6.7±5.6		1.55	–1.2	<.01	1.07	–.87	.03[k]
Percentage change (M±SD)	–48.0±33.0		–37.0±34.8		–55.0±34.3		12.00	–6.46	<.01	7.55	–4.82	.04
IDS-C-30 anxiety subscale score (M±SD)[l]	2.5±2.0		3.0±2.2		2.3±2.2		.19	–.04	.06	.05	–.03	.78
Last QOLI score (M±SD)[m]	.09±2.24		.02±2.52		1.11±2.22		–.01	1.07	<.01	–.21	.35	.21

[a] Adjusted for treatment, education, employment, diastolic blood pressure, hypochondriasis, panic disorder, clinical setting, Quality of Life Inventory score, and Work and Social Adjustment Scale score (all covariates measured at baseline or presentation)

[b] Percentages are based on available data for each characteristic.

[c] Significant after Bonferroni correction (p<.0166)

[d] Frequency, Intensity, and Burden of Side Effects Rating

[e] Models were unestimable.

[f] Remission was achieved if one of the last two consecutive 16-item self-rated Quick Inventory of Depressive Symptomatology scores was <6, the other <8.

[g] 16-item Quick Inventory of Depressive Symptomatology–Self-Rated. Possible scores range from 0 to 27, with higher scores indicating greater depressive symptom severity. A score <6 indicates no depression.

[h] Possible scores range from 0 to 40, with higher scores indicating greater impairment. An extremely nonnormal distribution required binning.

[i] Systematic Assessment of Treatment-Emergent Events. Possible scores range from 0 to 55, with higher scores indicating greater treatment-emergent events and worsening side effects. Values for adjusted and unadjusted analyses are standardized betas.

[j] Values for adjusted and unadjusted analyses are standardized betas.

[k] Hispanics differed significantly from blacks after Bonferroni correction (p<.0166).

[l] Inventory of Depressive Symptomatology–Clinician-Rated anxiety subscale. This 30-item scale is a sum of the following items: mood (anxious), somatic complaints, sympathetic arousal, panic and phobia symptoms, and gastrointestinal symptoms. Possible scores range from 0 to 18, with a score ≥7 indicating presence of anxiety. Values for adjusted and unadjusted analyses are standardized betas.

[m] Quality of Life Inventory. Possible scores range from –6 to 6, with higher scores indicating higher overall quality of life. Values for adjusted and unadjusted analyses are standardized betas.

ables. Variables that remained in the final stepwise model were considered as potential confounders in the adjusted models. The moderating effect of race-ethnicity on treatment was evaluated on two outcomes, severity of depression (QIDS-SR-16) and side effect burden (FIBSER burden subscale), at 12 and 28 weeks. For severity of depression, a linear regression model was fit, and for side effect burden an ordinal logistic regression model was fit. Both models included main effects for treatment and race-ethnicity, as well as the two-way interaction between treatment and race-ethnicity. All analyses were considered to be exploratory, and a type I error or a p value <.05 was used as a threshold to identify statistical significance. When three-group comparisons were made, the p value for significance was adjusted to p<.017. No adjustments were made for multiple comparisons, so results should be interpreted accordingly.

Results

Of 835 participants invited to consent to be screened for the study, 734 (88%) signed consent; of those, 665 (91%) were eligible and were randomly assigned to a treatment group.

Available data on race and ethnicity indicated that the enrolled sample consisted of 431 whites, 174 blacks, 22 Asian American or Pacific Islanders, seven Native Americans, and nine participants who endorsed more than one group. Because of the small numbers in the latter groups, we restricted comparisons to 352 non-Hispanic whites (59%), 169 blacks (28%), and 79 white Hispanics (13%). As shown in Table 1, Hispanics had a significantly higher rate of employment (67%) compared with whites (50%, p<.01) and blacks (41%, p<.01).

Table 4

Race and ethnicity as predictors of post–12-week continuation-phase outcomes for 600 patients treated for depression

Outcome	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Unadjusted OR			Adjusted OR[a]		
	N	%[b]	N	%[b]	N	%[b]	Black and white	Hispanic and white	p	Black and white	Hispanic and white	p
Early termination	110	31	84	50	25	32	2.19	.98	<.01	1.97[c]	1.00	.01
FIBSER maximum rating[d]												
Frequency							.77	1.16	.23	.74	1.49	.06
No side effects	50	15	18	12	6	8						
10%–25% of the time	93	27	52	34	29	37						
50%–75% of the time	107	32	58	38	22	28						
90%–100% of the time	89	26	25	16	21	27						
Intensity							1.00	1.69	.08	.96	2.26	<.01[e]
No side effects	43	13	18	12	5	6						
Minimal to mild	105	31	42	28	27	35						
Moderate to marked	138	41	70	46	25	32						
Severe to intolerable	53	16	23	15	21	27						
Burden							1.25	1.51	.17	1.03	1.86	.07
No impairment	73	22	27	18	9	12						
Minimal to mild	144	43	58	38	40	51						
Moderate to marked	88	26	54	35	17	22						
Severe to intolerable	34	10	14	9	12	15						
FIBSER last rating[d]												
Frequency							1.21	1.18	.57	1.14	1.72	.18
No side effects	171	51	71	46	41	53						
10%–25% of the time	120	36	53	35	21	27						
50%–75% of the time	27	8	27	18	12	15						
90%–100% of the time	19	6	2	1	4	5						
Intensity							1.20	1.06	.64	1.15	1.63	.25
No side effects	166	49	72	47	42	54						
Minimal to mild	124	37	47	31	20	26						
Moderate to marked	34	10	30	20	13	17						
Severe to intolerable	13	4	4	3	3	4						
Burden							1.37	1.07	.32	1.25	1.74	.21
No impairment	210	62	86	56	49	63						
Minimal to mild	98	30	41	27	20	26						
Moderate to marked	20	6	24	16	8	10						
Severe to intolerable	9	3	2	1	1	1						
≥1 serious adverse event	17	5	15	9	10	13	1.71	3.36	.02	1.33	3.90[c]	.04
≥1 psychiatric serious adverse event[f]	6	2	5	3	3	4						

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Blacks had significantly more years of education than Hispanics (mean of 13.2 years versus 12.1 years, p<.01), and whites had significantly more years of education than both of these groups (14.2 years, p<.01). Whites had the earliest age of first major depressive episode (mean age=22.8), which was significantly earlier than for blacks (mean age=26.5, p<.01) (Table 1).

Compared with whites (50%), a significantly greater percentage of blacks (61%, p=.01) had chronic depression; there was no difference between blacks and Hispanics (60%). Hispanics were more likely to be seen in primary care settings (87%) compared with whites (49%, p<.01) or blacks (47%, p<.01) (Table 2).

On some measures, blacks had the highest levels of psychiatric and medical comorbidity. Compared with whites and Hispanics, a greater percentage of blacks had agoraphobia, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and social anxiety disorder (PDSQ), although anxious features did not significantly differ on the HRSD-17 or IDS-C-30. Depressive symptom severity did not differ at a clinically important level across groups. Black participants scored higher on the ASRMS (mean=2.5 out of a possible 20) than both whites (1.2, p<.01) and Hispanics (1.1, p<.01), but all scores were low and not indicative of manic behavior. On the QOLI, whites reported the poorest quality of life (mean score=–1.4 out of a possible 6), followed by blacks (–1.0, p<.01) and Hispanics (–.4, p<.01) (Table 2).

A greater proportion of black participants exited the study early compared with whites and Hispanics (Table 3). Approximately 20% exited by week 4 (versus about 11% of other groups); 27% exited by week 6 (versus about 14% of other groups), and 42% exited before completing week 12 (versus about 21% of whites and 26% of Hispanics). The odds ratio

Table 4

Continued from previous page

Outcome	Whites (N=352)		Blacks (N=169)		Hispanics (N=79)		Unadjusted OR			Adjusted OR[a]		
	N	%[b]	N	%[b]	N	%[b]	Black and white	Hispanic and white	p	Black and white	Hispanic and white	p
Remission[g]	169	48	59	35	45	57	.59	1.62	<.01	.81	1.35	.30
QIDS-SR-16 score[h]												
Last score <6	161	46	57	34	45	58	.59	1.74	<.01	.84	1.77	.08
Score reduction by ≥50%	206	61	81	49	50	65	.59	1.33	<.01	.77	1.20	.36
Last Work and Social Adjustment Scale score[i]							1.97	1.00	<.01	1.50	1.11	.16
0	82	24	27	18	22	28						
1–10	102	30	31	21	21	27						
11–20	76	23	29	19	12	15						
21–30	40	12	35	23	12	15						
31–40	37	11	29	19	11	14						
SAFTEE score reductions[j]												
Maximum (M±SD)	9.7±6.3		10.7±7.5		10.1±5.8		1.05	1.06	.70	.98	1.03	.90
Last (M±SD)	4.6±4.9		5.5±5.1		4.7±5.8		.18	–.07	.17	.05	.02	.91
QIDS-SR-16 score[h,k]												
Last (M±SD)	7.3±5.3		8.7±5.6		6.5±6.1		1.22	.78	<.01	1.07	.81	.11
Percentage change (M±SD)	–52.0±33.2		–42.0±36.6		–57.0±35.9		10.20	–6.47	<.01	4.08	–4.38	.27
IDS-C-30 anxiety subscale score (M±SD)[l]	2.4±2.1		2.9±2.2		2.3±2.3		.19	–.06	.08	.07	.06	.78
Last QOLI score (M±SD)[m]	.41±2.27		.23±2.50		1.77±2.28		–.11	1.44	<.01	–.28	.60[c]	.03

[a] Adjusted for treatment, education, employment, diastolic blood pressure, hypochondriasis, panic disorder, clinical setting, Quality of Life Inventory score, and Work and Social Adjustment Scale score (all covariates measured at baseline or presentation).
[b] Percentages are based on available data for each characteristic.
[c] Significant after Bonferroni correction (p<.0166)
[d] Frequency, Intensity, and Burden of Side Effects Rating
[e] Hispanics differed significantly from blacks and whites after Bonferroni correction (p<.0166).
[f] Models were unestimable.
[g] Remission was achieved if one of the last two consecutive 16-item self-rated Quick Inventory of Depressive Symptomatology scores was <6, the other <8.
[h] 16-item Quick Inventory of Depressive Symptomatology–Self-Rated. Possible scores range from 0 to 27, with higher scores indicating greater depressive symptom severity. A score <6 indicates no depression.
[i] Possible scores range from 0 to 40, with higher scores indicating greater impairment. An extremely nonnormal distribution required binning.
[j] Systematic Assessment of Treatment-Emergent Events. Possible scores range from 0 to 55, with higher scores indicating greater treatment-emergent events. Values for adjusted and unadjusted analyses are standardized betas.
[k] Values for adjusted and unadjusted analyses are standardized betas.
[l] Inventory of Depressive Symptomatology–Clinician-Rated anxiety subscale. This 30-item scale is a sum of the following items: mood (anxious), somatic complaints, sympathetic arousal, panic and phobia symptoms, and gastrointestinal symptoms. Possible scores range from 0 to 18, with a score ≥7 indicating presence of anxiety. Values for adjusted and unadjusted analyses are standardized betas.
[m] Quality of Life Inventory. Possible scores range from –6 to 6, with higher scores indicating higher overall quality of life. Values for adjusted and unadjusted analyses are standardized betas.

(OR) for blacks to exit early was about 2.5 compared with whites. This same pattern of early termination by blacks was seen in continuation treatment (Table 4). In general, final doses received were similar, although blacks less often received the highest dose of bupropion-SR and escitalopram (data not shown), likely because of their early exit. In the acute phase, Hispanic participants had a higher maximum intensity (OR=2.28) and burden of side effects (OR=2.02) compared with whites (Table 3). Side effects during continuation treatment were equal across groups (Tables 3 and 4).

After 12 weeks and before adjustment for baseline differences, Hispanics had the highest remission (51%) and response (60%) rates and blacks the lowest (28% and 41%, respectively), and Hispanics had a significantly lower last QIDS-SR-16 score (6.7 out of a possible 40) than blacks (9.3), indicating less severe depression. After adjustment for baseline differences, the only significant difference at week 12 was that compared with blacks, Hispanics had a lower last QIDS-SR-16 score, and there were no significant differences in these three outcomes across groups at week 28 (Table 4). There were no significant differences regarding effect of treatment among the racial-ethnic groups at weeks 12 and 28 (Table 5).

Discussion

As in the STAR*D study, this study showed considerable socioeconomic and demographic baseline differences among racial-ethnic groups (14). Whether this represents an accurate picture of those seeking treatment in the general population or is related to the participating sites is unclear. Blacks had more general med-

Table 5

Selected acute-phase and continuation-phase outcomes by race-ethnicity and type of depression treatment for 600 patients[a]

	Whites						Blacks						Hispanics						
	Bupropion +escitalopram (N=115)		Escitalopram+ placebo (N=118)		Venlafaxine+mirtazapine (N=119)		Bupropion +escitalopram (N=57)		Escitalopram+ placebo (N=52)		Venlafaxine+mirtazapine (N=60)		Bupropion +escitalopram (N=27)		Escitalopram+ placebo (N=29)		Venlafaxine+mirtazapine (N=23)		
Outcome	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	p[b]
Acute phase																			
Early termination	32	28	27	47	4	15	20	17	22	42	7	24	25	21	22	37	6	26	.43
QIDS-SR-16 score[c]																			
Last score (M± SD)	8.0±5.1		9.0±5.2		7.0±6.1		7.7±5.1		9.1±4.9		6.5±5.5		8.1±5.5		9.7±5.8		6.6±5.5		.98
Last score <6	45	40	17	30	12	44	45	38	11	21	13	45	48	41	14	24	12	52	.87
Score reduction (M±SD %)	–47±32.4		–37±34.6		–53±38.0		–49±32.8		–38±31.9		–56±32.5		–49±34.0		–37±37.9		–54±33.1		.99
Score reduction ≥50%	61	54	24	44	15	56	64	56	20	39	17	61	63	57	24	41	15	65	.95
Last FIBSER burden rating[d]																			.76
No impairment	62	56	30	60	17	63	68	60	22	47	17	65	60	53	28	50	12	52	
Minimal to mild	37	34	13	26	9	33	38	33	19	40	7	27	38	34	20	36	8	35	
Moderate to marked	6	6	5	10	1	4	6	5	6	13	1	4	12	11	6	11	3	13	
Severe to intolerable	5	5	2	4	—	—	2	2	—	—	1	4	3	3	2	4	—	—	
Continuation phase																			
Early termination	40	35	29	51	6	22	34	29	26	50	9	31	36	30	29	48	10	44	.51
QIDS-SR-16 score[c]																			
Last score (M± SD)	7.1±5.1		8.5±5.6		5.2±5.8		6.9±5.3		8.1±5.2		6.8±5.6		7.8±5.5		9.3±6.1		7.7±6.9		.51
Last score <6	53	46	21	38	18	69	57	49	18	35	15	52	51	44	18	31	12	52	.73
Score reduction (M±SD %)	–51.0± 34.7		–41.0± 36.8		–65.0± 36.5		–55.0± 31.0		–45.0± 34.1		–55.0± 33.4		–50.0± 34.1		–41.0± 38.9		–49.0± 37.4		.59
Score reduction ≥50%	70	61	24	44	19	73	71	62	28	55	17	61	65	59	29	49	14	61	.72
Last FIBSER burden rating[d]																			.54
No impairment	71	64	30	60	17	63	76	67	26	55	21	75	63	56	30	54	11	48	
Minimal to mild	29	26	15	30	8	30	33	29	12	26	5	18	36	32	14	25	7	30	
Moderate to marked	6	5	4	8	2	7	2	2	9	19	1	4	12	11	11	20	5	22	
Severe to intolerable	5	5	1	2	—	—	2	2	—	—	1	4	2	2	1	2	—	—	

[a] Bupropion was sustained-release formula; venlafaxine was extended-release formula.

[b] Interaction of race-ethnicity group with treatment

[c] 16-item Quick Inventory of Depressive Symptomatology–Self-Rated. Possible scores range from 0 to 27, with higher scores indicating greater depressive symptom severity. A score <6 indicates no depression.

[d] Frequency, Intensity, and Burden of Side Effects Rating

ical and perhaps psychiatric comorbidity, and both blacks and Hispanics had higher rates of chronic depression compared with whites, although the comparison between Hispanics and whites was not statistically significant. These differences likely represent socioeconomic realities and poorer access to care or greater reluctance to seek care for members of minority groups, perhaps leading to increased chronicity and comorbidity (1–7). Despite these differences, baseline severity of depression was similar across groups.

Although more Hispanics were recruited from primary care sites (perhaps reflecting help-seeking behavior), outcomes for Hispanics were equal to (or better than) those in the other groups, similar to the findings of STAR*D and other studies using measurement-based care (14,52). In the unadjusted analyses at 12 weeks, blacks fared worst and Hispanics best in achieving remission. Once adjustments were made for baseline differences, outcomes were similar among groups.

There were few differences in side

effects among the groups and no differences in adverse events. Compared with whites, Hispanics were more likely to have higher scores for maximum intensity and burden of side effects during the acute phase but not the continuation phase. Despite this, Hispanic participants did not terminate treatment earlier than participants in the other groups, suggesting that the side effect load was tolerable. Despite putative differences in pharmacogenetics in racial-ethnic populations and their effects on treatment response (53–56), we saw no significant differential pattern of side effects or outcome across groups that could be attributed to genetic differences.

Blacks exited the acute and continuation phases at higher rates than both of the other groups. This may account for their poorer remission and response rates, because they may have exited treatment before benefiting from treatment, and those who dropped out very early were considered nonremitters. Blacks had more comorbid anxiety disorders, according to PDSQ score, but baseline anxiety symptoms, as measured by the HDRS-17 and the IDS-C-30 anxiety subscales, did not differ among groups. When additional analyses controlled for the presence of generalized anxiety disorder, outcomes did not significantly differ. Perhaps the PDSQ, a self-rated scale that approximates psychiatric diagnoses, yielded a different pattern of response than the two clinician-rated scales—an area of study in which cultural factors may have a part and that may deserve further scrutiny. Black participants were also more likely to be unemployed and have lower annual incomes—both factors linked to attrition in prior studies (16,57).

It has been reported that for blacks in particular, and to some degree for Hispanics, antidepressant medication may be a less acceptable treatment for depression compared with psychosocial treatments (58) and that medication adherence may be poorer among patients from racial-ethnic minority groups (59). These could be additional factors contributing to the early exit of blacks from this study. Previous depression research studies have reported higher dropout rates for blacks (14,16) in community samples of participants with mental disorders (59,60) and in studies of other chronic diseases (61–63). This presents a major challenge to clinicians, and new strategies must be devised to address this issue. Perhaps eliciting patient concerns about enrolling in medication trials and providing more specific education about these concerns would enhance adherence and decrease dropout.

This study demonstrated that, after adjustment for baseline differences in sociodemographic characteristics and comorbidity, antidepressant medication outcomes across racial-ethnic groups were similar regardless of whether a single agent or two agents were used. This finding confirms and extends previous findings (10,11,14,15) that when dosing of medications based on monitoring of symptoms and side effects is performed, there are no differences in outcome across racial-ethnic groups. Furthermore, there was no indication that a particular medication combination was more effective in any racial-ethnic group. One might argue that blacks, who on average had lower maximum doses of escitalopram and bupropion-SR, may have received medication at too low a dose. However, this "undermedication" was likely accounted for by higher rates of early termination in this group.

Several limitations of the study should be considered. Our strategy was to have participants self-identify their background, but these groupings do not imply sociocultural or genetic homogeneity, and it is likely that there was substantial heterogeneity in all three study groups. Assigning participants to the categorical dimensions of race or ethnicity is problematic, with no acceptable gold standard (64). The sample size in the groups was relatively modest, although it was larger than that in many outcome studies of this type. CO-MED did not use a placebo group, so we cannot say for certain how the outcomes of the treatment groups would compare with those from no active treatment. Finally, enrollees had chronic or recurrent major depressive disorder, and thus we cannot generalize the results to patients with less chronic and single-episode major depressive disorder.

Conclusions

After adjustment for baseline sociodemographic and comorbidity differences, outcomes for participants receiving single or combination antidepressant treatment were similar for white, black, and Hispanic participants. This study adds to the literature showing that disparities in outcome among participants from different racial-ethnic groups can be minimized with measurement-based care.

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References

1. Kessler RC, Berglund P, Demler O, et al: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289:3095–3105, 2003
2. Young AS, Klap R, Sherbourne CD, et al: The quality of care for depressive and anxiety disorders in the United States. Archives of General Psychiatry 58:55–61, 2001
3. Harman JS, Edlund MJ, Fortney JC: Disparities in the adequacy of depression treatment in the United States. Psychiatric Services 55:1379–1385, 2004
4. Virnig B, Huang Z, Lurie N, et al: Does Medicare managed care provide equal treatment for mental illness across races? Archives of General Psychiatry 61:201–205, 2004
5. Miranda J, Cooper LA: Disparities in care for depression among primary care patients. Journal of General Internal Medicine 19:120–126, 2004
6. Schraufnagel TJ, Wagner AW, Miranda J, et al: Treating minority patients with depression and anxiety: what does the evidence tell us? General Hospital Psychiatry 28:27–36, 2006
7. González HM, Croghan T, West B, et al: Antidepressant use in black and white populations in the United States. Psychiatric Services 59:1131–1138, 2008
8. Rollman BL, Hanusa BH, Belnap BH, et al: Race, quality of depression care, and recovery from major depression in a primary care setting. General Hospital Psychiatry 24:381–390, 2002
9. Lagomasino IT, Dwight-Johnson M, Miranda J, et al: Disparities in depression treatment for Latinos and site of care. Psychiatric Services 56:1517–1523, 2005
10. Roy-Byrne P, Perera P, Pitts C, et al: Paroxetine response and tolerability among ethnic minority patients with mood or anxiety disorders: a pooled analysis. Journal of Clinical Psychiatry 66:1228–1233, 2005
11. Bailey RK, Mallinckrodt CH, Wohlreich MM, et al: Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy. Journal of the National Medical Association 98:437–447, 2006
12. Miranda J, Chung JY, Green BL, et al: Treating depression in predominantly low-income young minority women. JAMA 290:57–65, 2003
13. Rush AJ, Trivedi MH, Wisniewski SR, et al: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. American Journal of Psychiatry 163:1905–1917, 2006
14. Lesser IM, Castro DB, Gaynes BN, et al: Ethnicity/race and outcome in the treatment of depression: Results from STAR*D. Medical Care 45:1043–1051, 2007
15. Lesser IM, Myers HF, Lin KM, et al: Ethnic differences in antidepressant response: a prospective multisite clinical trial. Depression and Anxiety 27:56–62, 2010
16. Warden D, Trivedi MH, Wisniewski SR, et al: Predictors of attrition during initial (citalopram) treatment for depression: a STAR*D report. American Journal of Psychiatry 164:1189–1197, 2007
17. Nelson JC, Mazure CM, Jatlow PI, et al: Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biological Psychiatry 55: 296–300, 2004
18. Blier P, Gobbi G, Turcotte JE, et al: Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. European Neuropsychopharmacology 19:457–465, 2009
19. Blier P, Ward HE, Tremblay P, et al: Combination of antidepressant medications from treatment initiation for major depressive disorder: a double-blind randomized study. American Journal of Psychiatry 167: 281–288, 2010
20. Rush AJ, Trivedi MH, Stewart JW, et al: Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes: a single-blind randomized study. American Journal of Psychiatry 168:689–701, 2011
21. Kroenke K, Spitzer RL, Williams JB: The Patient Health Questionnaire–2: validity of a two-item depression screener. Medical Care 41:1284–1292, 2003
22. Kroenke K, Spitzer RL, Williams JBW: The PHQ-9: validity of a brief depression severity measure. Journal of General Internal Medicine 16:606–613, 2001
23. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Rev. Washington DC, American Psychiatric Association, 2000
24. Hamilton M: A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23:56–61, 1960
25. Fava M, Rush AJ, Alpert JE, et al: Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. American Journal of Psychiatry 165:342–351, 2008
26. 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. Biological Psychiatry 54:573–583, 2003; Erratum p 585
27. 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. Psychological Medicine 34:73–82, 2004
28. Rush AJ, Gullion CM, Basco MR, et al: The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychological Medicine 26:477–486, 1996
29. Rush AJ, Carmody TJ, Reimitz PE: The Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. International Journal of Methods in Psychiatric Research 9:45–59, 2000
30. Zimmerman M, Mattia JI: A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. Archives of General Psychiatry 58:787–794, 2001
31. Zimmerman M, Mattia JI: The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. Comprehensive Psychiatry 42:175–189, 2001
32. Rush AJ, Zimmerman M, Wisniewski SR, et al: Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. Journal of Affective Disorders 87:43–55, 2005
33. Trivedi MH, Wisniewski SR, Morris DW, et al: Concise Health Risk Tracking (CHRT) Scale: a brief self-report and clinician rating of suicidal risk. Journal of Clinical Psychiatry 72:757–764, 2011
34. Altman EG, Hedeker D, Peterson JL, et al: The Altman Self-Rating Mania Scale.

Biological Psychiatry 42:948–955, 1997

35. Fava M, Iosifescu DV, Pedrelli P, et al: Reliability and validity of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire. Psychotherapy and Psychosomatics 78:91–97, 2009, Epub Feb 13, 2009

36. 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 and Rheumatology 49:156–163, 2003

37. Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. American Journal of Psychiatry 163:28–40, 2006

38. Trivedi MH, Daly EJ: Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. Drug and Alcohol Dependence 88(suppl 2):S61–S71, 2007

39. Trivedi MH, Rush AJ, Gaynes BN, et al: Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. Neuropsychopharmacology 32:2479–2489, 2007

40. Rush AJ, Bernstein IH, Trivedi MH, et al: An evaluation of the Quick Inventory of Depressive Symptomatology and the Hamilton Rating Scale for Depression: a Sequenced Treatment Alternatives to Relieve Depression trial report. Biological Psychiatry 59:493–501, 2006, Epub Sep 30, 2005

41. Wisniewski SR, Rush AJ, Balasubramani GK, et al: Self-rated global measure of the frequency, intensity, and burden of side effects. Journal of Psychiatric Practice 12: 71–79, 2006

42. Wisniewski SR, Eng H, Meloro L, et al: Web-based communications and management of a multi-center clinical trial: the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project. Clinical Trials 1:387–398, 2004

43. Fava M: Augmentation and combination strategies in treatment-resistant depression. Journal of Clinical Psychiatry 62(suppl 18):4–11, 2001

44. Papakostas GI, Petersen TJ, Kinrys G, et al: Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. Journal of Clinical Psychiatry 66:1326–1330, 2005

45. Leuchter AF, Lesser IM, Trivedi MH, et al: An open pilot study of the combination of escitalopram and bupropion-SR for outpatients with major depressive disorder. Journal of Psychiatric Practice 14:271–280, 2008

46. Reilly MC, Zbrozek AS, Dukes EM: The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 4:353–365, 1993

47. Mundt JC, Marks IM, Shear MK, et al: The Work and Social Adjustment Scale: a simple measure of impairment in functioning. British Journal of Psychiatry 180:461–464, 2002

48. Frisch MB: Manual and Treatment Guide for the Quality of Life Inventory. Minneapolis, Minn, National Computer Systems, Inc, 1994

49. Frisch MB, Clark MP, Rouse SV, et al: Predictive and treatment validity of life satisfaction and the Quality of Life Inventory. Assessment 12:66–78, 2005

50. Levine J, Schooler NR: General versus specific inquiry with SAFTEE. Journal of Clinical Psychopharmacology 12:448, 1992

51. Levine J, Schooler NR: SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacology Bulletin 22:343–381, 1986

52. Gaynes BN, Rush AJ, Trivedi MH, et al: Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. Journal of General Internal Medicine 23:551–560, 2008

53. McMahon FJ, Buervenich S, Charney D, et al: Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. American Journal of Human Genetics 78: 804–814, 2006

54. Laje G, Perlis RH, Rush AJ, et al: Pharmacogenetics studies in STAR*D: strengths, limitations, and results. Psychiatric Services 60:1446–1457, 2009

55. Mrazek DA, Rush AJ, Biernacka JM, et al: SLC6A4 variation and citalopram response. American Journal of Medical Genetics, part B 150:341–351, 2008

56. Binder EB, Owens MJ, Liu W, et al: Association of polymorphisms in genes regulating the corticotrophin-releasing factor system with antidepressant treatment response. Archives of General Psychiatry 67: 369–379, 2010

57. Warden D, Rush AJ, Wisniewski SR, et al: Income and attrition in the treatment of depression: A STAR*D report. Depression and Anxiety 26:622–633, 2009

58. Cooper LA, Gonzales JJ, Gallo JJ, et al: The acceptability of treatment for depression among Black, Hispanic, and White primary care patients. Medical Care 41: 479–489, 2003

59. Diaz E, Woods SW, Rosenheck RA: Effects of ethnicity on psychotropic medications adherence. Community Mental Health Journal 41:521–537, 2005

60. Fortuna LR, Alegría M, Gao S: Retention in depression treatment among ethnic and racial minority groups in the United States. Depression and Anxiety 27:485–494, 2010

61. Levkoff S, Sanchez H: Lessons learned about minority recruitment and retention from the Centers on Minority Aging and Health Promotion. Gerontologist 43:18–26, 2003

62. Davis RM, Hitch AD, Nichols M, et al: A collaborative approach to the recruitment and retention of minority patients with diabetes in rural community health centers. Contemporary Clinical Trials 30:63–70, 2009

63. Magruder KM, Bichun O, Miller S, et al: Retention of under-represented minorities in drug abuse treatment studies. Clinical Trials 6:252–260, 2009

64. Kaplan JB, Bennett T. Use of race and ethnicity in biomedical publication. JAMA 289:2709–2716, 2003