Do Menopausal Status and Use of Hormone Therapy Affect Antidepressant Treatment Response? Findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study

Susan G. Kornstein, MD,[1] Marisa Toups, MD,[2] A. John Rush, MD,[3] Stephen R. Wisniewski, PhD,[4]
Michael E. Thase, MD,[5] James Luther, MA,[4] Diane Warden, PhD,[2]
Maurizio Fava, MD,[6] and Madhukar H. Trivedi, MD[2]

Abstract

Background: Menopausal status and use of hormonal contraception or menopausal hormone therapy (HT) may affect treatment response to selective serotonin reuptake inhibitors (SSRIs). This report evaluates whether menopausal status and use of hormonal contraceptives or menopausal HT affect outcome in women treated with citalopram.

Methods: In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 896 premenopausal and 544 postmenopausal women were treated with citalopram for 12–14 weeks. Baseline demographic and clinical characteristics were used in adjusted analysis of the effect of menopausal status and use of hormonal contraceptives or menopausal HT on outcomes. Remission was defined as final Hamilton Rating Scale for Depression-17 ($HRSD_{17}$) ≤ 7 or Quick Inventory of Depressive Symptomatology-Self-Report ($QIDS-SR_{16}$) score ≤ 5 and response as $\geq 50\%$ decrease from the baseline $QIDS-SR_{16}$ score.

Results: Premenopausal and postmenopausal women differed in multiple clinical and demographic baseline variables but did not differ in response or remission rates. Premenopausal women taking hormonal contraceptives had significantly greater unadjusted remission rates on the $HRSD_{17}$ and the $QIDS-SR_{16}$ than women not taking contraception. Response and remission rates were not different between postmenopausal women taking vs. not taking HT. Adjusted results showed no significant difference in any outcome measure across menopause status in women who were not taking contraception/HT. There were no significant differences in adjusted results across HT status in premenopausal or postmenopausal women.

Conclusions: In this study, citalopram treatment outcome was not affected by menopausal status. Hormonal contraceptives and HT also did not affect probability of good outcome.

Introduction

MAJOR DEPRESSIVE DISORDER (MDD) is approximately twice as common in women as in men and is ranked as the second leading cause of health-related disability in women.[1,2] Among other factors, the presentation of MDD has been shown to be influenced by gender,[3–5] menopausal status,[6] and the presence of hormonal contraceptives[7] or menopausal hormone therapy (HT).[6]

Research suggests that antidepressant response to some medications may differ by sex, age, or menopausal status.[8–13] In particular, several studies have shown that selective serotonin reputable inhibitors (SSRIs) may be less effective for depression in older women compared to younger women or

[1]Department of Psychiatry and Institute for Women's Health, Virginia Commonwealth University, Richmond, Virginia.
[2]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas.
[3]Departments of Clinical Sciences and Psychiatry, University of Texas Southwestern Medical Center at Dallas, and Duke-National University of Singapore, Singapore.
[4]Epidemiology Data Center, GSPH, University of Pittsburgh, Pittsburgh, Pennsylvania.
[5]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania.
[6]Department of Psychiatry, Massachusetts General Hospital, Boston, Masschusetts.

in postmenopausal women compared to premenopausal or perimenopausal women.[10,11] In addition, some studies have reported that response to SSRIs in postmenopausal depressed women is enhanced when the women are also taking HT.[10,14,15] There are no published data on the effect of hormonal contraceptives on antidepressant outcome in depressed women, although a study of women with premenstrual dysphoric disorder found no effect of concomitant use of oral contraceptives on sertraline response.[16]

The purpose of this report is to determine if treatment outcomes with the SSRI citalopram in women differ according to menopausal status or the presence of hormonal contraceptives or menopausal HT. Using data from the National Institute of Mental health (NIMH)-supported Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, we compared response and remission rates between premenopausal and postmenopausal women with MDD who were not taking hormonal contraceptives or menopausal HT. We also evaluated differences between response and remission rates in premenopausal women who were and were not taking hormonal contraceptives and in postmenopausal women who were and were not taking HT.

Materials and Methods

Study overview and organization

The rationale, design, and methods of STAR*D have been detailed elsewhere.[17,18] Briefly, STAR*D aimed to prospectively determine which of several treatments are most effective for outpatients with nonpsychotic MDD who have an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s). Treatment was provided at 18 primary and 23 psychiatric care, public, or private sector settings.

Study population

To enhance generalizability, STAR*D enrolled only self-declared treatment-seeking outpatients 18–75 years of age, identified by their clinicians as having nonpsychotic MDD requiring treatment. Advertising for symptomatic volunteers was proscribed. Broadly inclusive entry criteria were used.[17,18] Patients were eligible if they met DSM-IV criteria for single or recurrent nonpsychotic MDD (established by treating clinician and confirmed by a DSM-IV checklist), scored ≥14 (moderate severity) on the clinical research coordinator (CRC)-rated 17-item Hamilton Rating Scale for Depression (HRSD$_{17}$),[19] and were not treatment resistant to an adequate antidepressant treatment trial during the current MDD episode.[20] Exclusion criteria are detailed elsewhere.[17,18]

All risks, benefits, and adverse events associated with STAR*D participation were explained to participants, who provided written informed consent before study entry. The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Boards at the national and data coordinating centers and the respective regional centers and clinical sites.

Baseline measures

At baseline, trained CRCs based at each site collected standard demographic information, self-reported psychiatric history, and current general medical comorbidites as evaluated by the Cumulative Illness Rating Scale (CIRS),[21] which was completed using a manual to guide scoring.[22] CRCs administered the initial HRSD$_{17}$ and assessed depressive symptoms using the 16-item Quick Inventory of Depressive Symptomatology-Clinician-Rated (QIDS-C$_{16}$).[23,24] The participant completed the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR$_{16}$)[23,24] for assessment of depressive symptoms. Participants also completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[25] to estimate the presence of 11 potential concurrent DSM-IV psychiatric disorders. Based on prior reports,[26] we defined the presence of concomitant axis I disorders using thresholds with a 90% specificity in relation to the gold standard diagnosis rendered by a structured interview.

Research outcomes assessors (ROAs) masked to treatment and not located at any clinical site collected the HRSD$_{17}$ and the 30-item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C$_{30}$)[24,27,28] by telephone interview within 72 hours of study entry for assessment of depressive symptoms. Responses to items on these measures were used to estimate the presence of atypical,[29] melancholic,[30] and anxious[31] symptom features.

A telephone-based Interactive voice response system[32,33] collected health perceptions via the 12-item Short Form health survey (SF-12),[34] and quality of life via the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[35] and the Work and Social Adjustment Scale (WSAS).[36]

Course of treatment measures

An integral part of our measurement-based care intervention[20,37] was the collection of clinically relevant information at each clinic visit to inform treatment decision making. Depressive symptom severity was obtained at each clinic visit with the QIDS-SR$_{16}$ and the QIDS-C$_{16}$. Side effects were assessed using the Frequency, Intensity, and Burden of Side Effects Rating Scale (FIBSER),[38] which uses three 7-point subscales to evaluate frequency, intensity, and global burden measures, respectively.

Intervention

Treatment consisted of up to 14 weeks of citalopram in the first step of STAR*D, with the aim of reaching symptom remission, defined as a QIDS-C$_{16}$ score ≤5 or an HRSD$_{17}$ score <7. The protocol[18] required a fully adequate dose of citalopram for a sufficient time to maximize the likelihood of achieving remission and ensure that participants who did not remit were truly resistant to the medication. Dose adjustments were guided by recommendations in a treatment manual (<www.star-d.org>). Individualized starting doses and dose adjustments were used to minimize side effects, maximize safety, and optimize the chances of therapeutic benefit for each participant. Citalopram was to begin at 20 mg/day and be raised to 40 mg/day by weeks 2–4 and to 60 mg/day (final dose) by weeks 4–6. Dose adjustments were guided by symptom changes based on the QIDS-C$_{16}$, and side effect burden was based on the FIBSER and on how long a participant had received a particular dose.

The protocol recommended treatment visits at weeks 0 (baseline), 2, 4, 6, 9, and 12 (with an optional week 14 visit if needed). After an optimal trial (based on dose and duration), participants who reached remission (QIDS-C$_{16}$ <5) or

response (response defined as an improvement $\geq 50\%$ over the baseline QIDS-C_{16} score without remission) could enter a 12-month naturalistic follow-up, but all who did not reach remission were encouraged to enter the subsequent randomized trial (Level 2 of STAR*D). Participants could discontinue citalopram before 12 weeks if (1) intolerable side effects required a medication change, (2) an optimal dose increase was not possible because of side effects or participant choice, or (3) significant symptoms (QIDS-C_{16} score ≥ 9) were present after 9 weeks at maximally tolerated doses. Participants could opt to move to the next treatment level if they had intolerable side effects or if their QIDS-C_{16} score was >5 after an adequate trial in terms of dose and duration. Intensive efforts were made to provide consistent high-quality care, including the use of a treatment manual, initial didactic instruction, ongoing support and guidance by the CRC, the use of the QIDS-C_{16} and the FIBSER at each visit, and a centralized treatment monitoring and feedback system (<www.star-d .org>).[20,39]

Safety assessments

Side effects were monitored clinically. Serious adverse events (SAEs) were monitored using a multitiered approach[39] that involved the CRCs, study clinicians, the interactive voice response system, the clinical manager, safety officers, regional center directors, and the NIMH data safety and monitoring board.

Concomitant medications

Concomitant treatments for current medical illnesses, associated symptoms of depression (e.g., sleep and agitation), and citalopram side effects were permitted at study entry and during the treatments, based on clinical judgment.

Main outcome measures

The primary outcome measure was the HRSD$_{17}$ collected by ROAs using telephone-based structured interviews at entry and exit from citalopram treatment. The secondary outcomes included the QIDS-SR$_{16}$ and FIBSER collected at baseline and at each treatment visit.

Group assignment/definition of menopausal status

Participants were divided into three groups, premenopausal, perimenopausal, and postmenopausal, according to (1) age and (2) self-report. Menopausal status was determined based on the participant's response to the following question: Is the patient postmenopausal or posthysterectomy or male? A woman was classified as premenopausal if she was <40 years of age. Of those classified as premenopausal, 49 (4.74 %) answered yes to the above question (indicating that they were postmenopausal or posthysterectomy). These women were still included in the premenopausal group because of the very low prevalence (1%–2%) of naturally occurring menopause in women <40 years old. Those in this age group who were posthysterectomy but still had ovaries were likely to still be premenopausal, and those who also had both ovaries removed were likely to be taking menopausal HT and would thus be excluded from the analyses. Women who were at least 40 years old and who reported not being postmenopausal or posthysterectomy were classified as perimenopausal. Finally,

women who were at least 40 years old and reported being postmenopausal or posthysterectomy were operationally defined as postmenopausal. A small number of these women may have had a hysterectomy without ovariectomy and were still cycling. Women who either had experienced natural menopause or had undergone a hysterectomy were included in the study, with the exception of those women on HT. Concomitant medications were assessed at baseline and at every study visit. We reviewed the list of medications reported by each participant in order to determine which participants were taking either hormonal contraceptives of any kind, including parenteral formulations, or menopausal HT.

Of the 4041 participants enrolled in the STAR*D study, 62.7% were women ($n = 2532$). The study sample consists of all women who enrolled in STAR*D, completed one return visit, and had a baseline ROA call to obtain the primary outcome measure, HRSD$_{17}$.[20] Of the 2532 women enrolled, 1996 (79%) met the HRSD$_{17}$ inclusion criteria, and 1833 (92%) completed at least one return visit. Of the analyzable sample ($n = 1883$), 393 (21%) were classified as perimenopausal or were not classified and were excluded from the analysis because of missing data. Of the remaining 1440 (76%) women, 896 (62%) were classified as premenopausal, and 544 (38%) were classified as postmenopausal. Of the 896 premenopausal women, 226 (25%) were taking hormonal contraceptives. Of the 544 postmenopausal women, 134 (25%) were taking menopausal HT. Figure 1 is a graphic representation of study flow.

Administration of hormonal medications, such as hormonal contraceptives and menopausal HT, could affect the presentation of depressive and menopausal symptoms as well as treatment response. Because of the variation in hormonal medications taken and their unknown effects, we excluded women taking these medications ($n = 360$) from the analyses comparing premenopausal and postmenopausal women. Thus, the analyses regarding effect of menopausal status on treatment response were conducted with a sample of 1080 women. Of these, 670 (62%) were classified as premenopausal, and 410 (38%) were classified as postmenopausal.

Statistical analysis

Remission was defined as an exit HRSD$_{17}$ score ≤ 7 (or last observed QIDS-SR$_{16}$ score ≤ 5). As defined by the original proposal, participants for whom the exit HRSD$_{17}$ score was missing were designated as not reaching remission. Response was defined as a reduction of $\geq 50\%$ from the baseline QIDS-SR$_{16}$ at the last assessment. Intolerance was defined *a priori* as either leaving treatment before 4 weeks or leaving at or after 4 weeks, with intolerance as the identified reason. The alpha level was set at 0.05 (two-sided). No adjustments were made for multiple comparisons, so results must be interpreted accordingly.

Summary statistics are presented as means and standard deviations (SD) for continuous variables and percentages for discrete variables. Student's *t* tests and Mann-Whitney *U* tests were used to compare continuous baseline clinical and demographic features, treatment features, and side effect and SAE rates between premenopausal women (not taking hormonal contraceptives) and postmenopausal women (not taking menopausal HT), as well as between premenopausal women taking vs. not taking hormonal contraceptives and between postmenopausal women taking vs. not taking
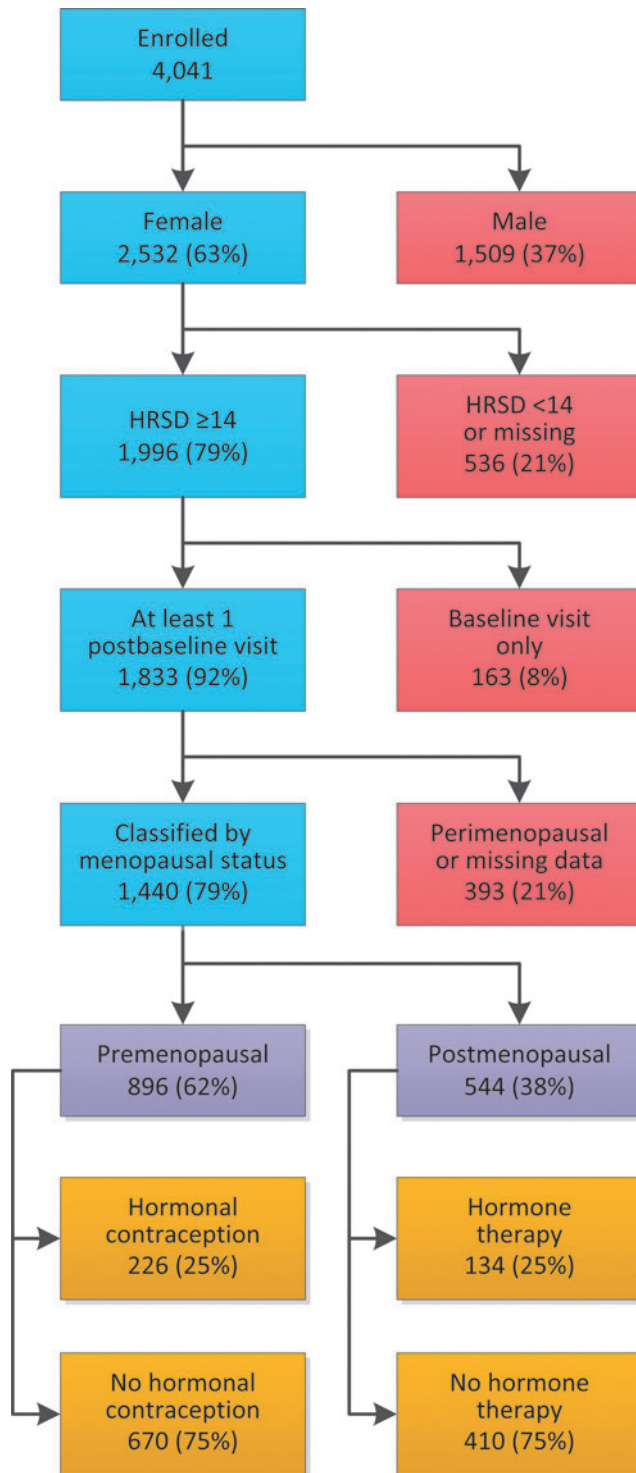
FIG. 1. Consort chart. Distribution of menopausal status and hormone therapy. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. HRSD, Hamilton Rating Scale for Depression.

menopausal HT. Chi-square tests compared discrete characteristics.

Logistic regression models were used to compare remission and response rates after adjusting for factors shown to differ between the groups at baseline. Kaplan-Meier curves were

used to present the cumulative probability of first remission and cumulative probability of first response, both measured using the QIDS-SR$_{16}$. Log-rank statistics were used to test if there was a statistically significant difference in the cumulative proportions.

Results

Baseline characteristics

Table 1 shows the sociodemographic characteristics of premenopausal women (not taking hormonal contraceptives) vs. postmenopausal women (not taking menopausal HT), as well as for premenopausal women by hormonal contraceptive status and for postmenopausal women by HT status. Postmenopausal women were older, more likely to be divorced or widowed, less educated, and less likely to be employed and had a lower household income than premenopausal women. Among all premenopausal women, those taking hormonal contraceptives were younger, more educated, more likely to be single, and more likely to have private insurance. Among all postmenopausal women, those taking menopausal HT were more likely to be white and less likely to be black or Hispanic and more likely to be married and were more educated and had a higher household income.

Table 2 shows clinical measures at baseline. Excluding those taking hormonal contraceptives or menopausal HT, postmenopausal women had an older age at first episode, longer duration of illness, fewer episodes, a longer duration of index episode, and greater likelihood of chronicity than premenopausal women. They also had lower QIDS-SR$_{16}$ scores, more anxious features, and higher mental but lower physical subscale scores on the SF-12. They were less likely to have a family history of depression and less likely to have attempted suicide and had less psychiatric but more general medical comorbidities. Among all premenopausal women, those taking hormonal contraceptives had a lower age at first episode, a lower HRSD$_{17}$ score, lower QIDS-SR$_{16}$ scores, higher Q-LES-Q scores, higher SF-12 physical subscale scores, and lower WSAS scores. Among all postmenopausal women, those taking HT had a greater number of episodes, less anxious features, and higher physical functioning on the SF-12.

Treatment characteristics and outcome

Treatment characteristics are shown in Table 3. Excluding those taking hormonal contraceptives or menopausal HT, postmenopausal women were less likely than premenopausal women to be seen in primary care settings. Postmenopausal women were also less likely to drop out of treatment before week 8, achieved a higher citalopram dose, and were less likely to develop a psychiatric SAE. Among all premenopausal women, those taking hormonal contraceptives were less likely to drop out of treatment before week 8 and reached a higher citalopram dose than those not taking contraceptives. Among all postmenopausal women, there were no differences in treatment characteristics by HT status.

Remission rates for each treatment group are shown in Table 4. Excluding those who were taking hormonal contraceptives or menopausal HT, 28.4% (190 of 670) of premenopausal women and 24.6% (101 of 410) of postmenopausal women remitted based on HDRS$_{17}$ scores. Using the QIDS-

TABLE 1. DEMOGRAPHIC MEASURES BY MENOPAUSAL AND HORMONE STATUS

	Premenopausal		Postmenopausal		p		
Measure	+HC (n=226)	−HC (n=670)	+HT (n=134)	−HT (n=410)	+HC vs. −HC within pre	+HT vs. −HT within post	Pre vs. Post No HC/HT
Age	27.2±5.8	29.8±5.7	54.7±8.1	54.3±7.6	<0.01	0.61	<0.01
Race					0.09	0.02	0.09
White	174 (77.0)	464 (69.4)	111 (82.8)	292 (71.4)			
Black	35 (15.5)	141 (21.1)	21 (15.7)	93 (22.7)			
Other	17 (7.5)	64 (9.6)	2 (1.5)	24 (5.9)			
Hispanic	26 (11.5)	112 (16.7)	14 (10.4)	86 (21.0)	0.06	<0.01	0.08
Education, years	14.0±3.1	13.4±2.9	13.2±3.7	12.3±3.9	0.01	0.02	<.001
Employment status					0.24	0.14	<0.01
Employed	153 (67.7)	415 (62.0)	64 (47.8)	175 (42.8)			
Unemployed	73 (32.3)	252 (37.7)	49 (36.6)	187 (45.7)			
Retired	0 (0.0)	2 (0.3)	21 (15.7)	47 (11.5)			
Monthly household income	2684±3410	2209±2597	2166±2072	1928±2688	0.09	0.04	<0.01
Medical insurance					0.05	0.07	0.04
Any private	134 (60.6)	327 (51.0)	78 (59.1)	189 (47.8)			
Public only	27 (12.2)	102 (15.9)	21 (15.9)	88 (22.3)			
None	60 (27.1)	212 (33.1)	33 (25.0)	118 (29.9)			
Marital status					<0.01	0.02	<0.01
Never married	113 (50.0)	265 (39.6)	7 (5.2)	49 (12.0)			
Married/cohabiting	88 (38.9)	268 (40.0)	60 (44.8)	139 (34.0)			
Divorced/separated	25 (11.1)	133 (19.9)	57 (42.5)	169 (41.3)			
Widowed	0 (0.0)	4 (0.6)	10 (7.5)	52 (12.7)			

HC, hormonal contraceptive; HT, hormone therapy; Post, postmenopausal; Pre, premenopausal.

SR_{16}, the remission rates were 32.8% (220 of 670) for premenopausal and 28.6% (117 of 409) for postmenopausal women. Examining premenopausal women by hormonal contraceptive status using the $HDRS_{17}$, we found that 36.3% (82 of 226) of women who were taking contraceptives remitted compared to 28.4% (190 of 670) of women not taking contraceptives. Based on $QIDS-SR_{16}$ criteria, 41.2% (93 of 226) of premenopausal women taking hormonal contraceptives and 32.8% (220 of 670) of premenopausal women not taking contraceptives remitted. Among postmenopausal women examined by HT status, 29.1% (39 of 134)) of women taking HT remitted on the $HDRS_{17}$ compared to 24.6% (101 of 410) of women not taking HT. Applying $QIDS-SR_{16}$ criteria, remission rates were 35.8% (48 of 134) for women taking HT and 28.6% (117 of 409) for those not taking HT.

Treatment outcome measures from the unadjusted and adjusted models are shown in Table 5. There were no outcome differences between premenopausal and postmenopausal women, with the exception that premenopausal women showed an increase in percent change on the $QIDS-SR_{16}$. Among premenopausal women, those taking hormonal contraceptives showed significantly greater remission rates, as measured by both the $HRSD_{17}$ (primary outcome) and the $QIDS-SR_{16}$, and lower exit $QIDS-SR_{16}$ scores. Postmenopausal women taking HT showed similar response and remission rates on both the $HRSD_{17}$ and the $QIDS-SR_{16}$ compared to those not taking HT. Because the groups differed on a number of baseline variables, adjusted analyses were performed for remission and response rates. Adjustments included baseline demographic and clinical features that differed significantly between groups at baseline (e.g., race, marital status, family history, suicide attempts, number of episodes, and baseline $QIDS-SR_{16}$), with the exception of age. Table 4 shows specific

adjustment factors for each analysis. After adjustment, there was no significant difference in $HRDS_{17}$ remission or $QIDS-SR_{16}$ response or remission rate between premenopausal and postmenopausal women. There was also no significant difference in $QIDS-SR_{16}$ exit score or percent change. When compared by hormonal contraceptive status, premenopausal women showed no differences in remission rates on the $HRDS_{17}$ and $QIDS-SR_{16}$ or in response rates, exit scores, or percent change on the $QIDS-SR_{16}$. Similarly, postmenopausal women did not show significant differences in remission rates on the $HRDS_{17}$ and $QIDS-SR_{16}$ or in response rates, exit scores, or percent change on the $QIDS-SR_{16}$ when compared by HT status.

Discussion

In this study, clinical outcomes in depressed women taking citalopram were unrelated to either menopausal or prescribed hormone status. Although we did find a trend in the unadjusted models toward higher response and remission rates in premenopausal compared to postmenopausal women, the differences were not statistically significant, with the exception of a greater percent change in premenopausal women on the $QIDS-SR_{16}$. We did find significantly greater remission rates in the unadjusted models between premenopausal women who were taking hormonal contraceptives compared to those who were not, as measured by both the $HRSD_{17}$ and the $QIDS-SR_{16}$, as well as lower exit $QIDS-SR_{16}$ scores. Among postmenopausal women, we did not find that HT caused any outcome differences in unadjusted or adjusted models. When adjusted for demographic and clinical differences between groups, outcome differences were no longer statistically significant. These results suggest that, overall, neither

TABLE 2. CLINICAL MEASURES BY MENOPAUSAL AND HORMONE STATUS

	Premenopausal		Postmenopausal		P		
Measure	+HC (n=226)	−HC (n=670)	+HT (n=134)	−HT (n=410)	+HC vs. −HC within Pre	+HT vs. −HT within Post	Pre vs. Post No HC/HT
Age at first episode	17.0±7.0	18.7±7.9	32.2±16.7	34.5±17.6	<0.01	0.19	<0.01
Age at first episode <18	137 (60.6)	338 (51.3)	34 (25.8)	93 (22.8)	0.02	0.49	<0.01
Duration of illness, years	10.3±7.8	11.1±8.0	22.7±16.6	19.9±16.6	0.16	0.06	<0.01
Number of episodes	4.2±5.6	4.6±7.7	6.4±11.4	4.2±8.7	0.93	<0.01	<0.01
At least 1 prior episode	165 (78.9)	483 (77.7)	104 (81.9)	257 (69.6)	0.70	<0.01	<0.01
Family history of depression	148 (65.8)	392 (59.0)	76 (56.7)	209 (51.2)	0.07	0.27	0.01
Ever attempted suicide	53 (23.5)	169 (25.3)	21 (15.7)	57 (13.9)	0.59	0.61	<0.01
No. of psychiatric comorbidities[a]					0.06	0.47	<0.01
0	80 (35.6)	184 (28.0)	58 (44.3)	143 (36.2)			
1	59 (26.2)	151 (23.0)	37 (28.2)	118 (29.9)			
2	41 (18.2)	132 (20.1)	12 (9.2)	52 (13.2)			
3	19 (8.4)	78 (11.9)	11 (8.4)	33 (8.4)			
4+	26 (11.6)	112 (17.0)	13 (9.9)	49 (12.4)			
No. of general medical comorbidities[b]					0.26	0.18	<0.01
0	151 (66.8)	409 (61.0)	24 (17.9)	115 (28.0)			
1	44 (19.5)	135 (20.1)	39 (29.1)	95 (23.2)			
2	17 (7.5)	82 (12.2)	25 (18.7)	78 (19.0)			
3	10 (4.4)	25 (3.7)	20 (14.9)	56 (13.7)			
4+	4 (1.8)	19 (2.8)	26 (19.4)	66 (16.1)			
Duration of index episode, months	16.8±30.8	20.4±43.2	31.9±58.4	31.7±59.9	0.30	0.80	<0.01
Duration of index episode ≥2 years	45 (20.0)	130 (19.6)	47 (35.1)	146 (35.9)	0.90	0.87	<0.01
HRSD$_{17}$	22.8±4.5	24.1±5.2	23.6±5.1	24.1±5.2	<0.01	0.27	0.87
QIDS-C$_{16}$	12.4±4.3	12.6±4.5	12.9±4.6	13.1±4.5	0.53	0.59	0.05
QIDS-SR$_{16}$	16.2±3.7	17.0±3.9	15.7±4.3	16.4±4.1	<0.01	0.10	0.01
Anxious features (HRSD)	113 (50.0)	358 (53.4)	68 (50.7)	261 (63.7)	0.37	<0.01	<0.01
Atypical features (IDS-C)	51 (22.6)	155 (23.1)	22 (16.4)	78 (19.0)	0.86	0.50	0.11
Melancholic features (IDS-C)	46 (20.4)	170 (25.4)	21 (15.7)	91 (22.2)	0.13	0.10	0.24
Q-LES-Q	42.7±13.1	38.2±14.2	40.9±15.6	38.2±15.3	<0.01	0.07	0.94
SF-12 Mental	23.6±7.7	23.8±7.7	27.6±8.6	27.7±8.8	0.84	0.87	<0.01
SF-12 Physical	54.5±9.3	51.6±10.5	45.5±12.2	42.5±11.8	<0.01	0.01	<0.01
WSAS	23.3±8.2	25.5±8.6	24.6±9.1	25.1±9.8	<0.01	0.55	<0.01

[a]From the Psychiatric Diagnostic Screening Questionnaire (PDSQ).
[b]From the Cumulative Illness Rating Scale (CIRS).
HRSD, Hamilton Rating Scale For depression; IDS-C, clinician-rated Inventory of Depressive Symptomatology; QIDS-C, -SR Clinician, Self-Rated, Quick Inventory of Depressive Symptomatology; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SF, Short-form health survey; WSAS, Work and Social Adjustment Scale.

menopausal status nor hormonal contraception or menopausal HT status impacts outcomes of depression treatment with citalopram.

These findings are in contrast to several previous results.[10,11,14,15] Thase et al.[10] examined antidepressant outcomes by age, sex, and menopausal HT use in a large pooled dataset. They found poorer SSRI response among older women compared to younger women; however, concomitant HT use appeared to eliminate this difference. In a study by Pinto-Meza et al.[11] of women patients taking SSRIs in primary care practices, postmenopausal women showed worse treatment response and poorer self-evaluation of global health status compared to premenopausal women. Schneider et al.[14] and Zanardi et al.[15] performed *post-hoc* analyses of older (postmenopausal) women taking SSRIs and found that those taking concomitant HT had higher rates of remission. However, the Zanardi sample included women with bipolar disorder

taking mood stabilizers as well as unipolar patients and is, thus, difficult to compare directly to the STAR*D sample. The Schneider et al. analysis included only estrogen therapy—women taking formulations containing progesterone were excluded—raising the possibility that this accounted for the difference in results. None of these analyses were adjusted for sociodemographic and baseline differences that may have contributed to outcomes.

Our findings suggest that previously seen differences in outcomes with SSRIs based on menopausal status or HT may be due to other factors. Premenopausal and postmenopausal women differ not just in hormonal status and age but also in numerous social and biologic ways that shift over the life span. Many specific stresses that impact depression, such as child-rearing and widowhood, vary across age. Also, we know that many of the diseases of aging, such as cardiovascular disease, may affect or even cause depression, which appears to be

Table 3. Treatment Measures by Menopausal and Hormone Status

	Premenopausal		Postmenopausal		p		
	+HC	−HC		−HT	+HC vs. −HC	+HT vs. −HT	Pre vs. Post
Measure	(n=226)	(n=670)	+HT (n=134)	(n=410)	within Pre	within Post	No HC/HT
Psychiatric care	153 (67.7)	450 (67.2)	60 (44.8)	178 (43.4)	0.88	0.78	<0.01
Weeks in treatment	10.6±4.1	9.7±4.5	9.9±4.3	10.3±4.2	0.02	0.24	0.02
<4	22 (9.7)	97 (14.5)	18 (13.4)	46 (11.2)	0.07	0.49	0.13
<8	49 (21.7)	228 (34.0)	38 (28.4)	106 (25.9)	<0.01	0.57	<0.01
No. of postbaseline visits	4.1±1.5	3.6±1.6	3.9±1.5	3.9±1.6	<0.01	0.73	<0.01
Weeks to first postbaseline visit	2.3±1.0	2.4±1.1	2.4±1.1	2.4±1.2	0.15	0.79	0.42
Maximum citalopram dose	43.5±16.0	39.7±15.9	40.6±17.2	42.0±16.9	<0.01	0.46	0.03
Exit citalopram dose	43.5±16.0	39.7±15.9	40.6±17.2	42.0±16.9	<0.01	0.46	0.03
Weeks on exit citalopram dose	2.8±1.9	2.6±2.2	2.6±1.5	2.7±2.0	0.13	0.84	0.51
Maximum SE frequency[a]					0.62	0.41	0.25
No side effects	26 (13.1)	93 (16.6)	16 (15.2)	72 (20.3)			
10%–25% of the time	59 (29.6)	159 (28.4)	28 (26.7)	108 (30.5)			
50%–75% of the time	64 (32.2)	182 (32.6)	32 (30.5)	96 (27.1)			
90%–100% of the time	50 (25.1)	125 (22.4)	29 (27.6)	78 (22.0)			
Maximum SE intensity[a]					0.68	0.72	0.17
No side effects	26 (13.1)	93 (16.6)	16 (15.2)	70 (19.8)			
Minimal to mild	57 (28.6)	157 (28.1)	30 (28.6)	103 (29.1)			
Moderate to marked	86 (43.2)	233 (41.7)	41 (39.0)	123 (34.7)			
Severe to intolerable	30 (15.1)	76 (13.6)	18 (17.1)	58 (16.4)			
Maximum SE burden[a]					0.21	0.15	0.08
No side effects	35 (17.6)	130 (23.3)	18 (17.1)	98 (27.7)			
Minimal to mild	95 (47.7)	223 (39.9)	43 (41.0)	126 (35.6)			
Moderate to marked	58 (29.1)	171 (30.6)	35 (33.3)	96 (27.1)			
Severe to intolerable	11 (5.5)	35 (6.3)	9 (8.6)	34 (9.6)			
Exited level due to intolerance[b]	32 (14.2)	119 (17.8)	25 (18.7)	69 (16.8)	0.21	0.63	0.70
At least 1 SAE	8 (3.5)	24 (3.6)	4 (3.0)	13 (3.2)	0.98	1.00	0.72
At least 1 psychiatric SAE	5 (2.2)	16 (2.4)	1 (0.7)	3 (0.7)	0.88	1.00	0.04

[a]From the Frequency, Intensity, and Burden of Side Effects Rating Scale (FIBSER).
[b]Exited prior to week 4 for any reason or after week 4 citing intolerable side effects.
SAE, serious adverse event; SE, side effect.

different neurobiologically than depression in younger patients. In addition, our group found within the same sample a range of differences in presentation of depression between premenopausal and postmenopausal women.[6] Perhaps these differences may account for the differences found in other studies.

This is the first published report, to our knowledge, on the effect of hormonal contraceptives on antidepressant response in depressed women. Contraceptives differ in formulation, particularly in estrogen/progesterone ratio, from menopausal HT and may have had different effects on mood and antidepressant outcome. Sex hormones are known to exert effects on monoamines as well as the hypothalamic-pituitary-adrenal (HPA) axis, both key factors in mood regulation. Differences in sex hormones are often used to explain the higher overall rates of depression in women and the fact that the gender difference

in prevalence of MDD appears at puberty. Our finding that treatment outcome was similar in women taking and not taking hormonal contraceptives, however, suggests that clinicians should view clinical decision making for depression in premenopausal women independent of that for contraception. Similarly, our finding of no significant difference in outcomes in postmenopausal women across HT status in a large sample and controlling for group differences suggests that MDD should not be considered a clinical indication for adding HT in postmenopausal depressed women. Nevertheless, there may be a subgroup of women whose depression is particularly sensitive to hormonal fluctuations (e.g., history of postpartum depression, history of premenstrual dysphoric disorder [PMDD]) for whom HT may improve treatment outcome; this should be the subject of future research.

Table 4. Remission Rates by Menopause and Hormone Therapy Status

	Within premenopausal				Within postmenopausal			
	+HC (n=226)		−HC (n=670)		+HT (n=134)		−HT (n=410)	
Remission	n	%	n	%	n	%	n	%
HRSD₁₇	82	39.3	190	28.4	39	29.1	101	24.6
QIDS-SR₁₆	93	41.2	220	32.8	48	35.8	117	28.6

Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

TABLE 5. UNADJUSTED AND ADJUSTED OUTCOMES BY MENOPAUSAL AND HORMONE THERAPY STATUS

	+HT vs. −HT												Post vs. Pre					
	Within Pre						Within Post						Within −HT					
	Unadjusted			Adjusted			Unadjusted			Adjusted			Unadjusted			Adjusted		
Outcome	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
HRSD$_{17}$ remission	1.439	(1.046-1.979)	0.03	1.194[a]	(0.908-1.831)	0.31	1.256	(0.813-1.941)	0.30	1.004[e]	(0.629-1.604)	0.99	0.826	(0.624-1.093)	0.18	1.145[i]	(0.818-1.602)	0.43
QIDS-SR$_{16}$ remission	1.430	(1.049-1.950)	0.02	1.168[b]	(0.903-1.874)	0.37	1.393	(0.922-2.106)	0.12	1.148[f]	(0.738-1.787)	0.54	0.820	(0.627-1.072)	0.15	1.226[j]	(0.823-1.825)	0.32
QIDS-SR$_{16}$ response	1.346	(0.993-1.823)	0.06	1.164[c]	(0.845-1.603)	0.35	1.021	(0.690-1.512)	0.92	0.855[f]	(0.563-1.297)	0.46	0.818	(0.639-1.047)	0.11	1.245[k]	(0.901-1.720)	0.18

	+HT vs. −HT												Post vs. Pre					
	Within Pre						Within Post						Within −HT					
	Unadjusted			Adjusted			Unadjusted			Adjusted			Unadjusted			Adjusted		
Outcome	β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p	β	(95% CI)	p
QIDS-SR$_{16}$ exit score	−1.146	(−2.059--0.234)	0.01	−0.525[d]	(−1.370-0.320)	0.62	−0.576	(−1.705-0.554)	0.32	1.070[g]	(−0.032-2.172)	0.06	0.392	(−0.342-1.126)	0.29	−0.632[l]	(−1.599-0.336)	0.20
QIDS-SR$_{16}$ % change	−4.162	(−9.468-1.144)	0.12	−1.726[d]	(−8.243-2.355)	0.54	−1.528	(−8.198-5.143)	0.65	5.801[h]	(−1.057-12.66)	0.10	4.844	(0.567-9.121)	0.03	−4.541[m]	(−10.56-1.477)	0.14

Adjusted for
[a] Education, number of psychiatric comorbidities, Q-LES-Q, SF-12 Physical, and QIDS-C$_{16}$.
[b] Recurrent depression, number of psychiatric comorbidities, Q-LES-Q, SF-12 Physical, and QIDS-C$_{16}$.
[c] Number of psychiatric comorbidities, Q-LES-Q, and SF-12 Physical.
[d] Education, recurrent depression, number of psychiatric comorbidities, number of general medical comorbidities, Q-LES-Q, SF-12 Physical, WSAS, and QIDS-C$_{16}$.
[e] Education, number of general medical comorbidities, and SF-12 Physical.
[f] Number of general medical comorbidities and SF-12 Physical.
[g] Education, number of episodes, number of psychiatric comorbidities, number of general medical comorbidities, SF-12 Mental and physical, QIDS-C$_{16}$, and anxious features.
[h] Education, number of episodes, number of general medical comorbidities, SF-12 Physical, QIDS-C$_{16}$, and anxious features.
[i] Education, number of psychiatric comorbidities, number of general medical comorbidities, SF-12 Physical, QIDS-C$_{16}$, and anxious features.
[j] Education, age at first episode, number of episodes, recurrent depression, number of general medical comorbidities, SF-12 Physical, and QIDS-C$_{16}$.
[k] Education, number of episodes, recurrent depression, number of general medical comorbidities, SF-12 Physical, QIDS-C$_{16}$, and anxious features.
[l] Education, age at first episode, number of episodes, number of psychiatric comorbidities, number of general medical comorbidities, Q-LES-Q, SF-12 Physical, QIDS-C$_{16}$, and anxious features.
[m] Education, age at first episode, number of episodes, recurrent depression, number of general medical comorbidities, SF-12 Physical, QIDS-C$_{16}$, and anxious features.
CI, confidence interval; OR, odds ratio.

Several limitations should be noted. The sample consisted of outpatients with nonpsychotic MDD and, therefore, may not be generalizable to all depressed women. Another limitation was the definition of menopausal status used, which was based on a combination of age and a question about menopause status and hysterectomy status. More detailed questions about irregular or skipped menstrual cycles and timing of cessation of menses would have allowed more accurate classification of menopausal status. Because this study was not randomized, we cannot well differentiate between effects caused by medications and those resulting from social or behavioral factors. Finally, there may be differences in the type of hormones prescribed for contraception that could affect outcomes and were not considered here; this is particularly true for contraceptive types that work through means other than ovarian suppression, such as intrauterine devices.

Further research in this area could clarify some of these issues. Although the STAR*D sample is large and reasonably well characterized and these secondary analyses were conducted to minimize confounding differences, future studies should more specifically characterize hormonal status in order to confirm these findings. The STAR*D sample used age and self-reported menopausal status and did not confirm reports with thorough clinical interview or laboratory values, which would have provided better sample characterization. Although there are potential ethical and practical issues in the design of such studies, the effect of hormonal contraceptives and menopausal HT on depression treatment outcomes could be tested prospectively. Specifically, premenopausal depressed women could be randomized to hormonal contraception or placebo as an adjunctive treatment (while using other methods of contraception). Similarly, postmenopausal depressed women could be randomized to HT or placebo as an adjunctive treatment. Such studies would provide high-quality evidence for or against efficacy by removing biases in the sample affecting women's likelihood of use of contraceptives or HT. Alternatively, studies comparing two or more types of antidepressant treatments or different formulations of hormonal contraceptives or menopausal HT could indicate specific medications or combinations to be further pursued or avoided depending on menopausal status. Finally, it is possible that careful collection of historical or biologic data could reveal a subgroup of women whose depression is responsive to adjunctive HT.

References

1. Kessler RC. Epidemiology of women and depression. J Affect Disord 2003;74:5–13.

2. Michaud CM, Murray CJL, Bloom BR. Burden of disease—implications for future research. JAMA 2001;285:535–539.

3. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in chronic major and double depression. J Affect Disord 2000;60:1–11.

4. Marcus SM, Young EA, Kerber KB, et al. Gender differences in depression: Findings from the STAR*D study. J Affect Disord 2005; 87:141–150.

5. Marcus SM, Kerber K, Rush AJ, et al. Gender differences in depression symptoms in treatment seeking adults: STAR*D confirmatory analyses, Compr Psychiatry 2008;49:238–246.

6. Kornstein SG, Young EA, Harvey AT, et al. The influence of menopausal status and postmenopausal use of hormone therapy on presentation of major depression in women. Menopause 2010;17:828–839.

7. Young EA, Kornstein SG, Harvey A, et al. Influences of hormone-based contraception on depressive symptoms in premenopausal women with major depression. Psychoneuroendocrinology 2007;32:843–853.

8. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry 2000;157: 1445–1452.

9. Martényi F, Dossenbach M, Mraz K, Metcalfe S. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: A double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. Eur Neuropsychopharmacol 2001;11:227–232.

10. Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: Sex-age interactions. J Womens Health 2005;14:609–616.

11. Pinto-Meza A, Usall J, Serrano-Blanco A, Suarez D, Haro JM. Gender differences in response to antidepressant treatment

prescribed in primary care. Does menopause make a difference? J Affect Disord 2006;93:53–60.

12. Grigoriadis S, Kennedy SH, Bagby RM. A comparison of antidepressant response in younger and older women. J Clin Psychopharmacol 2003;23:405–407.

13. Raskin A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis 1974;159:120–130.

14. Schneider LS, Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. Am J Geriatr Psychiatry 2001;9:393–399.

15. Zanardi R, Rossini D, Magri L, Malaguti A, Colombo C, Smeraldi E. Response to SSRIs and role of the hormonal therapy in post-menopausal depression. Eur Neuropsychopharmacol 2007;17:400–405.

16. Freeman EW, Rickels, K, Sondheimer SJ, Polansky M. Concurrent use of oral contraceptives with antidepressants for premenstrual syndromes. J Clin Psychopharmacol 2001; 21:450–542.

17. Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am 2003; 26:457–494.

18. Rush AJ, Fava M, Wisniewski SR, et al. STAR*D Investigators Group. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): Rationale and design. Control Clin Trials 2004;25:119–142.

19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

20. 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;163:28–40.

21. Linn BS, Linn MW, Gurrel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622–626.

22. Miller MD, Towers A. A manual of guidelines for scoring the Cumulative Rating Scale for Geriatrics (CIRS-G). Pittsburgh, PA: University of Pittsburgh, 1991.

23. 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;54:573–583.

24. 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;34:73–82.

25. Zimmerman M, Mattia J. A self-report scale to help make psychiatric diagnoses: The Psychiatric Diagnostic Screening Questionnaire. Arch Gen Psychiatry 2001;58:787–794.

26. Rush AJ, Zimmerman M, Wisniewski SR, et al. Comorbid psychiatric disorders in depressed outpatients: Demographic and clinical features. J Affect Disord 2005;87:43–55.

27. Rush AJ, Giles DE, Schlesser MA, Fulton C, Weissenburger JE, Burns C. The Inventory for Depressive Symptomatology (IDS): Preliminary findings. Psychiatry Res 1986;18:65–87.

28. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): Psychometric properties. Psychol Med 1996;26:477–486.

29. Novick JS, Stewart JW, Wisniewski SR, et al. Clinical and demographic features of atypical depression in outpatients with major depression: Preliminary findings from STAR*D. J Clin Psychiatry 2004;66:1002–1011.

30. Khan AY, Carrithers J, Preskorn SH, et al. Clinical and demographic factors associated with DSM-IV melancholic depression. Ann Clin Psychiatry 2006;18:91–98.

31. Fava M, Alpert JE, Carmin CN, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med 2004;34:1299–1308.

32. Mundt JC. Interactive voice response systems in clinical research and treatment. Psychiatr Serv 1997;48:611–612.

33. Kobak KA, Greist JH, Jefferson JW, Mundt JC, Katzelnick DJ. Computerized assessment of depression and anxiety over the telephone using interactive voice response. MD Comput 1999;16:64–68.

34. Ware JE Jr, Sherbourne DC. The MOS 36-item Short Form health survey (SF-36). I. conceptual framework and item selection, Med Care 1992;30:473–483.

35. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): A new measure. Psychopharmacol Bull 1993;29:321–326.

36. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: A simple measure of impairment in functioning. Br J Psychiatry 2002;180:461–464.

37. 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 2007;32:2479–2489.

38. Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA, for the STAR*D Investigators. Self-rated global measure of the Frequency, Intensity, and Burden of Side Effects. J Psychiatr Pract 2006;12:71–79.

39. 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. Clin Trials 2004;1:387–398.

Address correspondence to:
Susan G. Kornstein, MD
Department of Psychiatry and Institute for Women's Health
PO Box 980710
Virginia Commonwealth University School of Medicine
Richmond, VA 23298-0710

E-mail: skornste@vcu.edu