Short-Term Dynamic Psychotherapy Versus Pharmacotherapy for Major Depressive Disorder: A Randomized, Placebo-Controlled Trial

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ABSTRACT

Objective: To determine whether supportive-expressive psychotherapy (SET), a form of dynamic psychotherapy, and pharmacotherapy + clinical management (MED) for major depressive disorder (MDD) are more effective than pill-placebo + clinical management (PBO).

Method: This National Institute of Mental Health (NIMH)–sponsored randomized controlled trial was conducted (from November 2001 through June 2007) at the University of Pennsylvania Medical School. The sample included 156 patients diagnosed with MDD (*DSM-IV*) and having a 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) score ≥ 14 for at least 2 consecutive weeks. This was an underserved sample in which 41% were male, 52% were self-designated minorities, and 76% had an annual income under $30,000. Treatment lasted 16 weeks. Medication patients not responsive by week 8 (maximum dose 200 mg/d of sertraline) were switched to venlafaxine (maximum dose 375 mg/d). Nonresponsive placebo patients at week 8 were switched to a different placebo.

Results: Patients' depression improved over the 16 weeks ($P < .0001$), with no between-group differences ($P = .95$), even among severely ($HRSD_{17}$ score ≥ 20) depressed patients ($P = .45$). Response rates did not differ between groups ($P = .73$). Gender and minority status moderated outcome ($P = .014$), with psychotherapy more efficacious for minority men than MED ($P = .027$, Cohen $d = 1.02$) and PBO ($P = .019$, $d = 1.09$). PBO was more efficacious for white men than MED ($P = .03$, $d = 0.62$) and SET ($P = .003$, $d = 1.07$). For white women, MED ($P = .005$, $d = 0.77$) and SET ($P = .033$, $d = 0.71$) were more efficacious than placebo. No differences among treatments were found for minority women.

Conclusions: This trial of urban MDD patients failed to confirm that either active treatment was better than placebo. Minority status and gender had significant and differential effects on outcome that warrant replication in future studies.

Trial Registration: clinicaltrials.gov Identifier: NCT00043550

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See also Commentary on page 64.

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Few controlled studies have examined the efficacy of short-term dynamic psychotherapy (STDP) for Axis I disorders. Nevertheless, a meta-analysis of rigorous randomized controlled trials (RCTs) indicated that STDP was more efficacious than control conditions and as effective as other psychotherapies irrespective of psychiatric disorder.[1] Only 3 RCTs involving STDP for major depressive disorder (MDD) were identified and focused on geriatric depression,[2] middle-class white individuals,[3] and maternal depression.[4] Subsequent studies suggested that STDP may be more effective than no treatment for minor depression and more effective than supportive therapy during follow-up[5] but not different from pharmacotherapy for MDD.[6] The paucity of STDP RCTs is a serious concern, as psychodynamic therapy is widely practiced in the Western world.[7]

The present study offers the first randomized, placebo-controlled efficacy trial of STDP versus contemporary antidepressant therapy, a selective serotonin reuptake inhibitor (SSRI) followed, if clinically indicated, by a serotonin-norepinephrine reuptake inhibitor (SNRI). One model of STDP that offers a manualized treatment approach and has demonstrated validity and reliability of its constructs is supportive-expressive therapy (SET).[8] We hypothesized that both SSRI/SNRI and SET would be more efficacious than placebo. In light of previous RCTs of depression treatments,[9] SSRI/SNRI treatment was hypothesized to have greater efficacy than SET for patients with more severe depression.

Urban participants were recruited, with relatively high percentages of minority and male patients. National Institutes of Health (NIH) recommendations to examine the role of minority status and gender on patients' outcome were followed.[10,11]

METHOD

Participants

Three hundred seventy-four individuals, aged 18 to 70 years, were recruited through advertisements on public transportation and in free news publications, area physicians, and outpatient clinics. Individuals not meeting MDD diagnostic criteria[12] using the Structured Clinical Interviews for *DSM-IV*[13] or scoring less than 14 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[14,15] at 2 evaluations 1 week apart were excluded (n = 88, Figure 1). Additional exclusions were bipolar disorder (n = 6), current or past psychosis (n = 12), *DSM-IV* Axis I disorder judged more severe than the depression (n = 3), high suicide risk (n = 8), medical condition contraindicating study medications (n = 4), functional illiteracy (n = 3), self-withdrawal (n = 5), and current *DSM-IV* substance dependence (n = 18). Patients with substance abuse were allowed. The study (clinicaltrials.gov Identifier: NCT00043550) was approved by the institutional review board, and all patients signed informed consent prior to screening.

Study Design

Potential participants were evaluated for MDD after providing signed informed consent. To ensure stability of depression severity, patients meeting study criteria had a second evaluation within 10 days of the first and were then randomly assigned among the 3 treatments (SSRI/SNRI + clinical management [MED], placebo + clinical management [PBO], and SET) using an urn randomization,[16,17] blocking on gender, marital status, depression severity ($HRSD_{17}$ score ≥ 20), presence of Axis II disorders, and desired treatment (medication or therapy).

A planned sample size of 180 was determined through a method[18] that accounts for increased statistical power in repeated-measures designs.[19] Due to slower-than-anticipated recruitment, 156 patients (SET: n = 51; MED: n = 55; PBO: n = 50) were randomized. This sample afforded detection of a medium effect size of 0.48 with power > 80% when comparing MED or SET to PBO over the longitudinal period.

Diagnostic Assessment and Outcome Measures

Six experienced diagnosticians (MS- or PhD-level psychologists) confirmed diagnoses using the Structured Clinical Interview for *DSM-IV*.[13] Interjudge reliability as assessed by intraclass correlations was 0.92 for the $HRSD_{17}$ and 0.97 for MDD diagnosis. Psychopharmacologists, diagnosticians, and medicated patients were blind to treatment assignment. $HRSD_{17}$ assessments were conducted at weeks 2, 4, 6, 8, 12, 15, and 16.

Patients were considered responders at week 8 if their $HRSD_{17}$ score was ≤ 12 or reflected a 50% reduction from baseline $HRSD_{17}$ score. Response at 16 weeks was defined as $HRSD_{17}$ score ≤ 9 or 50% $HRSD_{17}$ score reduction *and* a $HRSD_{17}$ score ≤ 12. Remission was defined as no longer meeting criteria for MDD and $HRSD_{17}$ score < 8.[20]

Treatment Conditions

All treatments were provided for 16 weeks. Manualized, empirically studied SET[21–24] was provided by 4 white psychologists with more than 15 years of psychotherapy experience and at least 10 years of experience in SET. All had served as therapists and/or supervisors in prior SET studies. Patients received 45-minute sessions, twice weekly during the first 4 weeks of treatment and weekly for weeks 5 through 16.

The MED and PBO conditions were delivered by 8 experienced research psychopharmacologists following a manualized clinical management protocol[25] under the supervision of the last 2 authors (M.R. and K.R.). Patients were seen weekly for the first 6 weeks, after which they could be seen every 2 weeks at the discretion of the treating pharmacotherapist. Sertraline was initiated at 50 mg/d and raised in 50-mg increments to a maximum of 200 mg by week 4. At week 8, nonresponding MED patients had their medication titrated from sertraline to venlafaxine extended release (ER) over a 2-week period. An initial daily dose of 37.5 mg of venlafaxine was increased to 75 mg by the end of week 9 with maximum dose of 375 mg/d by week 12 as tolerated. Nonresponding PBO patients were switched to a second placebo using the same titration schedule. Side effects of study medication were monitored at each visit and handled by slowing the titration schedule or temporarily reducing dosage. The blind was broken at week 16. PBO patients were offered a free course of open medication.

Allegiance was counter-balanced by having experienced investigators from both treatment arms.

Clinical Points

- Among low-income, inner-city depressed patients, there is not much evidence supporting the efficacy of either pharmacotherapy or brief dynamic therapy in comparison with placebo.
- There is some preliminary evidence that minority men improved more following dynamic therapy than following pharmacotherapy and placebo, whereas white men improved more following placebo than following other treatments.
- Preliminary evidence also indicates that white women will improve more following pharmacotherapy or dynamic therapy than following placebo, whereas minority women improved similarly across treatments. Those results require replication.

Figure 1. Flow of Participants in a Study Comparing Supportive-Expressive Therapy Versus Medication Versus Placebo for Major Depressive Disorder

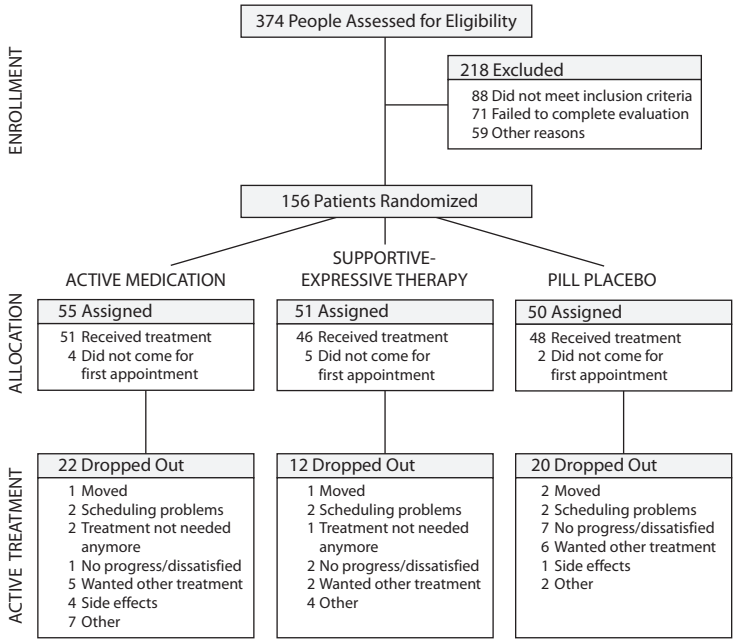

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Table 1. Demographic and Clinical Characteristics as a Function of Treatment Group[a]

Variable	MED (n = 55)	SET (n = 51)	PBO (n = 50)	Total (N = 156)	Statistical Test	*P* Value
Demographics						
Age, y, mean (SD)	38.0 (12.5)	36.2 (12.2)	38.3 (12.0)	37.5 (12.2)	$F_{2,153} = 0.47$	.63
Education, y, mean (SD)	13.3 (3.9)	13.1 (2.7)	14.1 (3.8)	13.5 (3.5)	$F_{2,150} = 1.77$	.28
Female	54.6 (30)	60.8 (31)	62.0 (31)	59.0 (92)	$\chi^2 = 0.70$	.70
Income > $30,000	23.6 (13)	23.5 (12)	26.0 (13)	24.4 (38)	$\chi^2 = 0.11$	.95
Married/cohabitating	29.1 (16)	31.4 (16)	28.0 (14)	29.5 (46)	$\chi^2 = 0.14$	.93
Employed	56.4 (31)	54.9 (28)	56.0 (28)	55.8 (87)	$\chi^2 = 0.03$	.99
Minority	43.6 (24)	62.7 (32)	50.0 (25)	51.9 (81)	$\chi^2 = 3.98$	.14
Clinical features						
Chronic/recurrent MDD	54.5 (30)	58.8 (30)	72.0 (36)	61.5 (96)	$\chi^2 = 3.61$	.16
Age at onset, y, mean (SD)	23.2 (12.8)	25.3 (12.8)	20.2 (9.0)	23.0 (11.9)	$F_{2,128} = 1.96$	.15
No. of prior episodes, mean (SD)	4.9 (6.9)	3.8 (6.3)	6.8 (9.1)	5.1 (7.5)	$F_{2,120} = 1.63$	.20
Length of current MDD episode, mo, mean (SD)	50.6 (99.8)	33.0 (53.3)	36.5 (80.7)	40.0 (79.5)	$F_{2,133} = 0.64$	.53
Melancholia	9.1 (5)	17.7 (9)	20.0 (10)	15.4 (24)	$\chi^2 = 2.69$	.26
Comorbidities						
Any disorder	91.8 (45)	86.3 (44)	86.0 (43)	84.5 (131)	$\chi^2 = 0.51$	.77
Any Axis I disorder	68.5 (37)	80.4 (41)	78.0 (39)	75.5 (117)	$\chi^2 = 2.25$	.32
Dysthymia	14.6 (8)	7.8 (4)	12.0 (6)	11.6 (18)	$\chi^2 = 1.18$	.55
Any anxiety disorder	32.7 (18)	52.9 (27)	50.0 (25)	44.9 (70)	$\chi^2 = 5.15$	.08
Present substance abuse/past dependence	38.2 (21)	37.3 (19)	30.0 (15)	35.3 (55)	$\chi^2 = 0.90$	.64
Any Axis II disorder	45.5 (25)	51.0 (26)	42.0 (21)	46.2 (72)	$\chi^2 = 0.84$	.66
Intake $HRSD_{17}$ score, mean (SD)	19.0 (3.4)	19.9 (3.9)	19.3 (3.8)	19.4 (3.7)	$F_{2,153} = 0.86$	.43

[a]Values shown as % (n) unless otherwise noted.
Abbreviations: $HRSD_{17}$ = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; MED = medication (SSRI + clinical management followed by SNRI if no response); PBO = placebo control + clinical management, followed by switch to another placebo if no response; SET = supportive-expressive therapy; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Statistical Analyses

Baseline differences in demographic and clinical characteristics were investigated using 1-way analysis of variance (ANOVA) for continuous variables and χ^2 tests of independence/Fisher exact test for categorical variables. Hierarchical linear modeling (HLM) was used for outcome and moderation analyses. Due to nonlinear change across treatment, a logarithmic transformation of time was used to quantify change.[19] Categorical rates of response/remission were examined using χ^2 tests for treatment differences and logistic regression for moderation effects.[26] Categorical analyses were conducted with the full intent-to-treat sample, using last observation carried forward (LOCF) for participants who failed to complete treatment or were lost to follow-up.

As missing data are inevitable, we implemented pattern-mixture models[27] to assess whether important estimates per the HLM model were dependent on missing data patterns, and to provide overall estimates of effects by averaging across the various missing-data patterns.[28] For the planned LOCF analyses, sensitivity of the results to the missing data pattern was examined for consistency of results across subsamples identified by patterns of available data.[29]

All analyses were conducted using SAS Version 9.1.3.[30] Overall significant effect for treatment, as well as the 2 moderating effects, used a Bonferroni-corrected α level of .0167 (.05/3).

RESULTS

Sample Characteristics

One hundred fifty-six MDD patients (64 men, 41%; 92 women, 59%) were randomized to 3 treatment groups. As Table 1 shows, differences among the treatments failed to emerge for any baseline demographic or clinical characteristic. Of note is the relatively large proportion of self-designated minorities (52%): 45% African American, 5% Latino, 2% Asian); annual family incomes less than US $30,000; chronic depression; and high comorbidity.

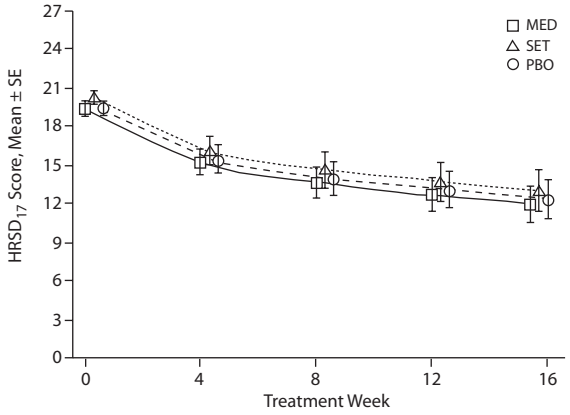
Pharmacotherapy

At week 8, 38% of MED patients (21/55) were nonresponsive and switched to venlafaxine ER while 30% of PBO patients (15/50) were switched to a second placebo. Across treatment there was 83% compliance (44/53; taken/prescribed) for MED and 78% compliance (39/50) for PBO. By week 8, 74% of MED patients (37/50) reached maximum dose of 200 mg sertraline and 85% of PBO (41/48) reached maximum dosage. By week 16, 86% of MED patients (12/14) who were responders and continued in treatment post–week 8 were at a maximum dose of 200 mg of sertraline and 71% of MED patients (15/21) who were nonresponders and continued in treatment post–week 8 were taking a maximum dose of 375 mg of venlafaxine, whereas 89% of PBO (17/19) who continued on the same placebo medication and 67% of PBO (10/15) who switched placebo medication achieved maximum dosage.

Attrition

Fifty-four patients (35%) dropped out prior to 16 weeks irrespective of treatment condition (MED: 40% [n = 22], SET: 23.5% [n = 12], and PBO: 40% [n = 20]; $\chi^2_2 = 4.11$, $P < .13$, N = 156). Higher attrition rates were observed in MED and PBO compared to SET, although pairwise differences were not statistically significant with an odds ratio of 2.17 (95% CI, 0.93–5.03; $\chi^2_1 = 3.24$, $P = .072$) for MED versus SET

Figure 2. Change in $HRSD_{17}$ Score as a Function of Medication, Supportive-Expressive Therapy, and Placebo Control[a]



[a]Hierarchical linear model assessing treatment comparison in rate of change per unit time, in which time is on the logarithm of week scale, showed no differences between the 3 treatment conditions ($F_{2,131} = 0.05$, $P = .95$).

Abbreviations: $HRSD_{17}$ = 17-item Hamilton Rating Scale for Depression; MED = medication (SSRI + clinical management followed by SNRI if no response); PBO = placebo control + clinical management, followed by switch to another placebo if no response; SET = supportive-expressive therapy; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

and 2.17 (95% CI, 0.92–5.12; $\chi^2_1 = 3.11$, $P = .078$) for PBO versus SET. Time to attrition was also similar among groups ($\chi^2_6 = 10.1$, $P < .12$, N = 156) whether prior to the first session (MED: 7.3% [n = 4], SET: 9.8% [n = 5], PBO: 4.0% [n = 2]), on or prior to midtreatment assessment (MED: 29.1% [n = 16], SET: 11.8% [n = 6], PBO: 26.0% [n = 13]), or prior to 16 weeks (MED: 3.6% [n = 2], SET: 2.0% [n = 1], PBO: 10.0% [n = 5]). Rates of treatment completion were also similar among MED (60.0%; n = 33), SET (76.5%; n = 39), and PBO (60.0%; n = 30).

Analysis of Active Treatment Outcomes

All treatments evidenced a deceleration in the rate of change (Figure 2). Therefore, a modification of time through a shifted logarithmic transformation was employed ($\log_e$[week+1]).[18] Significant improvement over time ($F_{1,133} = 159.19$, $P < .0001$) was found, although rates failed to differ among treatments ($F_{2,131} = 0.05$, $P = .95$). $HRSD_{17}$ slope estimates (± SE) were similar across conditions (MED: –2.67 ± 0.36, SET:–2.57 ± 0.35, PBO: –2.51 ± 0.36), suggesting that neither MED nor SET was more efficacious than PBO (Cohen $d = 0.03$ and 0.06). Estimated endpoint $HRSD_{17}$ scores were roughly equivalent.

Analysis of Potential Moderators: Depression Severity

No significant interaction between time, depression severity ($HRSD_{17}$ score ≥ 20), and treatment condition was found ($F_{2,128} = 2.10$, $P = .13$). Limiting the analysis to patients with high depression severity (17 MED, 18 SET, and 18 PBO) revealed no significant differences in rate of change ($F_{2,39} = 0.82$, $P = .45$). Contrary to expectations, slope estimates for patients receiving MED (–2.68 ± 0.85) and SET (–2.31 ± 0.85) did not differ significantly ($t_{39} = -0.30$, $P = .76$, Cohen $d = 0.05$), indicating that MED was no more effective than SET even among the more severely depressed patients.

Analysis of Potential Moderators: Gender by Minority Status

The role of minority status and gender on outcome[10,11] was examined post hoc, revealing a significant 3-way interaction ($F_{2,122} = 4.42$, $P = .014$). Simplifying the 3-way interaction, we tested the treatment effect within each of the 4 subgroups of the sample. As illustrated in the upper left box plot of Figure 3, minority men improved most rapidly within SET (–3.93 ± 0.96) compared to both MED (–1.70 ± 0.81) and PBO (–1.47 ± 1.02). The treatment effect within SET was statistically significant ($F_{2,25} = 3.95$, $P = .032$), with large effects for the pairwise contrasts of SET with MED and PBO ($t_{25} = 2.35$, $P = .027$, Cohen $d = 1.02$ [95% CI, 0.51–1.51] and $t_{25} = 2.52$, $P = .019$, $d = 1.09$ [95% CI, 0.58–1.58], respectively). As the upper right box plot indicates, among white men, improvement was faster for PBO (–3.87 ± 0.82) than for both MED (–2.30 ± 0.75) and SET (–1.33 ± 0.79). The treatment effect within this subgroup was statistically significant ($F_{2,33} = 5.48$, $P = .009$), with medium to large effects for the pairwise contrasts of PBO with MED and SET ($t_{33} = 2.24$, $P = .032$, $d = 0.62$ [95% CI, 0.13–1.10] and $t_{33} = 3.25$, $P = .003$, $d = 1.07$ [95% CI, 0.56–1.56], respectively). Within minority women, as seen in the lower left box plot, the rate of improvement was comparable across all 3 conditions (MED: –2.34 ± 0.93; SET: –2.40 ± 0.57; PBO: –2.59 ± 0.64). The treatment effect within this subgroup was nonsignificant ($F_{2,50} = 0.38$, $P = .69$), with all 3 pairwise comparisons having P values > .40. For white women, both MED (–3.65 ± 0.67) and SET (–3.56 ± 0.89) had a significantly greater rate of improvement than PBO (–1.88 ± 0.74) ($F_{2,36} = 4.77$, $P = .014$), with medium effects for the pairwise contrasts of MED and SET with PBO ($t_{36} = 2.97$, $P = .005$, $d = 0.77$ [95% CI, 0.28–1.25] and $t_{36} = 2.22$, $P = .033$, $d = 0.71$ [95% CI, 0.22–1.19]).

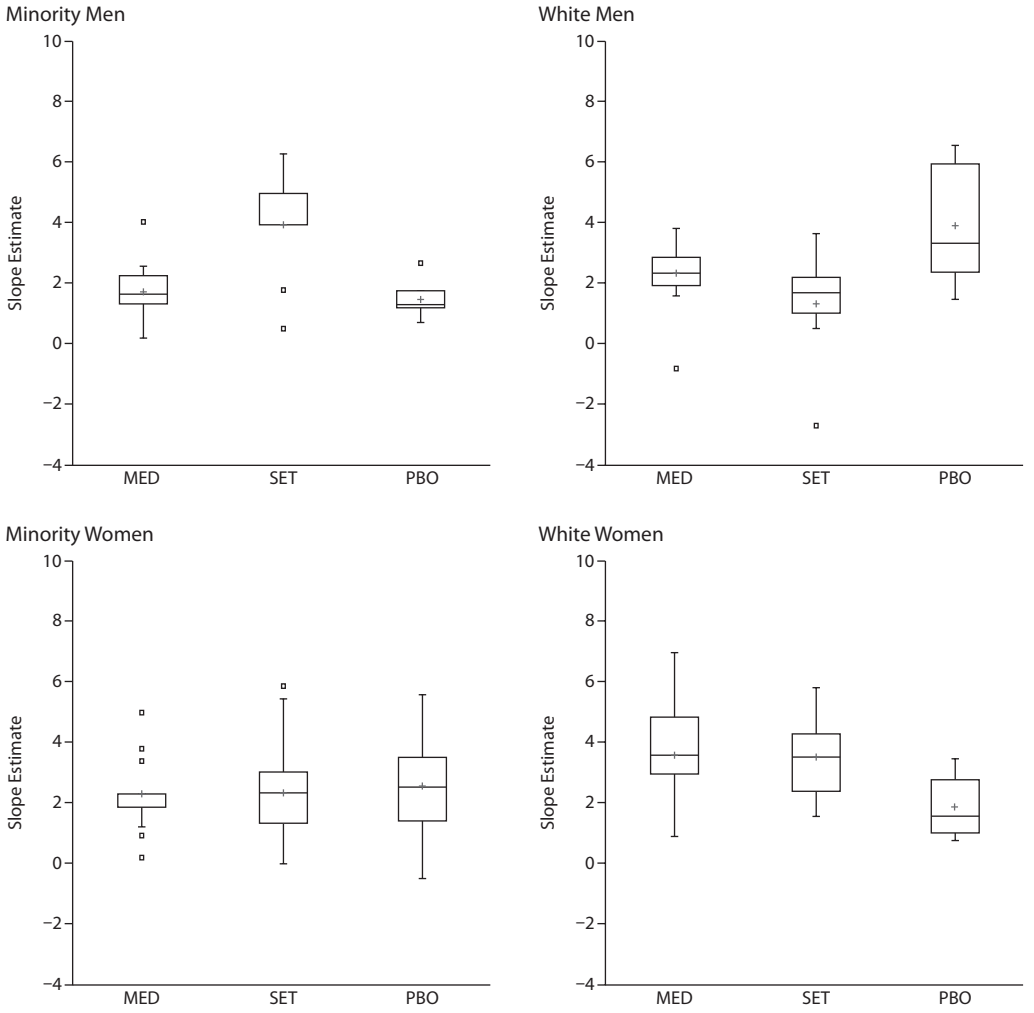
To determine whether socioeconomic status was driving the interaction of minority status, gender, and treatment over time, the analysis was redone with income and education as covariates. Adding covariates to the model increased slightly the significance of the interaction ($F_{2,129} = 4.85$, $P = .009$), suggesting that socioeconomic factors were not influencing the initial findings.

Analysis of Response and Remission

Using LOCF, analyses yielded similar results across treatment conditions for rates of response ($\chi^2_2 = 0.63$, $P = .73$, N = 156) and remission ($\chi^2_2 = 0.48$, $P = .79$, N = 156) at end of treatment. Rates of response were 30.9% (17/55) in MED, 27.5% (14/51) in SET, and 24.0% (12/50) in PBO. Rates of remission were 25.5% (14/55) in MED, 21.6% (11/51) in SET, and 20.0% (10/50) in PBO.

Response and remission rates were also examined as a function of minority status and gender. The interaction was nonsignificant for predicting response ($\chi^2_2 = 2.76$,

Figure 3. Rates of Change in $HRSD_{17}$ Score Over Time as a Function of Gender, Minority Status, and Treatment[a,b]



[a]Hierarchical linear model assessing interaction of gender by minority status by treatment in rate of change over time ($F_{2,122} = 4.42$, $P = .014$).
[b]The center horizontal line in each box represents the median estimated slope per group, whereas the "+" indicates the mean estimated slope per group.
Abbreviations: $HRSD_{17}$ = 17-item Hamilton Rating Scale for Depression; MED = medication (SSRI + clinical management followed by SNRI if no response); PBO = placebo control + clinical management, followed by switch to another placebo if no response; SET = supportive-expressive therapy; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

$P = .25$, N = 156) and remission ($\chi^2_2 = 2.42$, $P = .30$, N = 156), although the pattern mirrors that found in the main outcome analysis.

Analysis of Missing Data

To determine whether the lack of significance among treatments was driven by missing data, we classified 2 monotonic patterns of patients' available data (patients with data at week 16 [endpoint] vs patients with data only prior to week 16) and assessed the interaction of pattern, time, and treatment using HLM analysis. The pattern-mixture results were nonsignificant ($F_{2,128} = 0.61$, $P = .54$). Similarly, the pattern-mixture results regarding the gender-by–minority status–by-treatment interaction were also nonsignificant ($F_{2,110} = 1.15$, $P = .32$). Thus, the contrasts of parameter estimates generated by the original HLM models were valid and not biased by missing data. For the LOCF analysis, there was no indication that our 3 main analyses were sensitive to the patterns of missing data ($P > .41$[29]).

Analysis for Mid-Treatment Outcome (8 Weeks)

Because treatment nonresponse at week 8 in either MED or PBO required a switch to SNRI or second PBO, respectively, the consistency of rates of change between treatments was assessed before the switch and prior to much attrition. Similar to the week 16 analyses, rates of improvement failed to differ between conditions at midtreatment ($F_{2,129} = 0.22$, $P = .81$). $HRSD_{17}$ slope estimates were similar (MED: -2.33 ± 0.44; SET: -2.56 ± 0.43; PBO: -2.73 ± 0.43).

Even at week 8, rates of improvement were found to differ across the 3 treatments depending on gender and minority status ($F_{2,122} = 4.19$, $P = .01$). Minority men improved more

quickly with SET (−4.38 ± 1.29) than MED (−1.38 ± 0.97) or PBO (−1.16 ± 1.22; $t_{122} = 2.06$, $P = .04$, Cohen $d = 1.39$). By contrast, among white men, improvement rate was no better in PBO (−3.81 ± 1.00) than MED (−2.10 ± 0.95) or SET (−1.25 ± 0.97; $t_{122} = 1.76$, $P = .08$, $d = 0.95$). Improvement rates for minority women increased similarly over time (−1.80 ± 1.08 for MED; −2.33 ± 0.69 for SET; −3.21 ± 0.77 for PBO), although differences between conditions failed to be demonstrated ($t_{122} = 1.14$, $P = .25$, $d = 0.51$). White women improved more quickly in MED (−3.38 ± 0.80) or SET (−3.61 ± 1.07) than in PBO (−2.08 ± 0.88), though the difference was not significant ($t_{122} = 1.29$, $P = .20$, $d = 0.63$).

Adverse Events

No serious adverse events occurred during the study. One nonserious adverse event was a passive suicidal attempt in which a SET patient reported taking 4.5 mg of alprazolam to calm down following an argument. An hour later he took venlafaxine 187.5 mg, methylphenidate 30 mg, and oxycodone 5 mg with acetaminophen in response to continued anger. The patient was taken to the hospital emergency department and released without medical intervention. Three other patients (2 SET, 1 MED) were withdrawn from the study due to suicidal/homicidal thoughts.

DISCUSSION

This report describes the first placebo-controlled study of SET, a manualized and relatively well-studied form of STDP. Despite patients' significant improvement and skilled providers' employing manualized treatments, we failed to find overall differences among treatment conditions at either 8 or 16 weeks. Moreover, among the more severely depressed patients, those receiving medication did not improve more than those receiving psychotherapy or placebo. In the absence of an outcome difference between the medication and placebo groups, our trial may be classified as a failed trial.[31] Issues of design, rigor, or statistical power may be raised as reasons for these results, but 4 factors argue against such conclusions. First, the overall placebo response rate was 24%, a rate usually associated with good signal detection (ie, larger drug vs placebo differences).[32] Second, the 25.5% remission rate for the MED group is lower than observed at the end of the first treatment trial in STAR*D,[33] suggesting a lack of meaningful improvement with active medication rather than a strong placebo response. Third, pharmacotherapy treatments were administered double-blind and the design was placebo controlled, methodological features typically associated with lower response and remission rates. Finally, PBO is far from being a no-treatment condition.

Rather than study design or power issues, the relatively low efficacy and response rates are most likely due to characteristics unique to this sample. Unlike most efficacy trials,[34] our sample comprised economically disadvantaged, highly comorbid, chronic, recurrently depressed, urban patients. Since community samples are not as treatment responsive as patients in efficacy trials, and US Food and Drug Administration (FDA) data on SSRIs suggest lower efficacy than that found in published data,[35] our results are less surprising. Thus, we agree with Insel's[11(p129)] conclusions that there are "significant limitations of current pharmacological interventions" for depression despite administration with optimal clinical standards.

Furthermore, equality of outcome does not mean treatment equivalence for subgroups of patients.[11] Whereas minority men improved more rapidly in psychotherapy, white men improved more rapidly in PBO. For minority women, outcome was similar across the 3 treatments. White women, however, tended to improve more with medication or psychotherapy than with placebo. Secondary analyses assessing potential influences of socioeconomic status failed to explain our findings. Given previous research showing that minorities improve less than white individuals,[36] it is possible that SET was especially effective relative to medication for minorities, mostly black men (80% of our minority men were African American).

One possible reason for the differences among men is that socialization patterns of black men encourage community and family interdependence yet foster caution for exploitation.[37] Addressing interpersonal issues and wishes in a supportive relationship may have helped these men to share their concerns without fear of exploitation. Only among white women were our findings consistent with expectation, in that active treatments were more effective than placebo. In their meta-analysis, Walsh et al[32] reported that, on average, 60% of patients in placebo-controlled pharmacotherapy trials for depression are women. Assuming 15% would be minority, we estimate the participation of at least 51% white women in those RCTs. In a sample of placebo-controlled studies involving both pharmacotherapy and psychotherapy, the percentage of women tended to be a bit higher, ranging from 59% to 77%, and the percentage of white participants ranged from 82% to 96%: Elkin et al,[38] 70% women, 89% white participants; DeRubeis et al,[39] 59% women, 82% white; Dimidjian et al,[40] 66% women, 82% white; Jarrett et al,[41] 68% women, 93% white; Mynors-Wallis et al,[42] 77% women, 96% white. Summarizing data from those 5 placebo-controlled psychotherapy trials, we estimated that white women represented 58% of the entire sample (537 white women of 930 patients). However, with few investigators reporting results as a function of gender and/or race, it is not possible to determine whether our findings are unique. Of course, most studies have not examined the efficacy of STDP in general or SET in particular. The lack of similar findings and the post hoc nature of our findings necessitate replication. Recruiting diverse populations, as difficult as it may be, is crucial for enhancing our knowledge of whether treatments work and to better understand the mechanisms by which they do so. These findings should encourage future examinations of the specific needs of underserved and economically challenged groups with a focus on minority status and gender.

Two limitations are the relatively high level of attrition and small sample size for specific combinations within our moderation analysis. Research has shown high levels of

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attrition among African Americans, the less educated, and the less wealthy.[43] Our statistical methods[27,29] showed that the results were not sensitive to these attrition patterns. The small sample size for the moderation analyses may have limited power.[44] However, others[45,46] have recommended 5 to 7 as the minimal group sizes, which are consistent with our data. Finally, as shown in Figure 3, there were no substantial outliers or influential observations, thereby supporting the validity of our moderation analyses.

Drug names: alprazolam (Xanax, Niravam, and others), methylphenidate (Metadate, Daytrana, and others), oxycodone (OxyContin, Roxicodone, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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