ORIGINAL ARTICLE

A Double-blind Randomized Controlled Trial of Olanzapine Plus Sertraline vs Olanzapine Plus Placebo for Psychotic Depression

The Study of Pharmacotherapy of Psychotic Depression (STOP-PD)

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Context: Evidence for the efficacy of combination pharmacotherapy has been limited and without positive trials in geriatric patients with major depression (MD) with psychotic features.

Objectives: To compare remission rates of MD with psychotic features in those treated with a combination of atypical antipsychotic medication plus a serotonin reuptake inhibitor with those treated with antipsychotic monotherapy; and to compare response by age.

Design: Twelve-week, double-blind, randomized, controlled trial.

Setting: Clinical services of 4 academic sites.

Patients: Two hundred fifty-nine subjects with MD with psychotic features randomized by age (<60 or ≥60 years) (mean [standard deviation (SD)], 41.3 [10.8] years in 117 younger adults vs 71.7 [7.8] years in 142 geriatric participants).

Intervention: Target doses of 15 to 20 mg of olanzapine per day plus masked sertraline or placebo at 150 to 200 mg per day.

Main Outcome Measure: Remission rates of MD with psychotic features.

Results: Treatment with olanzapine/sertraline was associated with higher remission rates during the trial than olanzapine/placebo (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.12-1.47; $P<.001$); 41.9% of subjects who underwent combination therapy were in remission at their last assessment compared with 23.9% of subjects treated with monotherapy ($\chi^2_1=9.53$, $P=.002$). Combination therapy was comparably superior in both younger (OR, 1.25; 95% CI, 1.05-1.50; $P=.02$) and older (OR, 1.34; 95% CI, 1.09-1.66; $P=.01$) adults. Overall, tolerability was comparable across age groups. Both age groups had significant increases in cholesterol and triglyceride concentrations, but statistically significant increases in glucose occurred only in younger adults. Younger adults gained significantly more weight than older subjects (mean [SD], 6.5 [6.6] kg vs 3.3 [4.9] kg, $P=.001$).

Conclusions: Combination pharmacotherapy is efficacious for the treatment of MD with psychotic features. Future research must determine the benefits vs risks of continuing atypical antipsychotic medications beyond 12 weeks.

Trial Registration: clinicaltrials.gov Identifier: NCT00056472

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Group Information: The STOP-PD group members are listed on page 845.

MAJOR DEPRESSION (MD) with psychotic features is a severe but potentially treatable disorder.[1] Epidemiological studies[2,3] and studies of large samples of psychiatric patients[4,5] indicate that 15% to 20% of individuals with major depression have psychotic features. Higher prevalence rates approximating 45% have been reported among elderly inpatients with depression.[6,7] Major depression with psychotic features is associated with poorer short-term outcomes, a longer time to recovery, greater residual disability, and greater mortality than MD without psychosis.[2,4,5,8,9]

Expert guidelines[10,11] recommend treatment of MD with psychotic features with either electroconvulsive therapy (ECT) or pharmacotherapy that combines an antidepressant with an antipsychotic medication. The guidelines were based on studies demonstrating low response rates of MD with psychotic features to tricyclic antidepressant (TCA) monotherapy[12-16] and results from both a small controlled trial[16] and pooled analyses[17-20] favoring combination treatment or ECT.

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A recent meta-analysis demonstrating that combination therapy was superior to antipsychotic monotherapy included the only 3 controlled trials available.[21] The limited evidence for the efficacy of combination treatment for MD with psychotic features may contribute to the underrecognition of delusions in patients with MD[22] and the low use of antipsychotic medications to treat MD with psychotic features in community settings.[23,24] In contrast to trials in young adults,[16] geriatric trials have not demonstrated greater efficacy for combined TCA/conventional antipsychotic therapy compared with TCA/placebo for either acute[25] or post-ECT continuation treatment[26] but did demonstrate poorer tolerability of combination therapy.

The present study investigated the efficacy of combination treatment in patients with systematically diagnosed MD with psychotic features across a broad spectrum of illness severity and compared the efficacy and tolerability between persons aged 18 to 59 years and those aged 60 years and older. We compared olanzapine (an atypical antipsychotic medication reported to have acute antidepressant effects in placebo-controlled trials[27,28]) combined with placebo relative to olanzapine combined with sertraline hydrochloride, a selective serotonin reuptake inhibitor antidepressant reported to be effective for MD with psychotic features.[29] The design encouraged aggressive dosing of both medications during a 12-week trial to maximize remission rates that could be compared with the high remission rates associated with ECT.[14,17,18,30,31] The following hypotheses were tested: whether (1) combination therapy would be more effective than atypical antipsychotic monotherapy; (2) younger adults would achieve higher remission rates than older adults; and (3) younger adults would tolerate treatment better than older adults.

METHODS

PARTICIPANTS

Patients aged 18 years or older who were admitted to the inpatient or ambulatory services of the 4 participating academic sites between December 2002 and June 2007 were eligible for recruitment. The institutional review boards of the participating institutions and a data safety monitoring board at the National Institute of Mental Health approved study consent forms and monitored the study's progress. Informed consent was obtained from all subjects, either directly or through locally approved surrogate consent procedures. Strategies to identify eligible patients varied by institution and included review of new admissions, advertisements, and direct referrals by community psychiatrists.

Potentially eligible consenting subjects were assessed with the Structured Interview for Clinical Diagnosis[32] to assure that *DSM-IV-TR*[1] criteria for unipolar MD with psychotic features were met. Inclusion required the presence of at least 1 delusional belief (a fixed idea that was held contrary to the laws of logic), a score of 2 or higher on 1 of the conviction items of the Delusional Assessment Scale,[33] and a score of 3 or higher on the delusion severity rating item of the Schedule of Affective Disorders and Schizophrenia (SADS).[34] A SADS delusion severity score of 3 is assigned when there is no more than a transient ability to consider the implausibility of an irrational belief. The presence of at least 1 clearly defined delusion was required, with or without hallucinations, as studies of MD with psychotic features have generally considered delusional depression and MD with psychotic features to be synonymous.[35-37] The presence of moderately severe to severe depression was assured by requiring scores of 21 or higher on the 17-item Hamilton Depression Scale (HAM-D),[38] which was administered using the GRID-HAM-D method.[39]

This study focused on the treatment of MD with psychotic features rather than syndromes in which psychotic and depressive symptoms accompany dementia. Therefore, patients with dementia or histories of impaired cognition prior to the current depressive episode were excluded. Patients were excluded if they met criteria for another Axis I psychotic or mood disorder; current body dysmorphic disorder or obsessive-compulsive disorder; or substance abuse during the preceding 3 months. Additional exclusion criteria were the presence of an unstable medical condition that might interfere with completion of the 12-week trial; a neurological disease that might affect neuromuscular functioning, such as Parkinson disease; and ongoing need for medications known to cause depression or psychosis. Patients with known hyperlipidemia or diabetes mellitus, including insulin-dependent diabetes, were allowed to enroll if their metabolic conditions were stable. Patients were excluded if immediate ECT was indicated because of their refusal to eat or drink or imminent risk for suicide. Patients who demonstrated current suicidal ideation without immediate intent and those who had made a suicide attempt during the current episode were allowed to begin the study on an inpatient basis. Screening also involved baseline laboratory assessments, including measurement of thyroid-stimulating hormone, folate, and B_{12} concentrations; an electrocardiogram; and a toxicology screen to detect undisclosed illicit drug use. Finally, patients were excluded if they had received 15 mg or more of olanzapine per day for a minimum of 4 weeks during the current episode or if they were benefiting from their current psychotropic medications regimen.

INTERVENTION

Eligible subjects were randomized to sertraline plus olanzapine or olanzapine plus placebo using computer-generated lists, with investigators and raters blind to treatment assignments. Randomization was stratified by site and age, with a block size of 4. Subjects taking antidepressant or antipsychotic medications at entry had these tapered prior to randomization, though a washout period was not enforced because of the severity of illness anticipated in study participants. Subjects began taking 5 mg of olanzapine per day and 50 mg of sertraline hydrochloride or matching placebo per day, with dose increases permitted every 3 days as tolerated. Frail elderly subjects initially received 2.5 mg of olanzapine and 25 mg of sertraline or placebo (one-half of a 50-mg or placebo tablet). Olanzapine was administered openly, sertraline and placebo under double-blind conditions. An attempt was made to reach minimum doses of 10 mg of olanzapine per day and 100 mg of sertraline or placebo per day before the end of week 1. Doses were increased to 15 mg of olanzapine per day and 150 mg of sertraline or placebo per day during week 2, with further increases allowed to a maximum of 20 mg of olanzapine per day and 200 mg of sertraline per day, as tolerated, beginning in week 3. Slower titration or temporary dose reductions of 1 or both medications was allowed if adverse effects were suspected; however, subsequent dose increases were required to attempt to achieve minimum daily target doses of 15 mg of olanzapine per day and 150 mg of sertraline or placebo per day. For data analytic purposes, the subject's dose was considered the last one taken for

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a minimum of 7 days. Adjunctive lorazepam of up to 4 mg per day was allowed to control anxiety or agitation, and up to 2 mg of benztropine per day to control extrapyramidal symptoms. No other psychotropic drugs were allowed.

STUDY ASSESSMENTS

Baseline assessments were completed within 7 days of obtaining consent. Follow-up research assessments were conducted weekly for the first 6 weeks and then every other week until week 12 or termination. Research assessments included overall symptom severity using the Clinical Global Impressions, Severity of Illness Scale (CGI-S),[40] HAM-D, assessments for delusional ideation using the Delusional Assessment Scale and the SADS delusional item, the Brief Psychiatric Rating Scale,[41] and the Scale for Positive Symptoms.[42] At baseline, the Cumulative Illness Burden Scale[43] was used to assess general medical burden, and the Mini-Mental State Examination[44] was used to assess global cognitive functioning. Raters were trained to achieve adequate reliability prior to conducting study assessments and interrater reliability reassessed annually thereafter.

OUTCOME CRITERIA

Remission was defined as a HAM-D score of 10 or lower at 2 consecutive assessments. This criterion was applied to assure that remission from mood symptoms was sustained and to allow for comparability with ECT studies that typically use a 2-week HAM-D criterion.[31] Remission also required the absence of delusions (SADS delusional item score of 1) at the second remission of depression assessment. A 1-week remission of delusions criterion was applied to make the remission of psychosis outcome compatible with the standard duration criterion used in MD with psychotic features pharmacotherapy trials.[21] Subjects who were not delusional at both of 2 consecutive HAM-D assessments were considered remitted at both points; subjects who had been delusional at the first of the HAM-D assessments were considered to be remitted at the second assessment only, and subjects who were not delusional at the first assessment but had SADS scores higher than 1 at the second were classified as not remitted at either assessment. A HAM-D cutoff of 10 or lower was used because this has been a standard in geriatric antidepressant trials[45,46] and ECT studies.[31] Subjects who achieved a HAM-D score of 10 or lower without delusions for the first time at week 12 were assessed again at week 13 to determine whether the 2-week duration criterion was met.

Investigators were allowed to withdraw subjects for either clinically significant worsening or insufficient clinical improvement after 5 weeks of randomized treatment. Insufficient clinical response was operationally predefined as having both a CGI-Improvement scale score of 2 or less (no or minimal improvement) and a CGI-S score of 4 or more (moderately or more severely ill). Discontinuations initiated by subjects were categorized as perceived poor response, poor tolerability, or withdrawal of consent.

Safety and tolerability assessments considered the incidence of adverse events and evaluations conducted by the investigators. Adverse events were identified at each visit using research assistant interviews and subject reports. Increases of 2 points on a Udvalg for Kliniske Undersogelser (UKU) scale item[47] or scores of 3 on an item were classified as adverse events. Research psychiatrists quantified extrapyramidal symptoms using the Simpson Angus Scale[48] and incident akathisia using the Barnes Akathisia Scale.[49] Tardive dyskinesia was assessed using the Abnormal Involuntary Movement Scale,[50] applying modified Schooler-Kane criteria[51] without requiring a 2-week duration.

STATISTICAL ANALYSIS

Comparisons of baseline variables between the 2 treatment groups were made using χ^2 and *t* tests. Baseline factors that differed significantly between the 2 treatment conditions were identified to be used in sensitivity analyses of the efficacy results. We applied intent-to-treat principles to include all randomized subjects in the primary and secondary efficacy analyses. The primary analyses of treatment efficacy examined the longitudinal binary outcome of remission using mixed-effects logistic regression[52] with a random intercept that included treatment and time (ie, weeks from baseline) as fixed effects and a treatment × time interaction effect. The hypothesized difference in remission rates between the 2 treatment conditions over time was assessed by testing for the significance of an interaction between treatment assignment and time in the trial. The hypothesized age effect on treatment efficacy was tested by assessing the significance of a 3-way interaction between treatment, age, and time in a full model. The model used in the efficacy analysis was applied subsequently in each age group to assess the consistency of the efficacy results across the age groups. Also, site × treatment interactions were tested to evaluate site differences in efficacy.

Tolerability comparisons examined the incidence of adverse events and discontinuation rates due to poor tolerability in the 2 treatment arms and the 2 age groups. The young and old subgroups were compared for changes in metabolic parameters and for mean and maximum extrapyramidal symptoms scores during the trial. Secondary analyses compared remission rates between the 2 groups among subjects who completed the 12-week trial using the χ^2 test and changes in CGI-S score using mixed-effects linear regression models. Exploratory analyses for group differences in changes on HAM-D scores and SADS delusional rating item scores used mixed-effects linear regression.

We assessed data distribution for normality prior to conducting analyses. When necessary, data transformation or nonparametric tests were applied. Each statistical test used a 2-tailed α level of .05. Data are expressed as mean (standard deviation [SD]) except where noted.

SAMPLE SIZE AND POWER CALCULATIONS

Based on predicted remission rates of 40% in subjects who underwent combination therapy and 20% in subjects who underwent monotherapy, 260 subjects randomized into the 2 treatment groups would provide more than 80% power at a 2-tailed α level of .05. This power analysis was based on a simulation study using the mixed-effects model under an anticipated total attrition rate of 45% and a within-subject outcome correlation of 0.5 or less.

RESULTS

DISPOSITION OF SUBJECTS

Of the 375 patients who consented to participation, 65 (17.3%) were found not to meet criteria for unipolar MD with psychotic features. As illustrated in **Figure 1**, 51 of the 310 subjects who met psychiatric inclusion criteria either withdrew consent, met an exclusion criterion, or were excluded for other reasons prior to randomization. The intent-to-treat sample consisted of 259 subjects, of whom 129 were randomized to combination treatment and 130 to olanzapine plus placebo.

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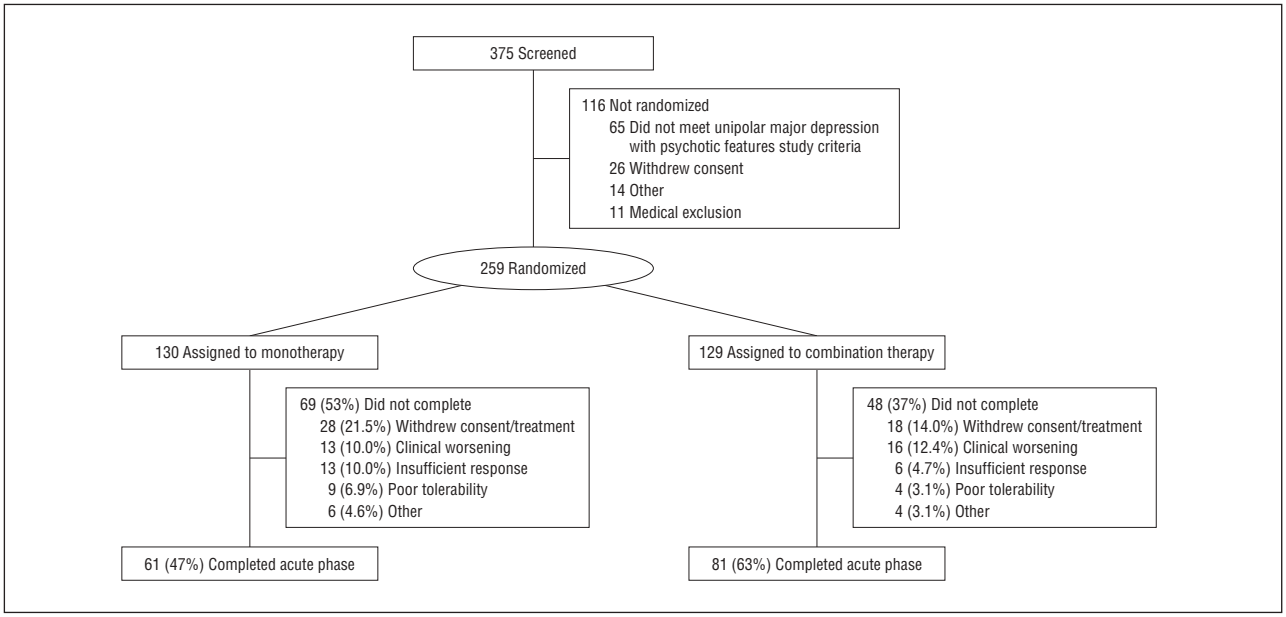

Figure 1. Study flowchart.

Table 1. Demographic and Clinical Characteristics of 259 Randomized Subjects

Characteristic	All Patients (N=259)	% Treatment With Olanzapine/Sertraline (n=129)	% Treatment With Olanzapine/Placebo (n=130)	χ^2	*df*	*P* Value
Age, mean (SD), y	58.0 (17.7)	57.4 (18.0)	58.5 (17.5)	t=0.51	257	.61
Age ≥60 y	54.8	55.0	54.6	0.005	1	.95
Race				6.21	2	.05
White	85.2	85.3	83.1			
African American	11.2	13.2	9.2			
Asian	4.6	1.6	7.7			
Male sex	35.9	35.7	36.2	0.007	1	.93
Married	40.9	37.2	44.6	3.0	4	.56
Inpatient	69.1	75.2	63.1	7.8	3	.05
First episode	30.1	28.7	31.5	0.39	1	.94
Mood congruent	56.0	54.6	57.4	0.2	1	.66
Suicide attempt (current)	18.5	21.7	15.4	1.7	1	.19
Test score, mean (SD)						
HAM-D	29.8 (5.2)	29.7 (5.0)	29.8 (5.5)	t=0.1	257	.92
BPRS	54.9 (10.1)	54.8 (9.7)	55.0 (10.6)	t=0.21	257	.83
CGI-S	5.1 (0.8)	5.1 (0.8)	5.1 (0.9)	t=0.29	257	.78
MMSE	26.9 (3.1)	27.0 (2.9)	26.9 (3.2)	t=−0.27	251	.79

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions, Severity of Illness Scale; HAM-D, 17-Item Hamilton Depression Scale; MMSE, Mini-Mental State Examination.

Clinical and sociodemographic characteristics of the randomized sample are presented in **Table 1**. The 2 groups were comparable for most major baseline variables, but differed by race and inpatient status at study entry. Among subjects in the olanzapine/sertraline group, 85.3% were white, 13.2% were African American, and 1.6% were Asian, compared with 83.1%, 9.2%, and 7.7%, respectively, in the olanzapine/placebo group (χ^2_1=6.21, P=.05). Frequencies of inpatient status at study entry were 75.2% in the olanzapine/sertraline group and 63.1% in the olanzapine/placebo group (χ^2_3=7.8, P=.05). The high baseline HAM-D and Brief Psychiatric Rating Scale scores and 18.5% frequency of suicide attempts during the current episode document the severity of illness in study participants. The mean ages of the 117 younger and 142 older subjects were 41.3 years (10.8 years) and 71.7 years (7.8 years), respectively.

DOSING

At the end of the study, mean daily doses of sertraline or placebo (168.9 mg [44.1 mg] vs 169.7 mg [35.0 mg]; t_{229}=0.15; P=.88) and olanzapine (14.3 mg [5.3 mg] vs 14.7 mg [4.7 mg]; t_{234}=0.55; P=.59) were comparable between the olanzapine/placebo and olanzapine/sertraline treatment groups, respectively. However, younger sub-

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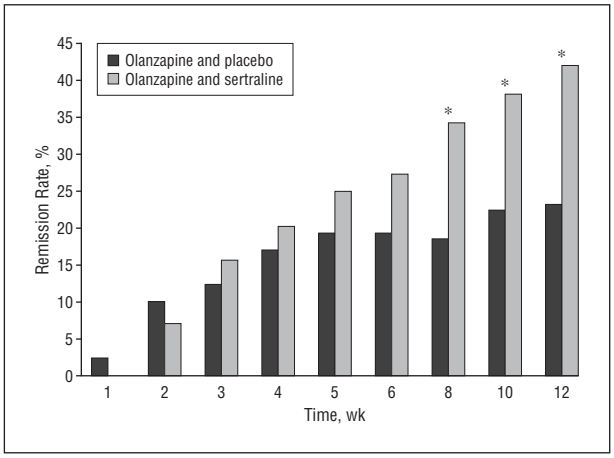

Figure 2. Remission rates in the intent-to-treat sample of 259 subjects randomized to olanzapine plus placebo vs olanzapine plus sertraline. *Statistically significant, using the Hochberg α level adjustments with a 2-sided family-wise α level of .05 from χ^2 analysis.[53]

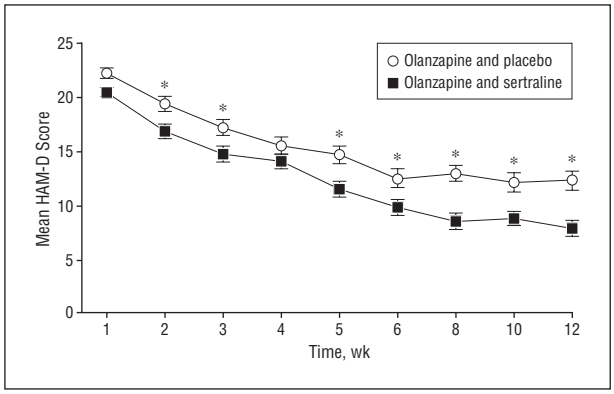

Figure 3. Hamilton Depression Scale (HAM-D) scores in subjects randomized to receive olanzapine plus placebo vs olanzapine plus sertraline. Overall treatment effect: $F_{1,1722}=14.32$, $P<.001$. *Statistically significant using the Hochberg α level adjustments[53] with a 2-sided family-wise α level of .05 from post hoc *t* tests.[54]

jects received significantly higher mean daily doses of olanzapine compared with older subjects (15.7 mg [4.7 mg] vs 13.4 mg [5.1 mg]; $t_{237}=3.53$; $P<.001$). Younger subjects also tended to receive higher mean daily sertraline/placebo doses (174.3 mg [34.1 mg] vs 165.7 mg [43.4 mg]; $t_{237}=1.72$; $P=.08$), but the difference was not statistically significant.

PRIMARY EFFICACY ANALYSIS

Olanzapine/Sertraline vs Olanzapine/Placebo

The treatment × time effect was statistically significant (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.12-1.47; $P<.001$), demonstrating that the increase in rates of remission over the course of the trial was greater in the olanzapine/sertraline group than in the olanzapine monotherapy group. The significantly greater efficacy of combination therapy was apparent between weeks 8 and 12 (**Figure 2**). Fifty-four of the 129 participants (41.9%) assigned to combination therapy were in remission at their last assessment compared with 31 of the 130 (23.9%) who received olanzapine monotherapy ($\chi^2_1=9.53$, $P=.002$). Expressed as number needed to treat, 1 additional patient achieved remission with combination treatment than with olanzapine monotherapy for every 5.5 patients treated. The effect of treatment × site interactions on efficacy were not significant (log-likelihood ratio = 4.1, $df=3$, $P=.25$). Treatment interactions with the hypothesized confounding variables of race (log-likelihood ratio = 0.0, $df=1$, $P>.99$) and inpatient status (log-likelihood ratio = 0.1, $df=1$, $P>.75$) were not significant either.

Analysis for Age Effect

The nonsignificant 3-way interaction between age, treatment, and time (OR, 1.05; 95% CI, 0.80-1.37; $P=.75$) indicated that the treatment × time effect was comparable across age groups. Subgroup analyses showed that the treatment × time effect was statistically significant and comparable in the younger (OR, 1.25; 95% CI, 1.05-1.50; $P=.02$) and older subgroups (OR, 1.34; 95% CI, 1.09-1.66; $P<.01$).

SECONDARY EFFICACY ANALYSES

Differences in CGI-S scores in the intent-to-treat sample significantly favored the olanzapine/sertraline group ($F_{1,1460}=5.63$; $P=.02$). Subjects allocated to olanzapine/sertraline in the intent-to-treat sample also had significantly lower HAM-D scores than those randomized to olanzapine/placebo at most points and during the trial overall ($F_{1,1722}=14.32$; $P<.001$) (**Figure 3**). However, decreases in the score for the SADS delusional item were comparable in the 2 treatment groups without significant differences at any point ($F_{9,1720}=1.25$; $P=.26$).

The planned analysis of study completers demonstrated that the remission rate was significantly greater in the subjects randomized to olanzapine/sertraline who continued to week 12 than in those randomized to olanzapine/placebo (66.7% vs 49.2%; $\chi^2_1=4.40$; $P=.04$).

ATTRITION AND TOLERABILITY

The overall attrition rate was 45.2% (Figure 1), with 88 of 117 noncompleters (75.2%) exiting the trial at or before the midpoint at week 6. Attrition was significantly lower in the olanzapine/sertraline than in olanzapine/placebo group (37.2% vs 53.1%; $\chi^2_1=6.58$; $P=.01$). The frequencies of reasons for attrition in the 2 treatment groups were statistically comparable. Fourteen percent of subjects randomized to olanzapine/sertraline compared with 21.5% of subjects randomized to olanzapine/placebo withdrew themselves from the study ($\chi^2_1=2.55$, $P=.11$); 12.4% vs 10.0% of subjects in the combination therapy vs the monotherapy group, respectively, were withdrawn because of significant clinical worsening ($\chi^2_1=0.38$, $P=.54$); 4.7% vs 10.0% were withdrawn because of insufficient response ($\chi^2_1=2.73$, $P=.1$); and 3.1% vs 6.9% discontinued treatment because of intolerable adverse effects ($\chi^2_1=1.98$, $P=.16$). Similarly, there were no significant treatment group differences in rates of adverse events that occurred in more than 10% of study subjects, with 54.3% of subjects treated with olanzapine/

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Table 2. Adverse Effects and Extrapyramidal Symptoms by Age

Adverse Effect	No. (%) All Patients (N=259)	Older Patients (n=142)	Younger Patients (n=117)	χ^2_1	*P* Value
Weight gain	140 (54)	64 (45)	76 (65)	10.21	.001
Somnolence/sedation	77 (30)	36 (25)	41 (35)	2.88	.09
Gastrointestinal effect	64 (25)	33 (23)	31 (27)	0.37	.55
Falling	36 (14)	23 (16)	13 (11)	1.39	.24
Orthostatic dizziness	33 (13)	21 (15)	12 (10)	1.19	.28
Pedal edema/edema	24 (9.3)	19 (13)	5 (4.3)	6.33	.01
Asthenia/lassitude	24 (9.3)	13 (9.2)	11 (9.4)	0.005	.95
Suicidal ideation	21 (8.1)	10 (7)	11 (9.4)	0.48	.49
Extrapyramidal symptoms, mean (SD)[a]					
Simpson Angus	2.1 (2.4)	2.9 (2.7)	1.2 (1.4)	$t_{222}=-6.59$	<.001
Peak Simpson Angus	3.3 (3.3)	4.3 (3.4)	2.2 (2.7)	$t_{257}=-5.72$	<.001
Akathisia[b]	20 (7.7)	9 (6.3)	11 (9.4)	0.845	.36
Tardive dyskinesia[c]	22 (8.5)	12 (8.5)	10 (8.6)	0.001	.98

[a] Although older subjects had significantly higher extrapyramidal symptom scores during the course of the trial, the interaction between age group and time was not significant ($F_{3,498}=1.89$, $P=.21$).
[b] Defined as a score of more than 1 on the objective scale of the Barnes Akathisia Scale and instances identified at clinical assessments.
[c] Defined as an increase of 2 or more on a single item of the Abnormal Involuntary Movement Scale or 2 points on more than 1 item at a single assessment.

sertraline meeting the UKU for significant weight gain (defined as an increase of ≥2.70 kg during the previous month) compared with 53.4% of subjects randomized to receive olanzapine/placebo ($\chi^2_1=0.005$, $P=.95$); 28.7% vs 30.8% of subjects in the combination therapy vs the monotherapy group, respectively, experienced somnolence/sedation ($\chi^2_1=0.14$, $P=.72$); 15.5% vs 12.3% experienced at least 1 fall ($\chi^2_1=0.55$, $P=.46$); and 15.5% vs 10.0% had orthostatic light-headedness ($\chi^2_1=1.76$, $P=.84$).

Serious adverse events involving increased suicidal thinking or behavior occurred in 5 subjects (2%), 4 of whom had been treated with olanzapine/sertraline, including a completed suicide at week 4 (3.1% vs 0.7%; Fisher exact, $P=.21$).

Table 2 summarizes the comparisons between younger and older subjects for the most common and clinically significant adverse events. Younger subjects were significantly more likely than older subjects to meet UKU criteria for significant weight gain (65.0% vs 45.1%, $\chi^2_1=10.21$, $P=.001$) but less likely to experience pedal edema (4.3% vs 13.4%, $\chi^2_1=6.33$, $P=.01$). There were no differences in incident akathisia or tardive dyskinesia by age group. Although older subjects had higher extrapyramidal symptom scores during the trial, the interaction between age group and extrapyramidal symptom severity was not significant ($F_{3,498}=1.89$, $P=.21$). Two younger subjects and 3 older subjects were prescribed adjunctive benztropine (Fisher exact test, $P>.99$). Rates of attrition due to poor tolerability in younger and older subjects were statistically comparable (4.3% vs 5.6%, respectively, $\chi^2_1=0.25$, $P=.62$).

Changes in metabolic parameters in the younger and older subjects from baseline to week 12 or termination are shown in **Figure 4**. Cholesterol and triglyceride concentrations increased significantly over time in both age groups ($F_{1,205}=34.85$, $P<.001$; and $F_{1,201}=22.11$, $P<.001$, respectively) without significant interactions with age ($F_{1,205}=0.89$, $P=.35$; and $F_{1,201}=0.74$, $P=.39$, respectively). Although a statistically significant increase in glucose concentrations was observed only in the younger adults, the interaction between age group and glucose increases was not significant ($F_{1,205}=1.97$, $P=.16$). Consistent with the UKU analysis, both age groups experienced significant increases in weight, with subjects younger than 60 years having significantly greater weight gain (6.5 kg [6.6 kg] vs 3.3 kg [4.9 kg], $F_{1,221}=11.10$, $P=.001$).

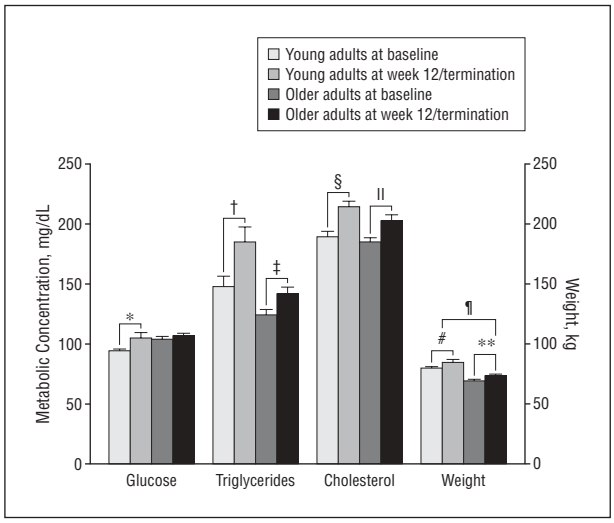

Figure 4. Metabolic values at baseline and week 12 (or termination) in young adult and older subjects. * Young age × time effect: $t_{205}=2.76$, $P=.006$; † young age × time effect: $t_{201}=3.73$, $P<.001$; ‡ old age × time effect: $t_{201}=2.88$, $P=.004$ (analysis was performed after log transformation owing to nonnormality); § young age × time effect: $t_{205}=4.58$, $P<.001$; ‖ old age × time effect: $t_{205}=3.73$, $P=.002$; ¶ interaction between time and age group: $F_{1,221}=11.1$; $P=.001$; # young age × time effect: $t_{221}=10.98$, $P<.001$; ** old age × time effect: $t_{221}=7.28$, $P<.001$.

COMMENT

Combination treatment with olanzapine plus sertraline was associated with a greater remission rate than with

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olanzapine monotherapy among patients with MD with psychotic features. The benefits of the combination therapy became more apparent as the 12-week trial progressed, with separation favoring olanzapine/sertraline from week 8 to the end of the trial. The higher categorical remission rate observed with olanzapine/sertraline compared with olanzapine/placebo was consistent with the significantly greater decreases in HAM-D scores observed with combination therapy.

Our hypothesis that pharmacotherapy would be more efficacious in the younger group was not supported. The greater efficacy of olanzapine/sertraline was comparable in both age groups; furthermore, the subgroup analyses demonstrated the efficacy of combination treatment compared with olanzapine alone in both the younger adults and geriatric subjects.

The rates and severity of adverse effects were similar in the 2 treatment groups. Older subjects did not demonstrate poorer overall tolerability. With the exception of a greater frequency of pedal edema, older subjects were not more likely to experience falls or sedation/somnolence or to have greater extrapyramidal symptoms.

Both age groups experienced significant increases in weight and both triglyceride and cholesterol levels. Fasting glucose levels increased significantly among younger adults only. The observed metabolic changes are consistent with those reported during olanzapine treatment among younger adults with schizophrenia.[55] In the absence of reliable measures of premorbid weight, we cannot estimate how much of the weight gained during the trial was due to the recovery of weight lost during the depressive episode. Our finding that older age was associated with less weight gain is consistent with other reports with atypical antipsychotic medications[56] and with olanzapine specifically.[57,58] In an analysis of data from a subgroup of subjects from this trial, we have shown that the lower weight gain experienced by older subjects is partially explained by their lower cumulative olanzapine dose.[59]

The positive findings must be considered in relation to the absence of an antidepressant monotherapy arm and previous combination pharmacotherapy trials for MD with psychotic features. Although most studies[12-14,16,60-62] report poor response rates of MD with psychotic features to TCA monotherapy, positive trials exist in patients with delusions that are congruent with depressed mood treated with high doses of amitriptyline[63] or imipramine.[64,65] The generally poor responsiveness to TCA monotherapy has contributed to the conceptualization of MD with psychotic features as a distinct entity[15,35,61] and the recommendation for combination therapy,[10,11] including in geriatric patients.[66] Nevertheless, a meta-analysis of the only 2 trials comparing combination therapy with antidepressant monotherapy did not demonstrate the superiority of combination treatment. Although this meta-analysis did demonstrate greater efficacy for combination therapy compared with antipsychotic monotherapy,[21] only 1 of the 2 trials that used an atypical antipsychotic medication[19] had positive results. Therefore, these results confirm and extend those of the meta-analysis.

The TCA studies cited previously[12-16] were shorter than the 12-week duration of our Study of Pharmacotherapy of Psychotic Depression (STOP-PD). It is possible that longer antidepressant monotherapy trials would result in higher remission rates. Our trial also differed in applying a criterion of 2 consecutive assessments to assure that remission was sustained, which may have contributed to the absence of separation between olanzapine/sertraline and olanzapine/placebo before week 8. Nevertheless, the HAM-D analysis demonstrated that combination treatment was statistically superior on HAM-D scores from week 2 to week 12 without differences between the treatment arms in changes of SADS delusional scores at any point. Therefore, the benefit of adding sertraline to olanzapine was specific for the rate of improvement of depressive symptoms.

The possible efficacy of selective serotonin reuptake inhibitor monotherapy for unipolar delusional depression was suggested by a reported intent-to-treat remission rate of 72% with 150 mg of sertraline per day compared with only 27% for 40 mg of paroxetine per day.[29] Methodological limitations in the trial design[67] and a separate report that patients with MD with psychotic features had a markedly lower response rate to 200 mg of sertraline per day than patients with nonpsychotic depression[68] highlight the need for additional trials to compare the efficacy of antidepressant monotherapy and combination treatment.

We have reported that prestudy antidepressant therapy was common among the first 100 study participants but that combination therapy was not.[24] Without accounting for prestudy treatment, we cannot assess whether resistance to prior antidepressant therapy influenced response to either treatment.

Illness severity of participants, with most recruited as inpatients, rendered randomization to placebo only and use of a placebo lead-in impractical. The low placebo response rates in previous trials of MD with psychotic features (0%[69] to 24.5%[19]) supported not including a placebo arm. Furthermore, the low early remission rate (<10% at week 2) decreases the likelihood that residual effects from pretrial treatment contributed to these results.

Although patients with major depression associated with hallucinations but not delusions meet *DSM-IV* criteria for MD with psychotic features, STOP-PD required the presence of delusions. Therefore, we cannot assess the efficacy of combination therapy for MD with psychotic features associated with hallucinations only. Also, the study focused on patients with unipolar MD with psychotic features and systematically excluded patients with histories that indicated periods of either mania or hypomania. Therefore, the results cannot be generalized to bipolar psychotic depression.

The 45.2% rate of attrition is a limitation. Attrition was comparable with the 48.1% rate reported in placebo-controlled antipsychotic trials[70] but higher than the approximately 35% overall rate estimated for antidepressant studies of nonpsychotic depression.[71] Although the severity of illness among study participants, with 69.1% entering as inpatients, presumably contributed to the high rate of attrition, the lack of systematic follow-up data from subjects who prematurely discontinued the study limits both generalizeability and our ability to apply the results to inform clinical practice.[71,72] Mixed-effects logis-

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tic regression was applied as the primary analytic strategy to allow for the use of all available data under the assumption of ignorable missingness.[71]

The significantly higher attrition rate among patients treated with olanzapine than those treated with olanzapine/sertraline may be attributable to both more frequent discontinuations by investigators owing to insufficient response and earlier self-withdrawal by individuals who were responding poorly to monotherapy. Also, considering symptoms to be caused by study medications rather than MD with psychotic features may have contributed to the numerically greater frequency of discontinuation attributed to intolerable adverse effects in subjects treated with olanzapine/placebo. The observation that 75.2% of instances of attrition occurred during the first 6 weeks indicates that the 12-week trial length does not explain the high attrition rate

This trial applied an innovative and rigorous approach to defining remission in MD with psychotic features. The remission criterion of 2 consecutive assessments has been used in a previous trial of MD with psychotic features[19] and a 2-week remission HAM-D cutoff of 10 points or lower has been used in ECT studies that included subjects with MD with psychotic features.[31,73] The current study added a systematic assessment to assure delusions were resolved as a criterion for remission. In the absence of studies that assessed for the absence of delusions at more than 1 assessment, determination that delusions were not present at the second HAM-D remission assessment was considered an appropriately stringent remission criterion.

This study's remission rates, greater than 30% at week 8 and rising to 41.9% at week 12, are comparable with those in studies summarized in recent meta-analyses comparing duloxetine[54] and venlafaxine[74] with selective serotonin reuptake inhibitors for nonpsychotic depression. The potential benefit of acute combination pharmacotherapy relative to ECT, which is generally considered the treatment of choice for MD with psychotic features, warrants consideration. The efficacy of ECT has been well established, with a response rate of 87% when bilateral ECT is administered in academic centers.[31] The public health significance of the acute efficacy of ECT is tempered by the rapid increase in depressive symptoms that occurs within days of completing a course of ECT[73,75] and the markedly lower ECT remission rates (30%-47%) reported in community settings.[76] Therefore, evidence that a pharmacological treatment is efficacious offers physicians an alternative to ECT that may be preferred by some patients for reasons of stigma and practicality. Nevertheless, the adverse metabolic effects of atypical antipsychotic medications are problematic. Further study of the optimal duration of continued combination therapy is needed to balance the high risk of early relapse of MD with psychotic features[77,78] against the metabolic abnormalities and significant weight gain associated with atypical antipsychotic medications.

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