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# A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL OF OLANZAPINE PLUS SERTRALINE VERSUS OLANZAPINE PLUS PLACEBO FOR PSYCHOTIC DEPRESSION -- THE STOP-PD STUDY

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## Abstract

**Context:** Expert guidelines recommend that the pharmacological treatment of major depression with psychotic features (MDpsy) combines antidepressant with antipsychotic medications. However, evidence for the efficacy of combination pharmacotherapy has been limited and without positive trials in geriatric patients.

**Objective:** (1) Compare remission rates in MDpsy associated with combination atypical antipsychotic medication plus a serotonin-reuptake-inhibitor antidepressant (SSRI) to remission associated with antipsychotic monotherapy; (2) Compare the efficacy and tolerability of treatment in younger versus older adults.

**Design and Context:** Twelve-week double-blind randomized controlled comparison of olanzapine plus sertraline to olanzapine plus placebo conducted on clinical services of four academic sites.

**Patients and Interventions:** 259 subjects with MDpsy randomized by age ≥60 on a 1:1 basis; mean age of 117 younger adults = 41.3(10.8) versus 71.7(7.8) in 142 geriatric participants; target doses of olanzapine 15-20 mg/day plus masked sertraline or placebo at 150-200 mg/day.

**Results:** Olanzapine/sertraline was associated with a higher remission rates over the trial than olanzapine/placebo (OR=1.28, 95% CI =1.12-1.47, p<.001). 41.9% of combination subjects were in remission at their last assessment compared to 23.9% of olanzapine monotherapy subjects ($\chi^2_1$= 9.53, p=.002). Combination therapy was comparably superior in younger adult (OR=1.25, 95% CI =1.05-1.50, p=.02) and older subjects (OR=1.34, 95% CI =1.09-1.66, p=0.01). Secondary efficacy measures also supported combination treatment. Overall tolerability was comparable across age groups, with age-related differences in specific side effects. Both age groups had significant increases in cholesterol and triglyceride levels, but statistically significant increases in glucose occurred only in younger adults (t=2.76, df=205, p=.01). Although both age groups experienced significant weight gain, younger adults gained significantly more weight (14.5±14.7 versus 7.3±10.9 pounds, F=11.10, df=1,221, p=.001).

**Conclusions:** Combination pharmacotherapy is efficacious for the treatment of MDpsy. Future research must determine the benefits of continuing atypical antipsychotic medications beyond twelve weeks against the associated metabolic effects.

**Trial Registration and URL:** Clinicaltrials.gov

Registry ID: NCT00056472

### Keywords

Major depressive disorder with psychotic features; Delusional Depression; Randomized Trial; Treatment

## Introduction

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

Expert guidelines[10,11] recommend treatment of MDpsy 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 MDpsy 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. A recent meta-analysis demonstrating that combination therapy was superior to antipsychotic monotherapy included the only three controlled trials available[21]. The limited evidence for the efficacy of combination treatment for MDpsy may contribute to the under-recognition of delusions in patients with major depression[22] and the low utilization of antipsychotic medications to treat MDpsy in community settings.[23,24].

In contrast to young adult trials[16], geriatric trials have not demonstrated greater efficacy for combined TCA/conventional antipsychotic therapy compared to TCA/placebo for either acute[25] or post-ECT continuation treatment[26], but did demonstrate poorer tolerability to combination therapy.

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

## Methods

### Participants

Patients 18 years of age or older admitted to the inpatient or ambulatory services of the four participating academic sites between December of 2002 and June of 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 consented subjects were assessed with the Structured Interview for Clinical Diagnosis (SCID)[32] to assure that DSM-IV-TR[1] criteria for unipolar MD-Psy were met. Inclusion

required the presence of at least one delusional belief --a fixed idea that was held contrary to the laws of logic—, a score of ≥2 on one of the conviction items of the Delusional Assessment Scale (DAS)[33], and a score of ≥3 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 one clearly defined delusion was required, with or without hallucinations, as studies of MDpsy have generally considered delusional depression and MDpsy to be synonymous[35]-37. The presence of moderately severe to severe depression was assured by requiring scores of ≥21 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 MDpsy 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 three months. Additional exclusion criteria were the presence of an unstable medical condition that might interfere with completion of the twelve-week trial, a neurological disease, such as Parkinson's disease, that might affect neuromuscular functioning, and ongoing need for medications known to cause depression or psychosis. Patients with known hyperlipedemia 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 TSH, folate and B12 levels, an electrocardiogram, and a toxicology screen to detect undisclosed illicit drug use. Finally, patients were excluded if they had received olanzapine 15 mg/day or more for a minimum of four weeks during the current episode or if they were benefiting from their current psychotropic medications regiment.

## 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 ≥60 with a block size of four. Subjects taking antidepressant or antipsychotic medications at entry had these tapered prior to randomization but a wash out period was not enforced because of the severity of illness anticipated in study participants. Subjects began 5mg/day of olanzapine and 50 mg/day of sertraline or matching placebo, with dose increases permitted every three days as tolerated. Frail elderly subjects initially received 2.5 mg of olanzapine and 25 mg of sertraline/placebo (1/2 of a 50 mg or placebo tablet). Olanzapine was administered openly and sertraline or placebo under double-blind conditions. An attempt was made to reach minimum doses of 10 mg/day of olanzapine and 100 mg/day of sertraline or placebo before the end of week one. Doses were increased to 15 mg/day of olanzapine and 150 mg/day of sertraline or placebo during week two, with further increases allowed to a maximum of 20 mg/day of olanzapine or 200 mg/day of sertraline, as tolerated, beginning in week three. Slower titration or temporary dose reductions of one or both medications was allowed if side effects were suspected; however, subsequent dose increases were required to attempt to achieve minimum daily target doses of 15 mg/day of olanzapine and 150 mg/day of sertraline or placebo. For data analytic purposes, the subject's dose was considered the last dose taken for a minimum of seven days. Adjunctive lorazepam up to 4 mg/day was allowed to control anxiety or agitation and benztropine up to 2 mg/day to control extrapyramidal symptoms. No other psychotropics were allowed.

## Study assessments

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

## Outcome criteria

Remission was defined as a Ham-D score of ≤10 at two consecutive assessments. The two consecutive assessments Ham-D criterion was applied to assure that remission from mood symptoms was sustained and to allow for comparability with ECT studies that typically use a two-week Ham-D criterion[31]. Remission also required the absence of delusions, (SADS delusional item scores of 1), at the second assessment of the two-assessment remission of depression interval. A one-week remission of delusions criterion was applied to make the remission of psychosis outcome compatible with the standard duration criterion used in MDpsy pharmacotherapy trials[21]. Subjects who were not delusional at both of two consecutive Ham-D ≤10 assessments were considered remitted at both time points; subjects who had been delusional at the first of the Ham-D ≤10 assessments were considered as remitted at the second assessment only and subjects who were not delusional at the first assessment but had SADS scores of >1 at the second were classified as not remitted at either assessment. A Ham-D cut-off of ≤10 was used because this cut-off has been a standard in geriatric antidepressant trials[45,46] and ECT studies[31]. Subjects who achieved a Ham-D score of ≤10 without delusions for the first time at week twelve were assessed again at week thirteen to determine whether the two-week duration criterion was met.

Investigators were allowed to withdraw subjects for either clinically significant worsening or for insufficient clinical improvement after five weeks of randomized treatment. Insufficient clinical response was operationally pre-defined as having both a CGI-improvement score of ≤ 2 (no or minimal improvement) and a CGI-S score of ≥4 (moderately or more severely ill). Discontinuations initiated by subjects were categorized as due to 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 UKU scale item[47] or scores of 3 on an item were classified as adverse events. Research psychiatrists quantified extrapyramidal symptoms (EPS) 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 (AIMS)[50], applying modified Schooler Kane criteria[51] without requiring a two-week duration.

## Data Analysis

Comparisons of baseline variables between the two treatment groups utilized Chi Square and t-tests. Baseline factors that differed significantly between the two treatment conditions were identified to be used in sensitivity analyses of the efficacy results. We applied intent to treat (ITT) 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 (i.e., weeks from baseline) as fixed effects and a treatment by time interaction effect. The hypothesized difference in remission rates between the two 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 three-way interaction between treatment, age and time in a full model. The model applied 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 by 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 two treatment arms and the two age groups. The young and old subgroups were compared for changes in metabolic parameters and for mean and maximum EPS scores during the trial. Secondary analyses compared remission rates between the two groups among subjects who completed the twelve-week trial using Chi Square and changes in CGI-S using mixed effects linear regression models. Exploratory analyses for group differences in changes on Ham-D scores and SADS delusional rating scale scores used mixed effects linear regression. Data distribution was assessed for normality prior to conducting analyses. When necessary, data transformation or non-parametric tests were applied. Each statistical test used a two-tailed alpha-level of 0.05.

### Sample Size and Power Calculations

Based on a predicted remission rates of 40% in combination therapy subjects and 20% in monotherapy subjects, 260 subjects randomized into the two treatment groups would provide >80% power at a two-tailed alpha 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.

## Results

### Disposition of Subjects

A total of 375 patients signed consent of whom 65 (13.4%) were found not to meet criteria for unipolar MDpsy. 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 ITT sample consisted of 259 subjects, of whom 129 were randomized to combination treatment and 130 to olanzapine plus placebo.

Clinical and sociodemographic characteristics of the randomized sample are described in Table 1. The two groups were comparable for most major baseline variables, but differed for race and inpatient status at study entry. Among subjects in the olanzapine/sertraline group, 85.3% were Caucasian, 13.2% African-American, and 1.6% Asian, compared to a distribution of these races of 83.1%, 9.2% and 7.7% in the olanzapine/placebo group ($\chi^2_1$=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 ($\chi^2_1$= 7.8, p=.05). The high baseline Ham-D and BPRS scores and 18.5% frequency of suicide attempts during the current episode document the severity of illness in study participants. The mean (S.D.) ages of the 117 younger adult and 142 older subjects were 41.3(10.8) and 71.7(7.8) respectively.

### Dosing

End of study daily doses of sertraline or placebo (168.9(44.1) mg. vs. 169.7(35.0) mg, t=0.15, df=229, p=.88) and olanzapine (14.3(5.3) mg versus 14.7(4.7) mg, t=.55, df =234, p=.59) were comparable between the two treatment groups. However, younger subjects received

significantly higher daily doses of olanzapine compared to older subjects (15.7(4.7) mg versus 13.5(5.1) mg, t= 3.45, df =234, p<.001). Younger subjects also tended to receive higher daily sertraline/placebo doses (174.3(34.1) mg versus 165.3(43.7) mg, t = 17.8, df =234, p=.08) but the difference was not statistically significant.

## Primary Efficacy Analysis

### Olanzapine/sertraline vs. olanzapine/placebo

The treatment by time effect was statistically significant (OR=1.28, 95% 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 eight and week twelve (Figure 2). Fifty-four of the 129 (41.9%) participants assigned to combination therapy were in remission at their last assessment compared to 31 of the 130 (23.9%) who received olanzapine monotherapy ($\chi^2_1 = 9.53$, p=.002). Expressed as number needed to treat, one additional patient achieved remission with combination treatment than olanzapine monotherapy for every 5.5 patients treated. Treatment by site interactions on efficacy were not significant (log-likelihood ratio = 4.1, df =3 p=.25). Also, 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.

## Analysis for age effect

The non-significant three-way interaction between age, treatment and time (OR = 1.05, CI=0.80, 1.37, p=.75) indicated that the treatment by time effect was comparable across age groups. Subgroup analyses showed that the treatment by time effect was statistically significant and comparable in the young (OR=1.25, 95% CI =1.05-1.50, p=.02) and old subgroups (OR=1.34, 95% CI =1.09-1.66, p<.01).

## Secondary Efficacy Analyses

CGI-S change scores in the ITT sample significantly favored the olanzapine/sertraline group (F= 5.63, df= 1,1460, p=.02). Also, in the ITT sample, subjects allocated to olanzapine/sertraline had significantly lower Ham-D scores than those randomized to olanzapine/placebo at most time points and during the trial overall (F=14.32, df=1,1722, p<.001) (Figure 3). However, decreases in SADS delusional item were comparable in the two treatment groups without significant differences at any time point (F=1.25, df=9,1720, p=.26).

The planned analysis of study completers demonstrated that the remission rate was significantly greater in the olanzapine/sertraline subjects who continued to week twelve than in the olanzapine/placebo completers (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 these 117 subjects (75.2%) exiting the trial at or before the week six midpoint. Attrition was significantly lower for the olanzapine/sertraline than in olanzapine/placebo subjects (37.2% vs. 53.1%, $\chi^2_1=6.58$, p=.01). The frequencies of reasons for attrition in the two treatment groups were statistically comparable. Attrition due to subject withdrawal was 14.0% for olanzapine/sertraline compared to 21.5% for olanzapine/placebo ($\chi^2_1 = 2.55$, p=0.11); for study discontinuation due to significant clinical worsening were 12.4% versus 10.0% ($\chi^2_1 = 0.38$, p =0.54); for insufficient response were 3.1% versus 6.9% ($\chi^2_1 = 2.73$, p=0.099); and for intolerable side effects were 3.1% versus 6.9%, ($\chi^2_1 = 1.98$, p=0.16). 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 olanzapine/

sertraline subjects meeting the UKU for significant weight gain (defined as an increase of 6 pounds or more during the previous month) compared to 53.4% of subjects randomized to olanzapine/placebo ($\chi^2_1$ =.005, p=0.95); 28.7% versus 30.8% respectively having somnolence/sedation ($\chi^2_1$ =.14, p=0.72); 15.5% versus 12.3% having experienced at least one fall ($\chi^2_1$ =.55, , p=0.46); and 15.5% compared to 10.0% having orthostatic light headedness ($\chi^2_1$ =1.76, p=0.84).

Serious adverse events involving increased suicidal thinking or behavior occurred in five subjects (2%). Four of these had been treated with olanzapine/sertraline, including a completed suicide at week four, and one event occurred with olanzapine/placebo (3.1% vs. 0.7%, Fisher's 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 age group differences in incident akathisia or tardive dyskinesia. Although older subjects had higher EPS scores during the trial, the interaction between age group and EPS severity was not significant (F=1.89, df=3,498, p=.212). Two younger subjects and three older subjects were prescribed adjunctive benztropine (Fisher's Exact p>.99). Rates of attrition due to poor tolerability in younger and older subjects were statistically comparable (4.3% vs 5.6%, $\chi^2_1$=.25, p=.62)

Changes in metabolic parameters in the younger and older subjects between baseline and week twelve or termination are described in Figure 4. Cholesterol and triglyceride levels increased significantly over time in both age groups (F=34.85, df=1,205, p<.001 and F=22.11, df =1,201, p<.001 respectively) without significant interactions with age (F=.89, df=1,205, p=.35. and F=.74, df=1,201, p=.39 respectively). Although a statistically significant increase in glucose levels was observed in the younger adults only, the interaction between age group and glucose increases was not significant (F=1.97, df=1,205, p=.16). Consistent with the UKU analysis, both age groups experienced significant increases in weight, with subjects below age 60 having significantly greater weight gain (14.5±14.7 pounds versus 7.3±10.9 pounds, F=11.10, df=1,221, p=.001).

## Comment

Combination treatment with olanzapine plus sertraline was associated with a greater remission rate than olanzapine monotherapy among patients with MDpsy. The benefits of the combination became more apparent over time during the twelve-week trial with separation favoring olanzapine/sertraline from week eight to the end of the trial. The higher categorical remission rate observed with olanzapine/sertraline compared to 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 to olanzapine alone in both the younger adults and geriatric subjects.

The rates and severity of adverse events were similar in the two 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, sedation/somnolence, or have greater extrapyramidal symptoms.

Both age groups experienced significant increases in weight and in 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[53]. In the absence of reliable measures of premorbid weight, we are unable to 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[54] and with olanzapine specifically[55,56]. 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[57].

The positive findings must be considered in relation to the absence of an antidepressant monotherapy arm and previous combination pharmacotherapy trials for MDpsy. Although most studies [12-14,16, 58-60] report poor response rates of MDpsy to TCA monotherapy, positive trials exist in patients with mood congruent delusions treated with high doses of amitriptyline[61] or imipramine[62,63]. The generally poor responsiveness to TCA monotherapy has contributed to the conceptualization of MDpsy as a distinct entity[15,35,59] and the recommendation for combination therapy[10,11], including in geriatric patients[64]. Nevertheless, a meta-analysis of the only two trials comparing combination therapy to antidepressant monotherapy did not demonstrate the superiority of combination treatment. Although this meta-analysis did demonstrate greater efficacy for combination therapy compared to antipsychotic monotherapy[21], only one of the two trials that used an atypical antipsychotic medication[19] was positive. Therefore, these results confirm and extend the results of the meta-analysis.

The TCA studies cited above were shorter then the twelve week duration of STOP-PD. It is possible that longer antidepressant monotherapy trials would result in higher remission rates. The present trial also differed in applying a two consecutive assessment criterion to assure that remission was sustained, which may have contributed to the absence of separation between olanzapine/sertraline and olanzapine/placebo before week eight. Nevertheless, the Ham-D analysis demonstrated that combination treatment was statistically superior on Ham-D scores from week two to week twelve without differences between the treatment arms in changes of SADS delusional scores at any time points. Therefore, the benefit of adding sertraline to olanzapine was specific for the rate of improvement of depressive symptoms.

The possible efficacy of SSRI monotherapy for unipolar delusional depression was suggested by a reported ITT remission rate of 72% with 150 mg/day of sertraline compared to only 27% for 40 mg/day of paroxetine[28]. Methodological limitations in the trial design[65] and a separate report that patients with MDpsy had a markedly lower response rate to 200 mg/day of sertraline than patients with nonpsychotic depression[66], highlight the need for additional trials to compare the efficacy of antidepressant monotherapy to combination treatment.

We have reported that pre-study antidepressant therapy was common among the first 100 study participants but that combination therapy was not[24]. Without accounting for pre-study 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 MDpsy trials (0%[66] to 24.5%[19]) supported not including a placebo arm. Furthermore, the low early remission rate (<10% at week two) decreases the likelihood that a carry-over from pre-trial treatment contributed to these results.

Although patients with major depression associated with hallucinations but not delusions meet DSM IV criteria for MDpsy, the STOP-PD study required the presence of delusions. Therefore, we are unable to assess the efficacy of combination therapy for MDpsy associated with hallucinations only. Also, the study focused on patients with unipolar MDpsy and systematically excluded patients with histories indicating 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 to the 48.1% reported in placebo controlled antipsychotic trials[68], but higher than the approximately 35% overall rate estimated for antidepressant studies of nonpsychotic depression[69]. 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[69, 70]. Mixed effects logistic regression was applied as the primary analytic strategy to allow for the use of all available data under the assumption of ignorable missingness[69].

The significantly higher attrition rate among olanzapine than olanzapine/sertraline subjects may be attributable to both more frequent discontinuations by investigators due to insufficient response and earlier self-withdrawal by individuals who were responding poorly to monotherapy. Also, considering symptoms as due to study medications rather than MDpsy may have contributed to the numerically greater frequency of discontinuation attributed to “intolerable side effects” in olanzapine/placebo subjects. The observation that 75.2% of instances of attrition occurred during the first six weeks indicates that the twelve-week trial length does not explain the high attrition rate

This trial applied an innovative and rigorous approach to defining remission in MDpsy. The two consecutive assessment remission criterion has been used in a previous MDpsy trial[19] and a two week remission Ham-D cutoff of ≤10 has been used in ECT studies that included MDpsy subjects[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 one assessment, determination that delusions were not present at the second Ham-D remission assessment was considered an appropriately stringent remission criterion.

The remission rates of greater than 30% at week eight that rose to 41.9% at week twelve are comparable to those in studies summarized in recent meta-analyses comparing duloxetine[71] and venlafaxine[72] to SSRI's for nonpsychotic depression. The potential benefit of acute combination pharmacotherapy relative to ECT, which is generally considered the treatment of choice for MDpsy, 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[73,74] and the markedly lower ECT remission rates (i.e., 30%-47%) reported in community settings[75]. 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 MDpsy[76,77] against the metabolic abnormalities and significant weight gain associated with atypical antipsychotic medications.

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## References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. American Psychiatric Association; Washington, DC: 2000. Text Revision
2. Johnson J, Horwath E, Weissman MM. The validity of major depression with psychotic features based on a community study. Arch Gen Psychiatry Dec;1991 48(12):1075–1081. [PubMed: 1845225]
3. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. Am J Psychiatry Nov;2002 159(11):1855–1861. [PubMed: 12411219]
4. Coryell W, Leon A, Winokur G, et al. Importance of psychotic features to long-term course in major depressive disorder. Am J Psychiatry Apr;1996 153(4):483–489. [PubMed: 8599395]
5. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. J Clin Psychiatry Sep; 2007 68(9):1411–1417. [PubMed: 17915981]
6. Post, F. The significance of affective symptoms in old age; a follow-up study of one hundred patients. Oxford University Press; New York: 1962.
7. Meyers BS, Greenberg R. Late-life delusional depression. J Affect Disord Sep-Oct;1986 11(2):133–137. [PubMed: 2948986]
8. Rothschild AJ, Samson JA, Bond TC, Luciana MM, Schildkraut JJ, Schatzberg AF. Hypothalamic-pituitary-adrenal axis activity and 1-year outcome in depression. Biol Psychiatry Sep 15;1993 34(6): 392–400. [PubMed: 8218607]

9. Vythilingam M, Chen J, Bremner JD, Mazure CM, Maciejewski PK, Nelson JC. Psychotic depression and mortality. Am J Psychiatry Mar;2003 160(3):574–576. [PubMed: 12611843]
10. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry Apr;2000 157(4 Suppl):1–45.
11. National Institute for Clinical Excellence. Depression: management of depression in primary and secondary care - NICE guidance. NICE; London: 2004. Vol Clinical Guideline 23
12. Friedman C, De Mowbray MS, Hamilton V. Imipramine (Tofranil) in depressive states: a controlled trial with inpatients. J Ment Sci Sep;1961 107:948–953. [PubMed: 13895237]
13. Hordern A, Holt NF, Burt CG, Gordon WF. Amitriptyline in Depressive States: Phenomenology and Prognostic Considerations. Br J Psychiatry Nov;1963 109:815–825. [PubMed: 14080576]
14. Avery D, Lubrano A. Depression treated with imipramine and ECT: the DeCarolis study reconsidered. Am J Psychiatry Apr;1979 136(4B):559–562. [PubMed: 426143]
15. Glassman AH, Roose SP. Delusional depression. A distinct clinical entity? Arch Gen Psychiatry Apr; 1981 38(4):424–427. [PubMed: 7212972]
16. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry Apr;1985 142(4):430–436. [PubMed: 3883815]
17. Kroessler D. Relative Efficacy Rates for Therapies of Delusional Depression. Convuls Ther 1985;1 (3):173–182. [PubMed: 11940821]
18. Parker G, Roy K, Hadzi-Pavlovic D, Pedic F. Psychotic (delusional) depression: a meta-analysis of physical treatments. J Affect Disord Jan;1992 24(1):17–24. [PubMed: 1347545]
19. Rothschild AJ, Williamson DJ, Tohen MF, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. J Clin Psychopharmacol Aug;2004 24(4):365–373. [PubMed: 15232326]
20. Andreescu C, Mulsant B, Rothschild A, Flint A, Meyers B, Whyte E. Pharmacotherapy of Major Depression with Psychotic Features: What is the Evidence? Psychiatric Annals 2006;36(1):31–38.
21. Wijkstra J, Lijmer J, Balk FJ, Geddes JR, Nolen WA. Pharmacological treatment for unipolar psychotic depression: Systematic review and meta-analysis. Br J Psychiatry May;2006 188:410–415. [PubMed: 16648526]
22. Rothschild AJ, Winer J, Flint AJ, Mulsant BH, Whyte EM, Heo M, Fratoni S, Gabriele M, Kasapinovic S, Meyers BS. Study of Pharmacotherapy of Psychotic Depression (STOP-PD) Collaborative Study Group: Missed Diagnosis of psychotic depression at 4 academic centers. J Clin Psychiatry 2008;69 (8):1293–1296. [PubMed: 18384244]
23. Mulsant BH, Haskett RF, Prudic J, et al. Low use of neuroleptic drugs in the treatment of psychotic major depression. Am J Psychiatry Apr;1997 154(4):559–561. [PubMed: 9090348]
24. Andreescu C, Mulsant BH, Peasley-Miklus C, et al. Persisting low use of antipsychotics in the treatment of major depressive disorder with psychotic features. J Clin Psychiatry Feb;2007 68(2): 194–200. [PubMed: 17335316]
25. Mulsant BH, Sweet RA, Rosen J, et al. A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. J Clin Psychiatry Aug;2001 62(8):597–604. [PubMed: 11561930]
26. Meyers BS, Klimstra SA, Gabriele M, et al. Continuation treatment of delusional depression in older adults. Am J Geriatr Psychiatry Fall;2001 9(4):415–422. [PubMed: 11739068]
27. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry Nov;2003 60(11):1079–1088. [PubMed: 14609883]
28. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry Jan;2001 158(1):131–134. [PubMed: 11136647]
29. Zanardi R, Franchini L, Gasperini M, Perez J, Smeraldi E. Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. Am J Psychiatry Dec;1996 153(12): 1631–1633. [PubMed: 8942464]
30. Flint AJ, Rifat SL. The treatment of psychotic depression in later life: a comparison of pharmacotherapy and ECT. Int J Geriatr Psychiatry Jan;1998 13(1):23–28. [PubMed: 9489577]

31. Petrides G, Fink M, Husain MM, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT Dec;2001 17(4):244–253. [PubMed: 11731725]
32. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Patient Edition (SCID-I/P). Biometrics Research Dept., New York State Psychiatric Institute; New York, N.Y.: 2001.
33. Meyers BS, English J, Gabriele M, et al. A delusion assessment scale for psychotic major depression: Reliability, validity, and utility. Biol Psychiatry Dec 15;2006 60(12):1336–1342. [PubMed: 17046724]
34. Spitzer, R.; Endicott, J. Schedule for Affective Disorders and Schizophrenia. 3rd ed.. Biometrics Research Dept., New York State Psychiatric Institute; New York, N.Y.: 1979.
35. Nelson JC, Bowers MB Jr. Delusional unipolar depression: description and drug response. Arch Gen Psychiatry Nov;1978 35(11):1321–1328. [PubMed: 30427]
36. Parker G, Hadzi-Pavlovic D, Hickie I, et al. Psychotic depression: a review and clinical experience. Aust N Z J Psychiatry Jun;1991 25(2):169–180. [PubMed: 1678937]
37. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry Jun;1992 149(6):733–745. [PubMed: 1590491]
38. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry Feb;1960 23:56–62. [PubMed: 14399272]
39. Williams JB, Kobak JA, Engelhardt N, Evans K, Lipsitz A, Olin J, Pearson J, Kalali A. The GRID-HAM-D standardization of the Hamilton Depression Rating Scale. Int Clin Psychopharacol 2008;23 (3):120–129.
40. Guy, W. ECDEU Assessment Manual for Psychopharmacology. US Dept. of Health, Education, and Welfare; Washington, DC: 1976. Clinical Global Impressions; p. 217-222.
41. Overall J, Gorham D. The Brief Psychiatric Rating Scale. Psychological Reports 1962;10:799–812.
42. Andreasen, N. The Scale for the Assessment of Positive Symptoms (SADS). Department of Psychiatry, University of Iowa; Iowa City: 1984.
43. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res Mar;1992 41(3):237–248. [PubMed: 1594710]
44. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res Nov;1975 12(3):189–198. [PubMed: 1202204]
45. Georgotas A, McCue RE, Hapworth W, et al. Comparative efficacy and safety of MAOIs versus TCAs in treating depression in the elderly. Biol Psychiatry Oct;1986 21(12):1155–1166. [PubMed: 3756264]
46. Reynolds CF 3rd, Frank E, Kupfer DJ, et al. Treatment outcome in recurrent major depression: a post hoc comparison of elderly (“young old”) and midlife patients. Am J Psychiatry Oct;1996 153(10): 1288–1292. [PubMed: 8831436]
47. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1–100. [PubMed: 2887090]
48. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19. [PubMed: 4917967]
49. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry May;1989 154:672–676. [PubMed: 2574607]
50. Guy, W. ECDEU Assessment Manual for Psychopharmacology. US Dept. of Health, Education, and Welfare; Washington, DC: 1976. Abnormal Involuntary Movement Scale (AIMS); p. 534-537.
51. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry Apr;1982 39(4):486–487. [PubMed: 6121550]
52. Hedeker D, Gibbons RD. A random-effects ordinal regression model for multilevel analysis. Biometrics Dec;1994 50(4):933–944. [PubMed: 7787006]
53. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med Sep 22;2005 353(12):1209–1223. [PubMed: 16172203]

54. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. J Clin Psychiatry May;2002 63 (5):425–433. [PubMed: 12019668]
55. Kinon BJ, Kaiser CJ, Ahmed S, Rotelli MD, Kollack-Walker S. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. J Clin Psychopharmacol Jun;2005 25(3):255–258. [PubMed: 15876905]
56. Lipkovich I, Citrome L, Perlis R, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. J Clin Psychopharmacol Jun;2006 26(3):316–320. [PubMed: 16702898]
57. Smith E, Rothschild AJ, Heo M, et al. Weight gain during olanzapine treatment for psychotic depression: effects of dose and age. Int Clin Psychopharmacol May;2008 23(3):130–137. [PubMed: 18408527]
58. Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL. Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry Feb;1977 34(2):197–204. [PubMed: 843179]
59. Charney DS, Nelson JC. Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry Mar;1981 138(3):328–333. [PubMed: 6110345]
60. Kocsis JH, Croughan JL, Katz MM, Butler TP, Secuda S, Bowden CL, Davis JM. Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. Am J Psychiatry May;1990 147(5):621–624. [PubMed: 2183635]
61. Spiker DG, Dealy RS, Hanin I, Weiss JC, Jupfer DJ. Treating delusional depressives with amitriptyline. J Clin Psychiatry May;1986 47(5):243–246. [PubMed: 3516978]
62. Bruijn JA, Moleman P, Mulder PGH, van den Broek WW. Treatment of mood-congruent psychotic depression with imipramine. Affect Disord 2001;66:165–174.
63. Birkenhager TK, van den Broek WW, Mulder PG, Moleman P, Bruijn JA. Efficacy of imipramine in psychotic versus nonpsychotic depression. J Clin Psychopharmacol April;2008 28(2):166–170. [PubMed: 18344726]
64. Alexopoulos GS, Katz IR, Reynolds CF 3rd, Carpenter D, Docherty JP, Ross RW. Pharmacotherapy of depression in older patients: a summary of the expert consensus guidelines. J Psychiatr Pract Nov; 2001 76:361–376. [PubMed: 15990550]
65. Rothschild AJ, Phillips KA. Selective serotonin reuptake inhibitors and delusional depression. Am J Psychiatry Jun;1999 156(6):977–978. [PubMed: 10360159]
66. Simpson GM, El Sheshai A, Rady A, Kingsbury SJ, Fayek M. Sertraline as monotherapy in the treatment of psychotic and nonpsychotic depression. J Clin Psychiatry Aug;2003 64(8):959–965. [PubMed: 12927014]
67. Spiker DG, Kupfer DJ. Placebo response rates in psychotic and nonpsychotic depression. J Affect Disord Jan-Feb;1988 14(1):21–23. [PubMed: 2963048]
68. Kemmler G, Hummer M, Widschwendter C, Fleischacker W. Dropout rates in placebo-controlled and active-controlled clinical trials of antipsychotic drugs: A meta-analysis. Arch Gen psychiatry Dec;2005 62:1305–1312. [PubMed: 16330718]
69. Leon AC, Mallinckodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: Methodological issues in psychopharmacology. Biol Psychiatry 2006;59:1001–1005. [PubMed: 16503329]
70. Lavori P. Clinical trials in psychiatry: Should protocol deviation censor patient data? Neuropsychopharmacology 1992;6(1):39–48. [PubMed: 1571068]
71. Thase ME, Pritchett YI, Ossanna MJ, Swindle RW, Xu J, Detke MJ. Efficacy of duloxetine and selective serotonin reuptake inhibitors: Comparisons as assessed by remission rates in patients with major depressive disorder. J Clin Psychopharmacol Dec;2007 27(6):672–676. [PubMed: 18004135]
72. Nemeroff CB, Entsuah R, Benattia I, Demitrack M, Slan DM, Thase ME. Comprehensive Analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol Psychatry 2008;63:424–434.
73. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA Mar 14;2001 285 (10):1299–1307. [PubMed: 11255384]
74. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med Mar 25;1993 328(12): 839–846. [PubMed: 8441428]

75. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry Feb 1;2004 55(3):301–312. [PubMed: 14744473]

76. Robinson DG, Spiker DG. Delusional depression. A one year follow-up. J Affect Disord Jul;1985 9 (1):79–83. [PubMed: 3160751]

77. Flint AJ, Rifat SL. Two-year outcome of psychotic depression in late life. Am J Psychiatry Feb;1998 155(2):178–183. [PubMed: 9464195]

78. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800–803.

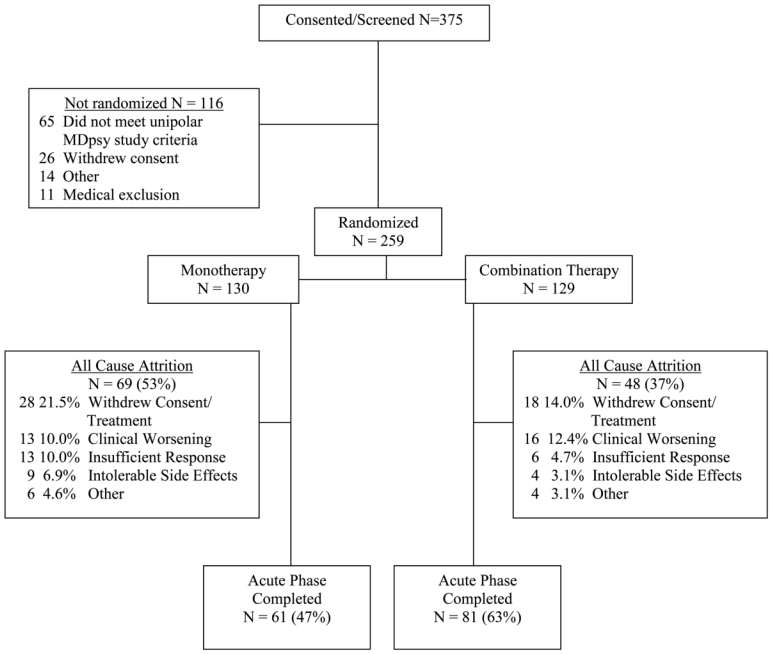
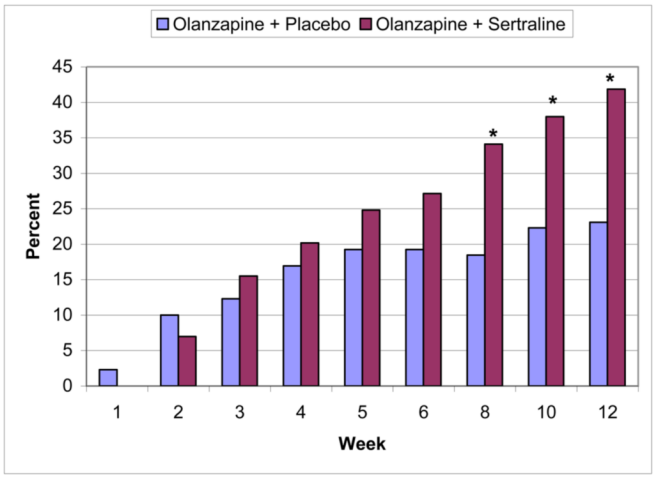



**Figure 1.**
CONSORT CHART



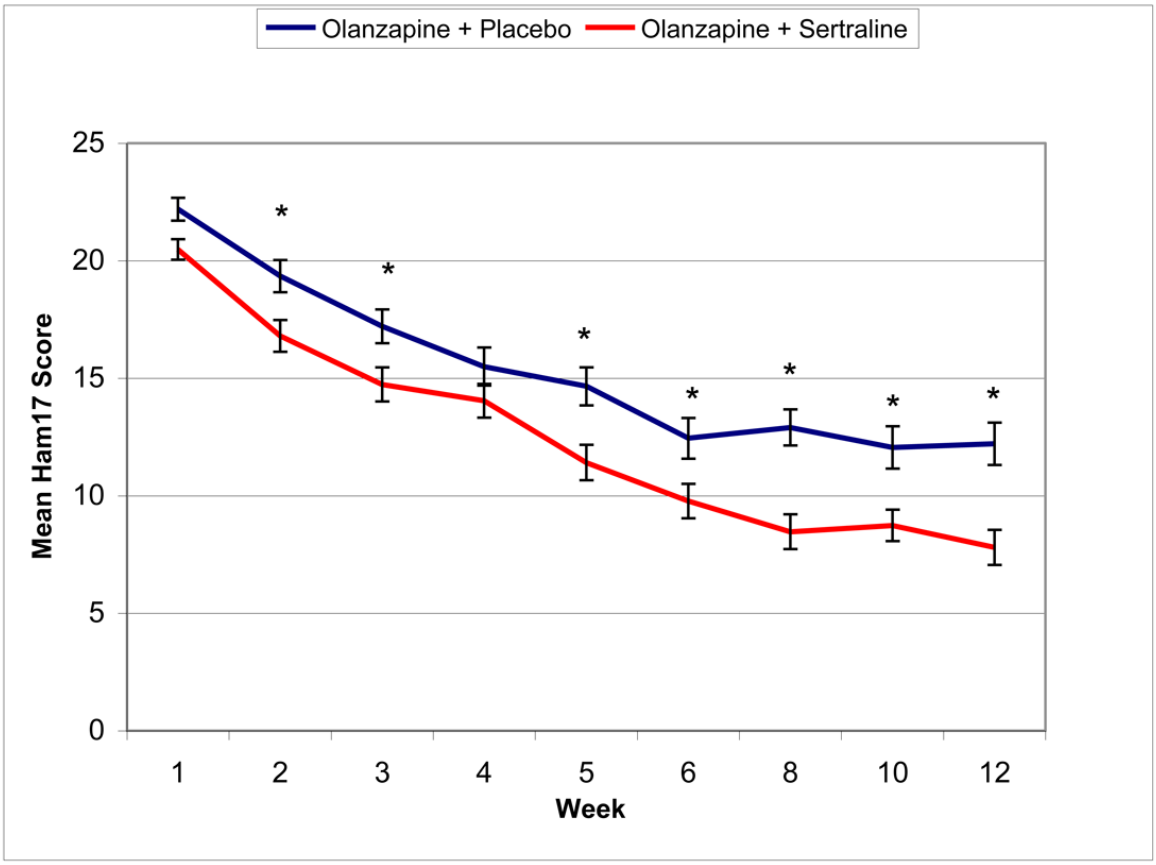

*Statistically significant using the Hochberg alpha-level adjustments with a two-sided family-wise alpha level = 0.05[78] from chi-square analysis.

| Week | $\chi^2$ | DF | P |
|---|---|---|---|
| 1 | 3.01 | 1 | 0.0827 |
| 2 | 0.76 | 1 | 0.3829 |
| 3 | 0.55 | 1 | 0.4572 |
| 4 | 0.45 | 1 | 0.5033 |
| 5 | 1.17 | 1 | 0.2789 |
| 6 | 2.27 | 1 | 0.1318 |
| 8 | 8.19 | 1 | 0.0042 |
| 10 | 7.56 | 1 | 0.0060 |
| 12 | 10.42 | 1 | 0.0012 |

**Figure 2.**

Remission Rates in the ITT sample of 259 Subjects Randomized To Olanzapine Plus Placebo Versus Olanzapine Plus Sertraline At Each Assessment

*Statistically significant using the Hochberg alpha-level adjustments with a two-sided family-wise alpha level = 0.05[78] from chi-square analysis.




Overall treatment effect: F(1,1722)=14.32, p<.001

*Statistically significant using the Hochberg alpha-level adjustments[78] with a two-sided family-wise alpha level = 0.05[71] from post-hoc t-tests.

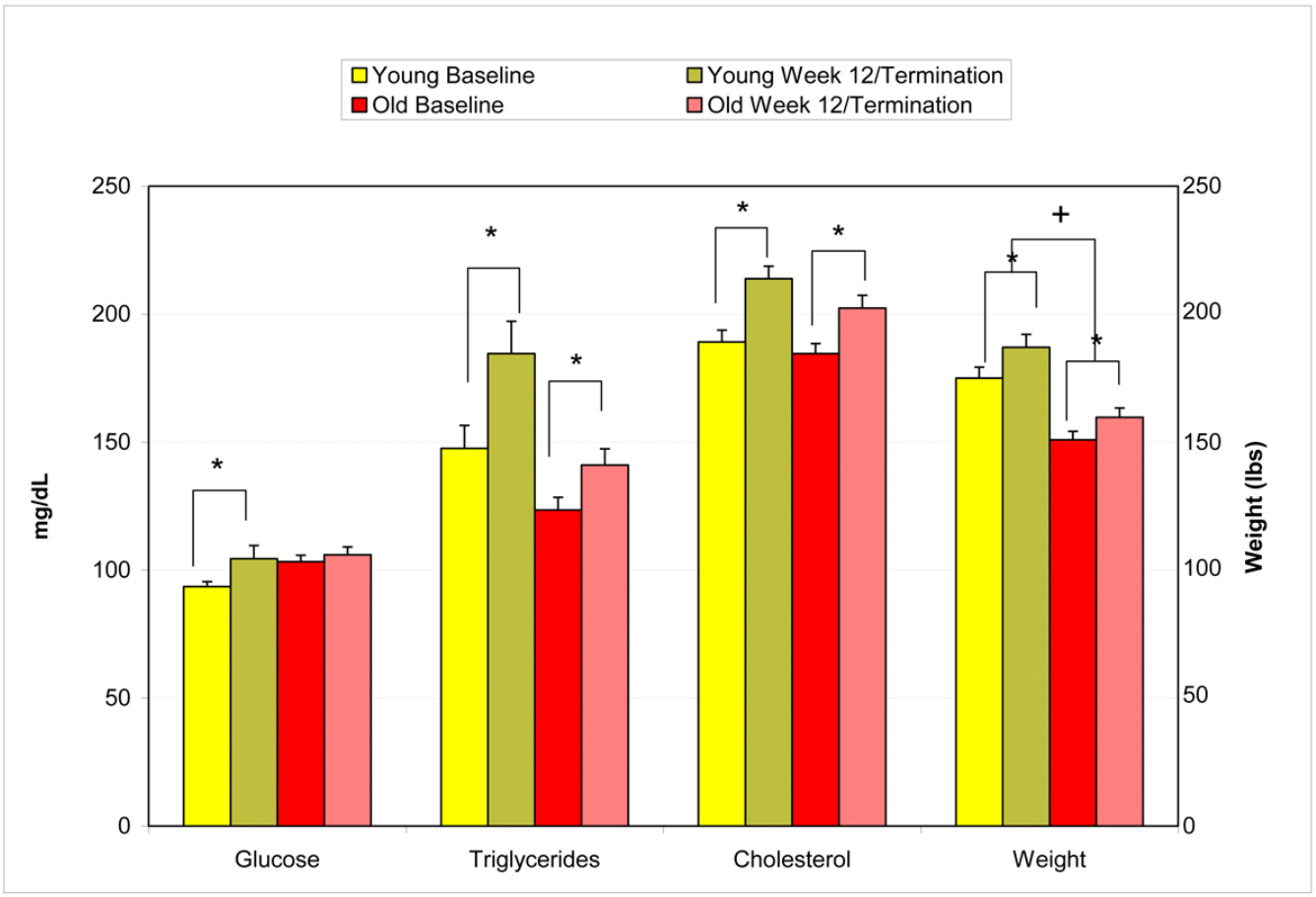
| Week | t-value | DF | P |
|---|---|---|---|
| 1 | 1.76 | 1722 | 0.0794 |
| 2 | 2.58 | 1722 | 0.0100 |
| 3 | 2.45 | 1722 | 0.0142 |
| 4 | 1.79 | 1722 | 0.0741 |
| 5 | 3.14 | 1722 | 0.0017 |
| 6 | 3.1 | 1722 | 0.0020 |
| 8 | 4.74 | 1722 | <.0001 |
| 10 | 3.87 | 1722 | 0.0001 |
| 12 | 4.79 | 1722 | <.0001 |

**Figure 3.**

Ham-D Scores during the Trial in Olanzapine plus Placebo versus Olanzapine plus Sertraline Subjects

Overall treatment effect: F(1,1722)=14.32, p<.001

*Statistically significant using the Hochberg alpha-level adjustments[78] with a two-sided family-wise alpha level = 0.05[71] from post-hoc t-tests.




*Glucose: Young Time Effect: t=2.76, df=205, p=.006

*Triglycerides: Old Time Effect: t=2.88. df=201, p=.004; Young Time Effect: t=3.73, df=201, p<.001. Statistics performed after log transformation due to non-normality.

*Cholesterol: Old Time Effect: t=3.73, df=205, p=.002; Young Time Effect: t=4.58, df=205, p<.001

*Weight: Old Time Effect: t=7.28, df=221, p<.001; Young Time Effect: t=10.98, df=221,p<.001; Statistics performed after log transformation due to non-normality.

+Interaction between time and age group: F=11.1, df=1,221, p=.001

**Figure 4.**

Metabolic Values at Baseline and Week 12 or Termination in Young Adult and Older Subjects

*Glucose: Young Time Effect: t=2.76, df=205, p=.006

*Triglycerides: Old Time Effect: t=2.88. df=201, p=.004; Young Time Effect: t=3.73, df=201, p<.001. Statistics performed after log transformation due to non-normality.

*Cholesterol: Old Time Effect: t=3.73, df=205, p=.002; Young Time Effect: t=4.58, df=205, p<.001

*Weight: Old Time Effect: t=7.28, df=221, p<.001; Young Time Effect: t=10.98, df=221,p<.001; Statistics performed after log transformation due to non-normality.

+Interaction between time and age group: F=11.1, df=1,221, p=.001

## Table 1

Demographic and Clinical Characteristics of 259 Randomized Subjects

| Socio-Demographic Variables | All (N=259) | Olanz/Sert (N=129) | Olanz/Pbo (N=130) | t or $\chi^2$ | df | P-Value |
|---|---|---|---|---|---|---|
| Age (Range = 18-93) | 58.0(17.7) | 57.4(18.0) | 58.5(17.5) | 0.51 | 257 | 0.61 |
| % ≥60 | 54.8% | 55.0% | 54.6% | 0.005 | 1 | 0.95 |
| Race | | | | 6.21 | 2 | 0.05 |
| % Caucasian | 85.2% | 85.3% | 83.1% | | | |
| % African American | 11.2% | 13.2% | 9.2% | | | |
| % Asian | 4.6% | 1.6% | 7.7% | | | |
| % Male | 35.9% | 35.7% | 36.2% | 0.007 | 1 | 0.93 |
| % Married | 40.9% | 37.2% | 44.6% | 3.0 | 4 | 0.56 |
| % Inpatients | 69.1% | 75.2% | 63.1% | 7.8 | 3 | 0.05 |
| **Clinical Variables** | | | | | | |
| First Episode | 30.1% | 28.7% | 31.5% | 0.39 | 1 | 0.94 |
| Mood Congruent | 56.0% | 54.6% | 57.4% | 0.2 | 1 | 0.66 |
| Suicide Attempt (current) | 18.5% | 21.7% | 15.4% | 1.7 | 1 | 0.19 |
| Ham-D (17) | 29.8(5.2) | 29.7(5.0) | 29.8(5.5) | 0.1 | 257 | 0.92 |
| BPRS (18) | 54.9(10.1) | 54.8(9.7) | 55.0(10.6) | 0.21 | 257 | 0.83 |
| CGI-S | 5.1(0.8) | 5.1(0.8) | 5.1(0.9) | 0.29 | 257 | 0.78 |
| MMSE | 26.9(3.1) | 27.0(2.9) | 26.9(3.2) | −0.27 | 251 | 0.79 |

* Results are Mean (SD) unless otherwise specified

**Table 2**

Adverse Events and EPS in 142 Older and 117 Younger Subjects

| | Total N (%) | Old (142) (N) (%) | Young (117) N (%) | t or $\chi^2$ | df | P-Value |
|---|---|---|---|---|---|---|
| Weight Gain | 140 (54) | 64 (45) | 76 (65) | 10.21 | 1 | 0.001 |
| Somnolence/sedation | 77 (30) | 36 (25) | 41 (35) | 2.88 | 1 | 0.09 |
| Gastrointestinal | 64 (25) | 33 (23) | 31 (27) | 0.37 | 1 | 0.55 |
| Fall | 36 (14) | 23 (16) | 13 (11) | 1.39 | 1 | 0.24 |
| Orthostatic Dizziness | 33 (13) | 21 (15) | 12 (10) | 1.19 | 1 | 0.28 |
| Pedal edema/edema | 24 (9.3) | 19 (13) | 5 (4.3) | 6.33 | 1 | 0.01 |
| Asthenia/Lassistude | 24 (9.3) | 13 (9.2) | 11 (9.4) | 0.005 | 1 | 0.95 |
| Suicidal Ideation | 21 (8.1) | 10 (7) | 11 (9.4) | 0.48 | 1 | 0.49 |
| Extrapyramidal Symptoms | | | | | | |
| Mean(SD) Simpson Angus* | 2.1(2.4) | 2.9(2.7) | 1.2(1.4) | −6.59 | 222 | <0.001 |
| Mean(SD) Peak Simpson Angus | 3.3(3.3) | 4.3(3.4) | 2.2(2.7) | −5.72 | 257 | <0.001 |
| Akathisia** | 20 (7.7) | 9 (6.3) | 11 (9.4) | 0.845 | 1 | 0.36 |
| Tardive dyskinesia*** | 22 (8.5) | 12 (8.5) | 10 (8.6) | 0.001 | 1 | 0.98 |

* Although older subjects had significantly higher EPS scores over the course of the trial, the interaction between age group and time was not significant (F=1.89, df=3,498, p=.212).

** Akathisia is defined as >1 on the objective scale of the Barnes Akathisia Scale and instances identified at clinical assessments.

*** Tardive dyskinesia was defined as an increase of 2 or more on a single item of the AIMS or two points on more than one item at a single assessment.