Published in final edited form as:
Psychiatry Res. 2012 May 30; 197(3): 221–226. doi:10.1016/j.psychres.2012.02.015.

Factors associated with non-completion in a double-blind randomized controlled trial of olanzapine plus sertraline versus olanzapine plus placebo for psychotic depression

Judith Weissman, Ph.D., J.D.[1], **Alastair Flint, M.B.**[2,3,4], **Barnett Meyers, M.D.**[1], **Samiran Ghosh, Ph.D.**[1], **Benoit Mulsant, M.D.**[2,5,6], **Anthony Rothschild, M.D.**[7], and **Ellen Whyte, M.D.**[6] **on behalf of the STOP-PD Study Group**

[1]Department of Psychiatry Weill Medical College of Cornell University and New York Presbyterian Hospital–Westchester Division

[2]Department of Psychiatry, University of Toronto

[3]Department of Psychiatry, University Health Network, Toronto

[4]Toronto General and Toronto Rehab Research Institutes, Toronto

[5]Centre for Addiction and Mental Health, Toronto

[6]Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine

[7]University of Massachusetts Medical School and UMass Memorial Health Care

Abstract

Objectives—High rates of attrition have been reported in randomized controlled trials of patients with severe psychiatric illness, including psychotic depression (MDpsy). The purpose of this study is to examine factors associated with overall attrition and with subtypes of attrition in the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD).

Design—Secondary analysis of data collected in a multi-site, randomized, placebo-controlled trial.

Setting—Clinical services of academic hospitals.

Participants—Two hundred and fifty-nine persons with MDpsy, aged 18–93 years.

Intervention—Random allocation to 12 weeks of treatment of either olanzapine plus sertraline or olanzapine plus placebo.

Measurements—Demographic and clinical variables associated with overall non-completion and sub-types of non-completion of randomized treatment.

Results—One hundred and seventeen (45.2%) subjects did not complete 12 weeks of randomized treatment. In a logistic regression analysis, inpatient entry status, olanzapine

Address for Correspondence: Dr. Alastair Flint, Toronto General Hospital, 200 Elizabeth St., 8 Eaton North–Room 238, Toronto, Ontario, M5G 2C4, Canada Phone: (416) 340-4788; Fax (416) 340-4198 alastair.flint@uhn.on.ca.

monotherapy, and higher cumulative medical burden were statistically significant independent predictors of overall non-completion. In a multinomial logistic regression model that examined predictors of subtypes of non-completion, subjects who entered the study as an inpatient were less likely to complete because of inadequate efficacy as determined by the investigator, and older subjects were less likely to complete because of poorer tolerability. Subjects who were assigned to olanzapine monotherapy, younger subjects, and subjects who entered the study as inpatients were less likely to complete because of reasons other than efficacy or tolerability.

Conclusions—Understanding factors that contribute to premature discontinuation in studies of MDpsy, and to the specific reasons for attrition, has the potential to improve the management of this disorder, as well as improve the design of future clinical trials of MDpsy.

Keywords

Major depressive disorder with psychotic features; Randomized controlled trial; Pharmacologic treatment; Attrition; Efficacy; Tolerability

1. Introduction

High attrition rates have been reported in placebo-controlled trials of patients with severe psychiatric illnesses, and particularly in trials of schizophrenia (Kemmler et al., 2005; Labelle et al., 1999). Major Depression with psychotic features (MDpsy) is also a severe, disabling disorder. It has poorer outcomes than major depression without psychotic features (Rothschild, 2003). Evidence-based expert guidelines recommend either electroconvulsive therapy (ECT) or the combination of an antidepressant medication and an antipsychotic medication (`combination treatment') for the treatment of MDpsy (American Psychiatric Association, 2003). Nevertheless, there has been limited evidence for the efficacy of combination therapy in MDpsy (Andreescu et al., 2006; Wjikstra et al., 2006). We recently reported that the combination of olanzapine and sertraline had greater efficacy than olanzapine plus placebo in the treatment of MDpsy, with 41.2% of subjects randomized to combination treatment achieving remission within twelve weeks (Meyers et al., 2009). However, 45.2% of the randomized subjects failed to complete the trial, raising the question of causes of attrition in this study. This question is important not only to researchers but also to clinicians: identifying baseline demographic and clinical factors that predict a low probability of completing a medication trial could lead to selecting ECT as an alternative evidence-based first-line treatment for these patients with MDpsy.

Factors related to patient, illness, and treatment can affect adherence with pharmacologic treatment and participation in clinical trials. Little is known about factors that contribute to non-completion in clinical trials of MDpsy or to poor adherence with pharmacotherapy in MDpsy. Previous randomized clinical trials comparing combination treatment with either antidepressant monotherapy or antipsychotic monotherapy in the acute treatment of MDpsy have reported non-completion rates of 12–59% (Anton & Burch, 1990; Rothschild et al., 2004; Spiker et al.,1985; Wijkstra et al., 2010), with the highest rate of non-completion being reported in the single study that included a placebo-only arm (Rothschild et al., 2004). In these published trials, reasons for non-completion were primarily lack of efficacy and adverse events. However, with the exception of the study by Spiker et al. (1985), none of these studies examined patient, illness, or treatment characteristics that could have contributed to non-completion. Spiker et al. (1985) found no difference between completers and non-completers on selected sociodemographic or clinical variables, but this analysis was limited by the small number of non-completers (n=7) and the relatively small sample size. Understanding factors that contribute to discontinuation in pharmacologic studies of MDpsy, and the specific reasons for attrition, has the potential to improve treatment adherence in

clinical practice, aid decision making in when to select ECT as an alternative treatment, and improve the design of future clinical trials for this disorder.

The Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was a NIMH-funded, 12-week randomized controlled trial that compared the efficacy and tolerability of olanzapine plus sertraline (`combination treatment') with olanzapine plus placebo (`monotherapy') in the treatment of adults aged 18 years or older with MDpsy (Meyers et al., 2009). We have reported in our initial analysis that efficacy was significantly higher and attrition was significantly lower in subjects randomized to olanzapine plus sertraline than in subjects randomized to olanzapine plus placebo (Meyers et al., 2009). However, to date, we have not determined whether other variables predict overall attrition or examined the predictors of specific types of attrition. Thus, the current study seeks to determine which sociodemographic and/or clinical variables were independently associated with overall non-completion and with specific types of non-completion in STOP-PD.

2. Methods

2.1 Participants

This study was approved by the Institutional Review Boards of the four participating sites and was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants, either directly or through IRB-approved surrogate consent procedures, after the study had been fully explained. Full details of the study's participants, design and methodology have been reported elsewhere (Meyers et al., 2009). To summarize, the study group consisted of inpatients and outpatients aged 18 years or older with MDpsy based on the Structured Clinical Interview for DSM-IV-TR (First et al., 2001). All subjects had to have a baseline 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1966) score of at least 21, a baseline Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer & Endicott, 1979) delusion severity score of at least 3 (`delusion definitely present'), and a score of 2 or higher on at least one of the baseline conviction items of the Delusion Assessment Scale (DAS; Meyers et al., 2006). Patients with any of the following were excluded: currently meeting or had met DSM-IV criteria for bipolar disorder, schizoaffective disorder, schizophrenia or other psychotic disorders; currently meeting DSM-IV criteria for body dysmorphic disorder or obsessive compulsive disorder; a history of substance abuse or dependence, including alcohol, within the last three months; a diagnosis of dementia or history of ongoing significant cognitive impairment (from informant report) prior to the index episode; an unstable medical illness; medical conditions (such as hypothyroidism), metabolic abnormalities (such as B12 deficiency), or medication (such as carbidopa) that could contribute to psychopathology, confound response to pharmacotherapy, or render participants unable to tolerate or complete the study; being pregnant, planning to get pregnant, or breast feeding; a documented history of being unable to tolerate either sertraline or olanzapine; failure to respond to olanzapine taken at a dose of 15 mg/day or greater for at least 4 weeks during the current depressive episode; or being sufficiently ill to require immediate open pharmacotherapy or ECT (e.g., due to imminent risk of suicide or refusal to eat).

2.2 Outcomes and measures

The main outcome in STOP-PD was remission, defined as a HAM-D score of 10 or lower at 2 consecutive assessments and the absence of delusions (SADS delusion item score of 1) at the second assessment. The protocol stipulated *a priori* that subjects would be discontinued from the study at the end of Week 5 if they had `significant clinical worsening' (worsening depression or psychosis or increased suicidality) or `insufficient clinical response', defined as having both a Clinical Global Impression (CGI; Guy, 1976)-improvement score of ≤ 2

(`no or minimal improvement') and a CGI-severity score of ≥4 (`moderately or more severely ill') after five weeks of randomized treatment. This protocol directive was made on clinical and ethical grounds, given the severity of the illness, the fact that half of the study group was not receiving antidepressant medication, and the availability of ECT as an alternative treatment for this severe illness. With the exception of this sub-group of patients, the goal was to have all other subjects complete 12 weeks of randomized treatment.

For this analysis, subjects were categorized as `completers' of 12 weeks of randomized treatment or `non-completers'. In order to examine the association between predictor variables and specific reasons for non-completion, the non-completers were further divided into four subgroups, based on the reason for discontinuation ascertained by the research psychiatrist at the time of the patient's discontinuation (i.e., before the blind was broken): (i) discontinued by the study investigator because of either `significant clinical worsening' or `insufficient clinical response' by the end of Week 5 (based on the aforementioned *a priori* criteria); (ii) discontinuation initiated by subjects, their families or their non-study physicians because of actual or perceived lack of efficacy; (iii) discontinuation because of poor tolerability (adverse effects or intercurrent medical events affecting tolerability); and (iv) discontinuation due to other reasons. Although non-completion described under categories (i) and (ii) both pertained to lack of treatment efficacy, we analyzed these categories separately, because they were intrinsically different: the first group was a `forced' discontinuation by the study investigator based on protocol-defined *a priori* criteria, whereas the second group was an `elective' discontinuation by the subject, surrogate, or non-study physician based on actual or perceived lack of efficacy. The fourth category, `other reason', comprised a variety of reasons for discontinuation, other than overt efficacy or tolerability; the most frequent reasons being `changed mind about participation in a research study', `refused further study medication', `lost to follow-up', and `protocol violation'. Each of these reasons had too few subjects to be analyzed separately; therefore they were combined into a heterogeneous group. Analyses were based on all subjects randomized to treatment. The four non-completer subgroups were mutually exclusive.

The baseline sociodemographic and clinical measures examined for their association with outcome were age, gender, race, Hispanic ethnicity, marital status, living arrangements, number of years of education, single versus recurrent index episode of depression, duration of index episode of depression, randomized treatment assignment, inpatient versus outpatient status at the time of consent, consent status (subject consent versus surrogate consent), and baseline scores of the following rating scales: 17-item HAM-D, SADS delusion severity, Brief Psychiatric Rating Scale (BPRS; Overall & Graham, 1962), the first 5 items of the Suicide Ideation Scale (Beck et al., 1979), Mini Mental State Examination (MMSE; Folstein et al.,1975) (a measure of global cognitive function), and Cumulative Illness Rating Scale-Geriatrics (CIRS-G; Miller et al., 1992) (a measure of cumulative medical burden).

2.3 Data analysis

Chi-square tests (for categorical variables) and analysis of variance (for continuous variables) were used to examine the relationship of each of independent variable with i) completion and overall non-completion, and ii) completion and the 4 subgroups of non-completion (tables 1 and 2). Variables with a main effect p-value < 0.1 were chosen for inclusion in the separate logistic regression models that examined the independent association of predictor variables with i) overall non-completion, and ii) the 4 sub-groups of non-completion, with the completer group serving as the reference. Variables with a p-value < 0.05 were considered statistically significant independent predictors of non-completion and remained in the final model.

3. Results

The study group consisted of 259 subjects (n=117 aged 18–59 and n=142 aged 60 years or older), of whom 129 were randomized to combination treatment and 130 to monotherapy. Clinical and sociodemographic characteristics of this sample have been previously described (Meyers et al., 2009). Table 1 provides descriptive data for each of the independent variables in this study.

One hundred and seventeen (45.2%) subjects did not complete the 12 weeks of randomized treatment. Thirty seven (14.3%) subjects did not complete because of the *a priori* Week 5 discontinuation criteria; 20 (7.7%) subjects did not complete because of discontinuation initiated by subjects, their families, or their non-study physicians because of actual or perceived lack of efficacy; 13 (5.0%) did not complete because of poor tolerability (n=11 due to adverse effects and n=2 due to intercurrent medical events affecting tolerability); and 47 (18.2%) did not complete for `other reasons'. Seventy five percent of discontinuations (n= 88/117) occurred during the first 6 weeks of the study.

With respect to the univariate analyses, inpatient status at study entry (χ^2_1=7.50, p = 0.006), surrogate consent (χ^2_1=6.28, p = 0.01), olanzapine monotherapy (χ^2_1=6.58, p = 0.01), and a higher CIRS-G total score (t_{255}=2.55, p=0.04) were associated with overall non-completion at p<0.1 levels of significance (Table 1). In a logistic regression model demonstrating good fit (Likelihood ratio χ^2_1 = 27.76, p <0.001) comparing completion versus overall non-completion as the outcome, inpatient entry status (Wald χ^2_1= 11.35, p<0.001; OR[95%CI]=2.76[1.52–4.98]), olanzapine monotherapy (Wald χ^2_1= 8.76, p=0.003; OR[95%CI]=2.22[1.32–3.84]), and higher CIRS-G total score (Wald χ^2_1= 5.39, p=0.02; OR[95%CI]=1.08[1.01–1.15]) were statistically significant independent predictors of overall non-completion.

Univariate analyses examining variables associated with sub-groups of non-completion found a main effect at the p<0.1 level of significance for marital status (χ^2_{12}=22.51, p=0.03), inpatient versus outpatient status at study entry (χ^2_4=13.35, p=0.009), randomized treatment assignment (χ^2_4=8.13, p=0.08), consent status (χ^2_4=8.91, p=0.06), age (F4,254= 4.41, p=0.001), and HAM-D score (F 4,254=2.43, p=0.04) (Table 2). In a multinomial logistic regression model that demonstrated good fit (likelihood ratio, χ^2_{12}=42.19, p<0.001), in which subgroups of non-completion were compared with completion, subjects were more likely to: meet the Week-5 discontinuation criteria if they entered the study as an inpatient (Wald χ^2_1= 9.32,p=0.002); discontinue because of poor tolerability if they were older (Wald χ^2_1= 4.11,p=0.04); or discontinue because of `other reasons' if they were assigned to olanzapine monotherapy (Wald χ^2_1= 6.45, p=0.01), were younger (Wald χ^2_1= 4.99, p=0.02), or entered the study as an inpatient (Wald χ^2_1= 4.10, p=0.04) (Table 3).

Interestingly, we found in a follow-up analysis that inpatient status at study entry was significantly associated with surrogate consent (χ^2_1= 12.11, p<0.001) and with higher baseline HAM-D scores (t_{257}=4.43, p<0.001), SADS delusion severity item scores (t_{257}=4.35, p<0.001), BPRS scores (t_{257}=4.78, p<0.001), and scores on the Suicide Ideation Scale's first five items (t_{253}=3.78, p<0.001) compared to outpatients/day patients. Inpatient status at study entry was not significantly associated with age.

4. Discussion

To summarize our findings, randomization to olanzapine monotherapy, inpatient status at study entry, and a higher level of physical illness were independent predictors of non-completion overall. Finer-grained analyses found that inpatient status was associated with discontinuation because of both insufficient clinical improvement by week 5 of the study

and `other reasons', whilst olanzapine monotherapy was associated with discontinuation because of `other reasons'. In addition, even though age was not significantly associated with non-completion overall, older age was associated with discontinuation because of poor tolerability, whereas younger age was associated with discontinuation because of `other reasons'.

As previously mentioned, more frequent non-completion in patients assigned to monotherapy was reported earlier (Meyers et al., 2009). Our current finding expands on this earlier report: non-completion in patients receiving monotherapy was found to be due to `other reasons', a residual, heterogeneous category comprising reasons other than poor efficacy or poor tolerability. Nevertheless, given than olanzapine monotherapy was less efficacious than combination therapy (Meyers et al., 2009), it is conceivable that patients receiving monotherapy were less satisfied with the treatment they were receiving and `voted with their feet' by changing their minds about participation in the study.

Since older and younger subjects' reasons for non-completion of the study had opposing associations with age, there was no age effect on overall non-completion. The association between younger age and non-completion for reasons other than poor efficacy or poor tolerability is consistent with similar findings in a study of outpatients with major depressive disorder (Warden et al., 2007). Younger patients with major depression may possibly be less committed to ongoing study participation (Warden et al., 2007), which would be consistent with the non-completion for `other reasons' in our study. Less commitment to study participation may make it difficult to overcome logistical hurdles such as travelling a distance to the study site or willingness to work within the confines of protocol specifications. On the other hand, we found that older subjects' non-completion was related to poor tolerability. This is not surprising given that age-related pharmacokinetic and pharmacodynamic changes, in the context of greater medical burden in later life, render older persons more vulnerable to medication adverse effects (Flint, 2001). However, it is important to note that only 5.6% of older subjects discontinued the study because of tolerability issues: the vast majority of older subjects were able to tolerate doses of sertraline and olanzapine comparable to doses tolerated by younger subjects (Meyers et al., 2009).

Over two-thirds (69%) of the subjects began the study on an inpatient basis; these subjects were less likely to complete randomized treatment because of both meeting the *a priori* criteria for discontinuation at week 5 (i.e. insufficient efficacy) and `other reasons'. Overall, the study group consisted of severely ill patients. Not surprisingly, inpatients were more severely ill than outpatients on several symptomatic measures, and this may have contributed to their higher likelihood of non-completion due to insufficient clinical response or clinical worsening. Severity of depressive symptoms and surrogate consent were associated with overall non-completion in the univariate model but not in the regression models. Both variables were significantly associated with inpatient status, which was a more robust predictor of non-completion than depression severity or surrogate consent.

Burden of physical illness predicted non-completion overall, but did not reach the predetermined level of significance for inclusion in the multinomial regression model that examined sub-types of non-completion. However, examination of Table 2 shows a gradient of increasing CIRS-G scores from completion, through non-completion because of efficacy issues, to non-completion because of poorer tolerability. This is consistent with other studies that have shown that medical burden can be associated with poorer outcome of treatment of depression (Katon et al., 2002; Oslin et al., 2002).

One-third of `non-completers' discontinued the study due to the protocol-prescribed investigator-initiated removal of subjects at the end of week 5. This event could have

affected the frequency of non-completion in other groups, for example by contributing to fewer patient-initiated withdrawals because of lack of efficacy or fewer patients changing their mind about participating in the study. Nevertheless, it allowed us to ascertain clinical factors associated with lack of improvement after 5 weeks of pharmacologic treatment; these factors can be used by clinicians to identify patients in whom ECT could be considered as first-line treatment if rapid improvement is desired. An additional limitation of this analysis is the lack of systematic follow-up of patients who withdrew or were withdrawn from protocolized treatment. Thus, we do not know to what extent patients elected to continue with pharmacotherapy outside of the study, or opted for ECT, or stopped treatment altogether; we also do not know the patient characteristics that would have led to discontinuation of protocolized treatment in favor of pursuing an alternative treatment such as ECT.

Although this study was characterized by a high rate of non-completion, this rate was comparable to rates reported in other double-blind studies of the acute pharmacologic treatment of MDpsy (Rothschild et al., 2010) and RCTs of antipsychotic treatment of schizophrenia that included placebo (Kemmler et al., 2005, Labelle et al., 1999). Strengths of the study included the randomized controlled double-blind design, the rigorous approach to ensuring that all patients had delusions (as opposed to other abnormal thoughts such as overvalued ideas, obsessions, or non-delusional worries), and close attention to ensuring inter-rater reliability in the completion of study measures throughout the period of the study (Meyers et al., 2009). The 12-week duration of the study was a strength in maximizing the time available for remission; this duration, which is longer than that of most other studies of the treatment of MDpsy, did not explain the high rate of non-completion, since 75% of discontinuations occurred during the first 6 weeks of the study.

In summary, this is the first study to examine predictors of non-completion of the pharmacologic treatment of MDpsy. We identified predictors of non-completion due to limited efficacy, poor tolerability, and reasons other than efficacy or tolerability. These findings provide important clinical information about which patients may be most vulnerable to premature discontinuation of pharmacologic treatment.

Acknowledgments

We thank Dora Kanellopoulos, M.A. for assistance with data management.

Supported by USPHS grants MH 62446, MH 62518, MH 62565, and MH 62624 from the National Institute of Mental Health.

References

American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). American Journal of Psychiatry. 2000; 157(suppl):1–45.

Andreescu C, Mulsant B, Rothschild AJ, Flint AJ, Meyers B, Whyte E. Pharmacotherapy of major depression with psychotic features: what is the evidence? Psychiatric Annals. 2006; 36(1):31–38.

Anton RF, Burch EA. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. American Journal of Psychiatry. 1990; 147:1203–1208. [PubMed: 2201223]

Beck AT, Kovacs M, Weissman M. Scale for suicide ideation. Journal of Consulting and Clinical Psychology. 1979; 47:343. [PubMed: 469082]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Patient Edition (SCID-I/P). Biometrics Research Department; New York: 2001.

Flint, AJ. Psychopharmacological management of the medically ill older person. In: Melding, PS.; Draper, B., editors. Geriatric Consultation Psychiatry. Oxford University Press; Oxford: 2001. p. 267-294.

Folstein M, Folstein S, McHugh P. “Mini mental state”: a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]

Guy, W. Clinical Global Impressions. US Department of Health, Education, and Welfare; Washington, DC: 1976. ECDEU Assessment Manual for Psychopharmacology; p. 217-222.

Hamilton M. A rating scale for depression. Journal of Neurology Neurosurgery and Psychiatry. 1960; 23:56–62.

Katon W, Russo J, Frank E, Barrett J, Williams JW Jr, Oxman T, Sullivan M, Cornell J. Predictors of nonresponse to treatment in primary care patients with dysthymia. General Hospital Psychiatry. 2002; 24:20–27. [PubMed: 11814530]

Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active control clinical trials of antipsychotic drugs: a meta-analysis. Archives of General Psychiatry. 2005; 62:1305–1312. [PubMed: 16330718]

Labelle A, Boulay LJ, Lapierre YD. Retention rates in placebo- and nonplacebo-controlled clinical trials of schizophrenia. Canadian Journal of Psychiatry. 1999; 44:887–892.

Meyers BS, English J, Gabriele M, Peasley-Miklus C, Moonseong H, Flint AJ, Mulsant BH, Rothschild AJ, the STOP-PD Study Group. A delusion assessment scale for psychotic major depression: reliability, validity, and utility. Biological Psychiatry. 2006; 60:1336–1342. [PubMed: 17046724]

Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte E, Peasley-Miklus C, Heo M, Papademetriou E, Leon A, the STOP-PD Study Group. A double-blind randomized controlled trial of olanzapine plus sertraline versus olanzapine plus placebo for psychotic depression - the STOP-PD study. Archives of General Psychiatry. 2009; 66:838–847. [PubMed: 19652123]

Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant BH, Reynolds CF 3d. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Research. 1992; 41:237–248. [PubMed: 1594710]

Oslin DW, Datto CJ, Kallan MJ, Katz IR, Edell WS, TenHave T. Association between medical comorbidity and treatment outcomes in late-life depression. Journal of the American Geriatrics Society. 2002; 50:823–828. [PubMed: 12028167]

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962; 10:799–812.

Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Andersen SW, Van Campen LE, Sanger TM, Tollefson GD. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. Journal of Clinical Psychopharmacology. 2004; 24:365–373. [PubMed: 15232326]

Rothschild AJ. Challenges in the treatment of depression with psychotic features. Biological Psychiatry. 2003; 53:680–690. [PubMed: 12706954]

Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, Perel JM, Rossi AJ, Soloff PH. The pharmacological treatment of delusional depression. American Journal of Psychiatry. 1985; 142:430–6. [PubMed: 3883815]

Spitzer, RL.; Endicott, J. Schedule for Affective Disorders and Schizophrenia. third edition. New York State Psychiatric Institute, Biometrics Research; New York: 1979.

Warden D, Trivedi MH, Wisniewski SR, Davis L, Nierenberg AA, Gaynes BN, Zisook S, Hollon SD, Balasubramani GK, Howland R, Fava M, Stewart JW, Rush AJ. Predictors of attrition during initial (citalopram) treatment for depression: a STAR*D report. American Journal of Psychiatry. 2007; 164:1189–1197. [PubMed: 17671281]

Wijkstra J, Burger H, van den Broek WW, Birkenhäger TK, Janzing JG, Boks MP, Bruijn JA, van der Loos ML, Breteler LM, Ramaekers GM, Verkes RJ, Nolen WA. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. Acta Psychiatrica Scandinavia. 2010; 121:190–200.

Wijkstra J, Lijmer J, Balk FJ, Geddes JR, Nolen WA. Pharmacological treatment for unipolar psychotic depression: systematic review and meta-analysis. British Journal of Psychiatry. 2006; 188:410–415. [PubMed: 16648526]

Psychiatry Res. Author manuscript; available in PMC 2013 May 30.

Table 1

STOP-PD Subjects' Demographic and Clinical Characteristics Associated with Study Completion and Non-Completion

Independent Variable	Completer (n=142) Mean (SD) (Range)	Non-Completer (n=117) Mean (SD) (Range)	t	df	P
Age (years)	57.7 (16.9) (19–86)	58.3 (18.7) (18–93)	0.29	257	0.77
Education (years)	12.6 (3.3) (11–20)	12.4 (3.6) (10–20)	−0.43	254	0.67
Duration of current depressive episode (months)	12.8 (30.1) (1–264)	10.9 (18.4) (1–120)	−0.59	254	0.55
SADS delusion severity score	5.7 (0.9) (3–7)	5.8 (0.9) (3–7)	0.63	257	0.52
MMSE total score	27.0 (3.1) (13–30)	26.8 (3.0) (15–30)	−0.64	251	0.52
CIRS-G total score	4.5 (3.7) (0–16)	5.5 (4.3) (0–21)	1.97	255	0.04
HAM-D (17-item) total score	29.4 (5.4) (21–45)	30.2 (5.0)	1.10	257	0.27
BPRS total score	54.1 (10.1) (34–89)	55.9 (10.2) (39–81)	1.41	257	0.16
Suicide Ideation Scale sum of first 5 items	2.3 (2.8) (0–10)	2.6 (3.4) (0–10)	0.91	257	0.36
Categorical Variables	**N (%)**	**N (%)**	**x^2**	**df**	**p**
Gender – Male	48 (33.8)	45 (38.5)	0.60	1	0.43
Hispanic Ethnicity	16 (11.3)	14 (11.9)	0.03	1	0.96
Race			0.26	2	0.87
White	121(85.2)	97(82.9)			
Black	15(10.6)	14(12)			
Asian	6(4.2)	6(5.1)			
Marital Status			2.08	3	0.55
Married	38(26.8)	29(24.8)			
Single	62(43.7)	44(37.6)			
Widowed	23(16.2)	26(22.2)			
Divorced/Separated	19(13.4)	18(15.4)			
Living Arrangements			0.95	1	0.32
Lives Alone	28(19.7)	29(24.8)			
Lives with Others	114(80.3)	88(75.2)			
Entry Status			7.50	1	0.006
Inpatient	88(62.0)	91(77.8)			
Other	54(38.0)	26(22.2)			

Independent Variable	Completer (n=142) Mean (SD) (Range)	Non-Completer (n=117) Mean (SD) (Range)	t	df	P
Treatment			6.58	1	0.01
Olanzapine +Sertraline	81(57.0)	48(41.0)			
Olanzapine + Placebo	61(43.0)	69(59.0)			
Lifetime Episodes of Major Depression			1.32	1	0.24
1	47(33.1)	31(26.5)			
>1	95(66.9)	86(73.5)			
Consent			6.28	1	0.01
Surrogate	19(13.4)	30(25.6)			
Self	123(86.6)	87(74.4)			

SADS: Schedule for Affective Disorders and Schizophrenia; MMSE: Mini-Mental State Examination; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; HAM-D: Hamilton Depression Rating Scale; BPRS: Brief Psychiatric Rating Scale

Table 2

STOP-PD Subjects' Demographic and Clinical Characteristics of Completer and Non-Completer Subtypes

Variable	Total Sample	Completers	Discontinuation due to:						
			Lack of Efficacy		Tolerability	Other Reasons			
			Investigator Initiated	Not Investigator Initiated					
N	**259**	**142**	**37**	**20**	**13**	**47**			
Continuous Variables			**Mean (SD)**				**ANOVA**		
							F	**df**	**P**
Age (years)	57.9 (17.7)	57.7 (16.9)	60.5 (18.4)	65.5 (11.5)	68.2 (12.7)	50.7 (20.2)	4.41	4,254	0.001
Education (years)	12.5 (3.4)	12.6 (3.3)	12.6 (3.6)	13.6 (3.9)	10.8 (4.7)	12.6 (3.3)	1.31	4,251	0.26
Duration of current depressive episode (months)	11.9 (25.4)	12.7 (30.1)	12.5 (23.0)	11.4 (18.2)	12.3 (16.9)	8.9 (15.0)	0.21	4,251	0.93
SADS delusion severity score	5.8 (0.9)	5.7 (0.9)	5.9 (0.8)	5.8 (1.1)	6.0 (0.6)	5.6 (1.0)	1.03	4,254	0.39
MMSE (17-item) total score	27.1 (3.0)	27.0 (3.1)	26.4 (3.2)	27.5 (2.6)	25.8 (2.7)	27.1 (3.1)	0.93	4,248	0.44
CIRSG total score	5.0 (4.0)	4.5 (3.7)	5.1 (3.6)	6.4 (4.3)	7.0 (5.1)	5.1 (4.5)	1.88	4,252	0.11
HAM-D total score	30.0 (5.2)	29.4 (5.4)	31.1 (5.4)	32.2 (4.9)	27.6 (3.9)	29.3 (4.8)	2.43	4,254	0.04
BPRS total score	54.1 (10.1)	54.1 (10.1)	57.6 (10.0)	55.4 (11.9)	51.6 (11.4)	55.9 (9.2)	1.34	4,254	0.25
Suicide Ideation Scale sum of first 5 items	2.4 (3.0)	2.3 (2.8)	2.1 (3.2)	2.2 (3.1)	1.8 (3.0)	3.4 (3.7)	1.46	4,254	0.21
Categorical Variables			**N (%)**				**X^2**	**df**	**p**
Gender---Male	93 (35.9)	48 (33.8)	12 (32.4)	10 (50.0)	2 (10.0)	21 (44.6)	6.14	4	0.18
Hispanic Ethnicity	30 (11.6)	16 (11.2)	3 (8.1)	3 (15.0)	1 (5.0)	7 (14.8)	1.37	4	0.84
Race							10.14	8	0.25
White	218(84.2)	121(85.2)	32(86.5)	19(95.0)	12(92.3)	34(72.3)			
Black	29(11.2)	15(10.6)	4(10.8)	0(0)	0(0)	10(21.3)			
Asian	12(4.6)	6(4.2)	1(2.7)	1(5.0)	1(7.7)	3(6.4)			
Marital Status							22.51	1	0.03
Married	106(40.9)	38(26.8)	10(27.0)	3(15.0)	0(0)	16(34.0)			
Single	67(25.9)	62(43.7)	11(29.7)	14(70.0)	6(46.2)	13(27.7)			
Widowed	49(18.9)	23(16.2)	11(29.7)	3(15.0)	3(23.1)	9(19.1)			
Divorced/Separated	37(14.3)	19(13.4)	5(13.5)	0(0)	4(30.8)	9(19.1)			

Variable	Total Sample	Completers	Discontinuation due to:						
			Lack of Efficacy		Tolerability	Other Reasons			
			Investigator Initiated	Not Investigator Initiated					
N	**259**	**142**	**37**	**20**	**13**	**47**			
Continuous Variables			**Mean (SD)**				**ANOVA**		
							F	**df**	**P**
Living Arrangements							4.80	4	0.30
Lives Alone	57(22)	28(19.7)	12(32.4)	2(10.0)	3(23.1)	12(25.5)			
Lives with Others	202(78)	114(80.3)	25(67.6)	18(90.0)	10(76.9)	35(74.5)			
Entry Status							13.35	4	0.009
Inpatient	179(69.1)	88(62.0)	33(89.2)	15(75.0)	7(53.8)	36(76.6)			
Other	80(30.9)	54(38.0)	4(10.8)	5(25.0)	6(46.2)	11(23.4)			
Treatment							8.13	4	0.08
Olanzapine + Sertraline	129(49.8)	81(57.0)	18(48.6)	8(40.0)	4(30.8)	18(38.3)			
Olanzapine + Placebo	130(50.2)	61(43.0)	19(51.4)	12(60.0)	9(69.2)	29(61.7)			
Lifetime Episodes of Major Depression							1.62	4	0.80
1	78(30.1)	47(33.1)	11(29.7)	5(25.0)	3(23.1)	12(25.5)			
>1	181(69.9)	95(66.9)	26(70.3)	15(75.0)	10(76.9)	35(74.5)			
Consent							8.91	4	0.06
Surrogate	49(18.9)	19(13.4)	12(32.4)	5(25.0)	4(30.8)	9(19.1)			
Self	210(81.1)	123(86.6)	25(67.6)	15(75.0)	9(69.2)	38(80.9)			

SADS: Schedule for Affective Disorders and Schizophrenia; MMSE: Mini-Mental State Examination; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; HAM-D: Hamilton Depression Rating Scale; BPRS: Brief Psychiatric Rating Scale

Table 3

Multinomial Logistic Regression Analyses Examining Independent Predictors of Non-Completion Subtype[a]

Variable		Discontinuation due to:			
		Lack of Efficacy		Tolerability	Other Reasons
		Investigator Initiated	Not Investigator Initiated		
Entry Status (Inpatient vs. Other)					
	β(SE)	0.86 (0.28)	0.36 (0.27)	−0.10 (0.30)	0.40 (0.19)
	x^2, df, p	9.32, 1, 0.002	1.71, 1, 0.19	0.12, 1, 0.72	4.10, 1, 0.04
	OR (CI)	5.58 (1.85–16.86)	2.07(0.69–6.17)	0.80 (0.24–2.62)	2.24 (1.02–4.92)
Treatment Status (Sertraline+Olanzapine vs. Sertraline+Placebo)					
	β(SE)	−0.26 (0.19)	−0.38 (0.24)	−0.52 (0.31)	−0.45 (0.17)
	x^2, df, p	1.92, 1, 0.16	2.39, 1, 0.12	2.74, 1, 0.09	6.45, 1, 0.01
	OR (CI)	0.58 (0.27–1.24)	0.46(0.17–1.21)	0.34(0.10–1.21)	0.40(0.20–0.81)
Age					
	β(SE)	0.009 (0.01)	0.02 (0.01)	0.04 (0.02)	−0.02 (0.009)
	x^2, df, p	0.76, 1, 0.38	3.32, 1, 0.06	4.11, 1, 0.04	4.99, 1, 0.02
	OR (CI)	1.01 (0.98–1.03)	1.02 (0.99–1.06)	1.04 (1.00–1.09)	0.97 (0.96–0.99)

[a]Completers are the reference group.