Published in final edited form as:

Compr Psychiatry. 2014 July ; 55(5): 1069–1076. doi:10.1016/j.comppsy.2014.02.001.

Differential impact of anxiety symptoms and anxiety disorders on treatment outcome for psychotic depression in the STOP-PD study

Simon J.C. Davies^{a,b,c}, Benoit H. Mulsant^{a,b,*}, Alastair J. Flint^{d,e}, Anthony J. Rothschild^f, Ellen M. Whyte^g, Barnett S. Meyers^h, and STOP PD Study Group

^aCentre for Addiction and Mental Health, Toronto, Canada

^bDepartment of Psychiatry, University of Toronto, Toronto, Canada

^cAcademic Unit of Psychiatry, University of Bristol, Bristol, UK

^dDepartment of Psychiatry, University of Toronto, Toronto, Canada

^eUniversity Health Network, Toronto, Canada

^fUniversity of Massachusetts Medical School and University of Massachusetts, Worcester, MA, USA

^gWestern Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

^hWeill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY, USA

Abstract

Background—There are conflicting results on the impact of anxiety on depression outcomes. The impact of anxiety has not been studied in major depression with psychotic features (“psychotic depression”).

Aims—We assessed the impact of specific anxiety symptoms and disorders on the outcomes of psychotic depression.

Methods—We analyzed data from the Study of Pharmacotherapy for Psychotic Depression that randomized 259 younger and older participants to either olanzapine plus placebo or olanzapine plus sertraline. We assessed the impact of specific anxiety symptoms from the Brief Psychiatric Rating Scale (“tension”, “anxiety” and “somatic concerns” and a composite anxiety score) and diagnoses (panic disorder and GAD) on psychotic depression outcomes using linear or logistic regression. Age, gender, education and benzodiazepine use (at baseline and end) were included as covariates.

Results—Anxiety symptoms at baseline and anxiety disorder diagnoses differentially impacted outcomes. On adjusted linear regression there was an association between improvement in depressive symptoms and both baseline “tension” (coefficient = 0.784; 95% CI: 0.169–1.400; $p = 0.013$) and the composite anxiety score (regression coefficient = 0.348; 95% CI: 0.064–0.632; $p = 0.017$). There was an interaction between “tension” and treatment group, with better responses in those randomized to combination treatment if they had high baseline anxiety scores (coefficient = 1.309; 95% CI: 0.105–2.514; $p = 0.033$). In contrast, panic disorder was associated with worse clinical outcomes (coefficient = -3.858 ; 95% CI: -7.281 to -0.434 ; $p = 0.027$) regardless of treatment.

Conclusions—Our results suggest that analysis of the impact of anxiety on depression outcome needs to differentiate psychic and somatic symptoms.

1. Background and aims

Previous studies have produced conflicting results on whether anxiety predicts a reduced response rate or failure to remit in unipolar depression [1–7] (see [8] for review). Two meta-analyses using the HAM-D anxiety-somatisation factor have suggested no difference overall in depression outcome for anxious and non-anxious patients [9,10]. Similarly, in a more recent meta-analysis of placebo-controlled trials of escitalopram, there was no difference in the outcomes of patients with major depression with and without anxiety. However, there was a major difference in outcome among those with severe major depression: the number needed to treat for remission was 4 among those with severe non-anxious depression and 22 among those with severe anxious depression [11]. Thus, the impact of anxiety on the outcome of unipolar depression remains unclear. It is possible that different types of anxiety symptoms (e.g., psychic vs. somatic), different anxiety disorders (e.g. panic disorder vs. generalized anxiety disorder (GAD)), or different types of depression (e.g., psychotic vs. non-psychotic major depression) have different impact of the outcome of major depression.

To our knowledge, despite the potential significance of anxiety in predicting the outcome of depressive disorders, the impact of baseline anxiety has not previously been studied in major depression with psychotic features (“psychotic depression”). Most evidence and expert opinion support the use of a combination of an antipsychotic plus an antidepressant in the treatment of psychotic depression [12]. Since both antidepressants and antipsychotics can be helpful in treating anxiety symptoms and anxiety disorders [13], it is important for clinicians to know whether anxiety impacts the outcome of psychotic depression.

In the Study of Pharmacotherapy for Psychotic Depression (STOP-PD), 259 younger and older participants were randomized to treatment with either olanzapine plus placebo or olanzapine plus sertraline [14]. In this analysis, we aimed to assess the impact of baseline anxiety symptoms and anxiety disorders on the outcomes of psychotic depression. We included several variables related to different anxiety constructs given the differing results among studies in patients with non-psychotic depression depending on their focus on psychic anxiety or anxiety factors including somatic features. We hypothesized that (1) both anxiety symptoms and anxiety disorders would have a negative impact on clinical outcomes; and (2) there would be an interaction between anxiety and treatment group, with a better response in those randomized to combination treatment if they presented with high baseline

anxiety scores. As previous relevant studies have included either younger or older patients, we also examined the impact of age group (under 60 vs. 60 years and above) as a covariate in the models.

2. Methods

2.1. Description of STOP-PD

STOP-PD has been described in detail elsewhere [14]. It is a four-centre randomized clinical trial in which younger and older participants with a diagnosis of major depression with psychotic features were treated openly with the atypical antipsychotic drug olanzapine and randomized under double blind controlled conditions to receive either the selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline or placebo. The local institutional review boards of the participating academic medical centres and a data safety monitoring board at the National Institute of Mental Health approved the study. Consent was obtained from all subjects, either directly (as informed, voluntary, written consent) or through locally approved surrogate consent procedures. The duration of treatment was 12 weeks. The target doses were 15–20 mg/day for olanzapine and 150–200 mg/day for sertraline. All participants met criteria for major depression with psychotic features according to DSM-IV using the Structured Clinical Interview for DSM-IV (SCID) and they scored 21 points or higher on the 17-item HAM-D. In addition they were required to have at least one delusional belief, a score of three or higher on the delusion severity rating of the Schedule of Affective Disorders and Schizophrenia (SADS), and a score of two or more on the conviction items of the Delusion Assessment Scale for Psychotic Major Depression (DAS). The primary outcome was remission of both depressive and psychotic symptoms. In total, 259 patients (of whom 142 were aged 60 or more) were randomized and 147 (57%) remained in the trial for 12 weeks. STOP-PD primary analysis reported that combination treatment with olanzapine plus sertraline was more effective than olanzapine plus placebo in inducing remission, the odds ratio for remission being 1.28 (95% confidence interval (CI): 1.18–1.47, $p < 0.001$).

2.2. Independent anxiety variables

The Brief Psychiatric Rating Scale (BPRS [15]) was administered to all participants prior to randomization and at all study visits using a semi-structured interview [16]. BPRS items 1 (“somatic concern”), 2 (“anxiety statements”), and 6 (“tension behaviour”) referring to three distinct anxiety-related constructs were used as anxiety variables, each one being scored from 1 (symptom absent) to 7 (severe/incapacitating) (see Appendix). A composite BPRS anxiety score generated by adding the scores of these three items was also examined as a further anxiety variable (score range: 3–21).

Diagnoses of current GAD and Panic Disorder were made through the Structured Clinical Interview for DSM-IV administered prior to randomization. These diagnoses were used as binary variables and were analysed separately from the measures of anxiety symptoms derived from the BPRS.

2.3. Outcome variables

In this analysis, we considered impact of anxiety on three outcomes variables: (1) improvement in depressive symptoms; (2) improvement in psychotic symptoms; (3) probability of remaining in the trial for 12 weeks.

Improvement in depressive symptoms was based on the HAM-D. In STOP-PD, the 17-item version of the HAM-D was administered at each visit using the GRID-HAM-D methods [17]. For this analysis, we dropped the two items that refer specifically to psychic anxiety (item 10) and somatic anxiety (item 11), so that the total HAM-D score was based on the remaining 15 items (HAM-D-15). Improvement in depressive symptoms was calculated by subtracting the HAM-D-15 score at the last completed study visit from the HAM-D-15 score at baseline.

Improvement in psychotic symptoms was based on a psychosis subscore of the BPRS calculated based on three BPRS items (4: Conceptual Disorganization; 12: Hallucinatory Behaviour; 15: Unusual Thought Content) with a range of 3–21. Improvement in psychotic symptoms was calculated by subtracting the BPRS psychosis subscore at the last completed study visit from the BPRS psychosis subscore at baseline.

Finally, probability of remaining in the trial for 12 weeks was used as a secondary outcome measure based on whether or not participants had attended their week 12 study visit period (as opposed to dropping out prematurely or completing the treatment protocol after 5 weeks due to clinical deterioration or lack of improvement).

2.4. Statistical methods

All analyses followed an intention to treat principle and used the computer software package STATA version 12 (College Station, TX, USA) [18]. Linear regression methods were employed for analysing improvement in depressive symptoms (HAM-D-15) and improvement in psychotic symptoms (BPRS psychosis subscale). Logistic regression methods were employed to analysing the probability of remaining in the trial. As per above, independent variables were baseline scores on three anxiety symptoms, overall anxiety scores, and diagnoses of Panic Disorder and GAD.

We performed both unadjusted and adjusted analyses. Potential confounding variables examined were gender, age group (as a dichotomous variable with cut off at 60 years), education (as a continuous variable denoting years of education completed), and two further dichotomous variables indicating that the participant was being prescribed a benzodiazepine at (1) the baseline study visit and (2) the final study visit. In addition, a dichotomous treatment group variable indicating whether the participant was randomized to sertraline or placebo was included.

We conducted further analyses introducing an interaction term into each of the above models, to examine whether there was a statistical interaction between the baseline anxiety measure and the treatment allocation at randomisation in the prediction of the outcome measures.

3. Results

3.1. Description of sample

The characteristics of the 130 participants randomized to receive olanzapine plus sertraline and 129 randomized to receive olanzapine plus placebo are summarized in Table 1. The treatment groups were well matched for age group, gender, and being prescribed benzodiazepines at baseline. However participants randomized to placebo had significantly more years of education than those randomized to sertraline (13.4 vs. 11.6 years, difference = 1.76 years, 95% CI of difference = 0.939–2.577; $p < 0.001$). They were more likely to be prescribed a benzodiazepine at their final study visit (40.0% vs. 30.2%) but this difference did not reach statistical significance ($\chi^2 = 2.711$, $p = 0.100$, $df = 1$).

3.2. Anxiety variables and composite anxiety score

In unadjusted regression analyses (Table 2), two of the three anxiety items – “anxiety statements” and “tension behaviour” – and the composite anxiety score were associated with greater improvement in depressive symptoms. The regression coefficient was 0.740 (95% CI: 0.065–1.414; $p = 0.032$) for “anxiety statements”; 0.697 (95% CI: 0.076–1.319; $p = 0.028$) for “tension behaviour”; and 0.286 (95% CI: 0.001–0.571; $p = 0.049$) for the composite anxiety score. There was no association between “somatic concerns” and improvement in depressive symptoms outcome. In these unadjusted analyses, none of the four anxiety variables were associated with improvement in psychotic symptoms or with the probability of remaining in the trial.

After adjusting for treatment group and the five potential confounding factors listed above, the association between “tension behaviour” and improvement in depressive symptoms became stronger (regression coefficient = 0.784; 95% CI: 0.169–1.400; $p = 0.013$), while the association with “anxiety statements” became weaker and no longer reached statistical significance (coefficient = 0.655; 95% CI: –0.0250 to 1.335; $p = 0.059$). The association between the composite anxiety score and improvement in depressive symptoms also increased in strength (coefficient = 0.348; 95% CI: 0.064–0.632; $p = 0.017$).

In the analyses of improvement in psychotic symptoms, unlike in those of the improvement in depressive symptoms, age appeared to exert a significant effect: there was a significant association between “tension behaviour” and improvement in psychotic symptoms in participants aged under 60 (coefficient = 0.626; 95% CI: 0.150–1.103; $p = 0.010$) but not in those aged 60 and over (coefficient = –0.028; 95% CI: –0.388 to 0.332; $p = 0.879$). Similarly, the association between the composite anxiety score at baseline and improvement in psychotic symptoms was significant among participants aged under 60 (coefficient = 0.291; 95% CI: 0.085–0.497; $p = 0.006$) but not in those aged 60 and older (coefficient = 0.021; 95% CI: –0.153 to 0.194; $p = 0.814$).

The addition of interaction terms to the regression models (Table 3) revealed that “tension behaviour” interacted significantly with treatment group both for improvement in depressive symptoms (coefficient = 1.309; 95% CI: 0.105–2.514; $p = 0.033$) and probability of remaining in the trial (coefficient = 0.356; 95% CI: 0.039–0.674; $p = 0.028$). The composite anxiety score was also associated with the same two outcomes (coefficient = 0.569; 95% CI:

0.013–1.125; $p = 0.045$ for improvement in depressive symptoms; coefficient = 0.188; 95% CI: 0.042–0.335; $p = 0.012$ for probability of remaining in the trial). As Figs. 1 and 2 illustrate, the presence of a statistical interaction between “tension behaviour” and treatment group in predicting improvement in depressive symptoms and probability of remaining in the trial meant that participants with high baseline “tension behaviour” who received sertraline had better outcomes than all other groups. However, no statistically significant interactions were identified between any of the anxiety variables and treatment group for improvement in psychotic symptoms.

3.3. GAD and panic disorder diagnoses

When the above analyses were repeated with the independent variables being anxiety disorder diagnoses (Table 4), the unadjusted model revealed a negative association between having a diagnosis of panic disorder and improvement in depressive symptoms (coefficient = -3.858 ; 95% CI: -7.281 to -0.434 ; $p = 0.027$) indicating that participants with panic disorder had about 4 points less improvement in their HAM-D-15 scores than those without panic disorder. There was no significant association between GAD diagnosis and improvement in depressive symptoms or between the two diagnoses and either improvement in psychotic symptoms or probability of remaining in the trial. Adjustment for treatment group and the five confounding covariates produced similar results (panic disorder regression coefficient = -3.864 ; 95% CI: -7.347 to -0.381 ; $p = 0.030$).

The addition of interaction terms into the models (Table 5) revealed that the diagnosis of GAD, but not panic disorder, interacted significantly or at a level approaching significance with treatment group for all three outcomes. The strongest interaction was for greater improvement in psychotic symptoms for participants receiving sertraline (coefficient = 3.03; 95% CI: 0.396–5.664; $p = 0.024$) with weaker non-significant effects for improvement in depressive symptoms (coefficient = 4.994; 95% CI: -0.759 to 10.748; $p = 0.089$) and probability of remaining in the trial (coefficient = 1.451; 95% CI: 0.094–2.996; $p = 0.066$). Overall, participants with GAD benefitted the most from the addition of sertraline to olanzapine.

4. Discussion

Anxiety symptoms at baseline and anxiety disorder diagnoses appeared to differentially impact outcomes in patients with psychotic depression who were treated in the STOP-PD randomized clinical trial. Although we initially hypothesized that the presence of anxiety symptoms and anxiety disorders in general would be associated with poorer clinical outcomes, the results indicate a marked disparity between the impact of various anxiety symptoms and disorders.

Contrary to our hypothesis, the presence of “tension behaviour” at baseline was associated with significantly better depression outcome. The regression coefficient of 0.784 in the adjusted analysis corresponds to an additional improvement of 0.784 points in HAM-D-15 score for each additional point in the BPRS “tension behaviour” item. Thus, on average, a participant with the highest baseline tension behaviour score (i.e., 7) would be expected to experience a decrease in HAM-D-15 score of 4.7 points more than a participant with the

lowest score (i.e., 1). Additionally, there was an interaction with treatment group, such that participants who both had high tension behaviour at baseline and were randomized to olanzapine plus sertraline had better outcome in terms both of improvement in depressive symptoms and probability of remaining in the trial for 12 weeks than those randomized to olanzapine plus placebo or those with lower baseline tension behaviour scores.

In contrast, a diagnosis of co-morbid panic disorder was associated with worse clinical outcomes across the whole sample in both adjusted and unadjusted analyses, while a diagnosis of GAD was not: a diagnosis of co-morbid GAD was associated with better outcomes on sertraline than on placebo.

Why should “tension behaviour” be associated with better treatment outcomes in patients with psychotic depression, especially in those given an SSRI combined with an antipsychotic? One possible explanation is that SSRI antidepressants like sertraline are effective treatments not only for depression but also for GAD, in which “tension behaviour” is a typical symptom. Therefore the benefits participants derive in having “tension behaviour” alleviated by an SSRI may impact directly or indirectly their depressive symptoms. For example, there may be a psychological benefit in having tension ameliorated so that participants who are aware of this improvement may become less hopeless and less depressed. Alternatively, the presence of tension behaviour may be a clinical marker for a biological subtype of psychotic depression (“agitated depression”) that responds differentially to antidepressant medications in general and to SSRIs in particular. This is congruent with some older studies emphasizing the importance of agitation [19] or severe psychomotor symptoms in differentiating psychotic vs. non-psychotic depression and their response to treatment [19].

Why then should the presence of co-morbid panic disorder, a condition that is also readily amenable to treatment with SSRIs, be associated with poorer outcome in contrast to our findings with tension behaviour? A co-morbid panic disorder or panic attacks also worsen prognosis in patients with schizophrenia [20–22]. Furthermore, persons with a tendency for paranoia can experience acute worsening of paranoia during a panic attack (e.g., have a ‘paranoia attack’). Unlike in GAD, the majority of panic disorder symptoms are somatic affecting the cardiovascular, respiratory, gastrointestinal and other bodily systems, with the remainder involving fear. Furthermore, epidemiological investigations, genetic analyses and biological studies have generally reported that GAD is closer to depressive disorders than to panic disorder in all of these domains [23–26]. Therefore a medication that successfully treats tension behaviour or GAD symptoms may be more likely to treat similar and overlapping depressive symptoms than one that treats panic disorder symptoms. In our analysis, tension behaviour is a strong predictor of good outcome regardless of treatment assignment while a GAD diagnosis predicts a positive outcome only in those who received sertraline. However, given the DSM-IV diagnostic hierarchy, some patients with major depression who would additionally meet GAD criteria are not diagnosed when the generalized anxiety is seen as secondary to the depression. Those patients would score highly on anxiety items and would contribute to the positive association between a higher composite anxiety score and improvement in depressive symptoms.

Whatever the mechanisms underlying our results, this analysis illustrates that clinicians treating patients with psychotic depression should pay attention to the presence of anxiety symptoms, especially “tension behaviour.” The presence of generalized anxiety symptoms and tension in particular should be seen as an indication favouring the use of an SSRI antidepressant.

We found little impact of age on the relation between baseline anxiety and improvement in depressive symptoms, but a much larger effect with the improvement in psychotic symptoms, whereby tension behaviour and overall anxiety predicted greater improvement in younger but not older patients. The cause of this differential effect is unclear. In younger patients, anxiety or agitation in the context of psychotic depression may indicate a different biological subtype that is more responsive to treatment.

Finally, the finding that tension behaviour but not somatic concern was associated with improved response and an interaction with treatment allocation raises an issue about previous studies of anxiety and non-psychotic depression. For instance, an analysis of the STAR-D trial that found that “anxiety” was associated with a worse prognosis used the anxiety-somatization factor of the HAM-D [5], consisting of six items, four of which relate either to somatic anxiety or to somatic bodily symptoms (i.e., somatic anxiety, somatic symptoms [gastro-intestinal], somatic symptoms [general], hypochondriasis). Our results suggest that the use of an instrument dominated by somatic rather than psychic anxiety features may explain why several studies have found that baseline “anxiety” negatively impact the outcome of depression [4,5]. The results of these studies are similar to our results with DSM-IV panic disorder. It is possible that analyses that differentiate somatic symptoms and other anxiety symptoms (e.g., tension behaviour) will find a different relation between anxiety and depressive outcomes.

The strength of this study are the relatively large number of patients, distribution of age over the life spectrum, treatment under randomized double-blind conditions, availability of both anxiety symptoms and categorical diagnoses, testing of a-priori hypotheses, and ability to control for potential confounding factors such as the use of benzodiazepines. Limitations include the retrospective nature of our analysis (i.e., the trial was not designed to test our hypotheses) and the absence of group treated with sertraline plus placebo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Tollefson GD, Holman SL, Sayler ME, Potvin JH. Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. *J Clin Psychiatry*. 1994; 55:50–9. [PubMed: 8077155]
2. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. *Depress Anxiety*. 2002; 16:4–13. [PubMed: 12203668]

3. Andreescu C, Lenze EJ, Dew MA, Begley AE, Mulsant BH, Dombrovski AY, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *Br J Psychiatry*. 2007; 190:344–9. [PubMed: 17401042]
4. Andreescu C, Mulsant BH, Houck PR, Whyte EM, Mazumdar S, Dombrovski AY, et al. Empirically derived decision trees for the treatment of late-life depression. *Am J Psychiatry*. 2008; 165:855–62. [PubMed: 18450930]
5. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008; 165:342–51. [PubMed: 18172020]
6. Papakostas GI, McGrath P, Stewart J, Charles D, Chen Y, Mischoulon D, et al. Psychic and somatic anxiety symptoms as predictors of response to fluoxetine in major depressive disorder. *Psychiatry Res*. 2008; 161:116–20. [PubMed: 18755514]
7. Andreescu C, Lenze E, Mulsant BH, Wetherell JL, Begley AE, Mazumdar S, et al. High worry severity is associated with poorer acute and maintenance efficacy of antidepressants in late-life depression. *Depress Anxiety*. 2009; 26:266–72. [PubMed: 19212971]
8. Nelson JC. Anxious Depression and Response to Treatment. *Am J Psychiatry*. 2008; 165:297–9. [PubMed: 18316424]
9. Papakostas GI, Stahl SM, Krishen A, Seifert CA, Tucker VL, Goodale EP, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *J Clin Psychiatry*. 2008; 69:1287–92. [PubMed: 18605812]
10. Nelson JC, Delucchi K, Schneider LS. Anxiety does not predict response to antidepressant treatment in late life depression: results of a meta-analysis. *Int J Geriatr Psychiatry*. 2009; 24:539–44. [PubMed: 19334041]
11. Papakostas GI, Fan H, Tedeschi E. Severe and anxious depression: Combining definitions of clinical sub-types to identify patients differentially responsive to selective serotonin reuptake inhibitors. *Eur Neuropsychopharmacol*. 2012; 22:347–55. [PubMed: 22099607]
12. Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *J Clin Psychiatry*. 2012; 73:486–96. [PubMed: 22579147]
13. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. *J Clin Psychiatry*. 2010; 71:839–54. [PubMed: 20667290]
14. Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte EM, Peasley-Miklus C, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry*. 2009; 66:838–47. [PubMed: 19652123]
15. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Research*. 1962; 10:799–812.
16. Mulsant BH, Stergiou A, Keshavan MS, Sweet RA, Rifai AH, Pasternak R, et al. Schizophrenia in late-life: elderly patients admitted to an acute care psychiatric hospital. *Schizophr Bull*. 1993; 19:709–21. [PubMed: 8303222]
17. Williams JB, Kobak KA, Bech P, Engelhardt N, Evans K, Lipsitz J, et al. The GRID-HAM-D standardization of the Hamilton Depression Rating Scale. *Int Clin Psychopharmacol*. 2008; 23:120–9. [PubMed: 18408526]
18. StataCorp. Stata Statistical Software: Release 12. StataCorp; College Station, TX: 2011.
19. Charney DS, Nelson JC. Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. *Am J Psychiatry*. 1981; 138:328–33. [PubMed: 6110345]
20. Goodwin R, Lyons JS, McNally RJ. Panic attacks in schizophrenia. *Schizophr Res*. 2002; 58:213–20. [PubMed: 12409161]
21. Morrison AP, Wells A. A comparison of metacognitions in patients with hallucinations, delusions, panic disorder, and non-patient controls. *Behav Res Ther*. 2003; 41:251–6. [PubMed: 12547384]
22. Huppert JD, Smith TE. Anxiety and schizophrenia: the interaction of subtypes of anxiety and psychotic symptoms. *CNS Spectr*. 2005; 10:721–31. [PubMed: 16142212]

23. Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry*. 1999; 56:921–6. [PubMed: 10530634]
24. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: The NEMESIS Study. *Arch Gen Psychiatry*. 2001; 58:597–603. [PubMed: 11386990]
25. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003; 60:929–37. [PubMed: 12963675]
26. Lenze EJ, Mulsant BH, Mohlman J, Shear KM, Dew MA, Schulz R, et al. Generalized anxiety disorder in late life: lifetime course and comorbidity with major depressive disorder. *Am J Geriatr Psychiatry*. 2005; 13:77–80. [PubMed: 15653943]

Fig. 1.

Interaction between baseline BPRS item 6 (tension behaviour) and treatment group in predicting improvement in depressive symptoms. Error bars reflect standard error. Coefficient for interaction terms (treatment group * baseline BPRS tension behaviour) after adjustments for age group, gender, education, benzodiazepine usage at baseline and at end of trial = 1.309 (95% CI: 0.105–2.514; $p = 0.033$).

Fig. 2.

Interaction between baseline BPRS item 6 (tension behaviour) and treatment group in predicting probability of remaining in the trial for 12 weeks. Red squares: olanzapine + placebo. Blue diamonds: olanzapine + sertraline. Coefficient for interaction term (treatment group * tension behaviour) after adjustments for age group, gender, education, benzodiazepine usage at baseline and at end of trial = 0.356 (95% CI: -0.039 to 0.674; $p = 0.028$).

Table 1

Characteristics of participants tabulated by treatment allocation.

N	<u>Olanzapine + sertraline</u>	<u>Olanzapine + placebo</u>	
	130	129	
Age 60 years	71 (55.0%)	71 (54.6%)	$X^2 = 0.005$, $p = 0.945$, $df = 1$
Female	83 (64.3%)	83 (63.9%)	$X^2 = 0.007$, $p = 0.934$, $df = 1$
Education (years)	11.6	13.4	$t = 4.229$, $p < 0.001$, $df = 254$
Benzodiazepines prescribed at baseline	43 (34.1%)	44 (33.1%)	$X^2 = 0.031$, $p = 0.860$, $df = 1$
Benzodiazepines prescribed at final visit	39 (30.2%)	52 (40.0%)	$X^2 = 2.711$, $p = 0.100$, $df = 1$
Current diagnosis of Generalized Anxiety Disorder	16 (12.3%)	23 (17.8%)	$X^2 = 1.544$, $p = 0.214$, $df = 1$
Current diagnosis of Panic Disorder	13 (10.0%)	13 (10.1%)	$X^2 = 0.000$, $p = 0.983$, $df = 1$

Table 2

Unadjusted and adjusted analyses for relation between baseline anxiety variables and outcome variables showing regression coefficients and their 95% confidence intervals (CI).

A. Unadjusted analysis				
	Tension behaviour	Anxiety statements	Somatic concern	Composite anxiety score
Linear regression Improvement in depressive symptoms ¹	0.697 (p = 0.028) 95% CI 0.076–1.319	0.740 (p = 0.032) 95% CI 0.065–1.414	0.020 (p = 0.930) 95% CI –0.421 to 0.461	0.286 (p = 0.049) 95% CI 0.001–0.571
Improvement in psychotic symptoms ²	0.230 (p = 0.114) 95% CI –0.556 to 0.516	0.206 (p = 0.192) 95% CI –0.104 to 0.517	0.028 (p = 0.783) 95% CI –0.174 to 0.230	0.097 (p = 0.146) 95% CI –0.034 to 0.228
Logistic regression Probability of remaining in the trial for 12 weeks	–0.049 (p = 0.518) 95% CI –0.198 to 0.100	0.009 (p = 0.915) 95% CI –0.152 to 0.170	–0.007 (p = 0.892) 95% CI –0.112 to 0.097	–0.012 (p = 0.734) 95% CI –0.080 to 0.056
B. Analyses adjusted for gender, age group, education, and benzodiazepine prescription at baseline and at last visit				
	Tension behaviour	Anxiety statements	Somatic concern	Composite anxiety score
Linear regression Improvement in depressive symptoms ¹	0.784 (p = 0.013) 95% CI 0.169–1.400	0.655 (p = 0.059) 95% CI –0.025 to 1.335	0.154 (p = 0.493) 95% CI –0.287 to 0.594	0.348 (p = 0.017) 95% CI 0.064–0.632
Improvement in psychotic symptoms ²	0.214 (p = 0.140) 95% CI –0.071 to 0.500	0.232 (p = 0.146) 95% CI –0.081 to 0.546	0.0979 (p = 0.342) 95% CI –0.105 to 0.300	0.128 (p = 0.055) 95% CI –0.003 to 0.260
Logistic regression Probability of remaining in the trial for 12 weeks	–0.0135 (p = 0.866) 95% CI –0.170 to 0.143	–0.0057 (p = 0.948) 95% CI –0.178 to 0.166	0.0309 (p = 0.585) 95% CI –0.080 to 0.142	0.00927 (p = 0.866) 95% CI –0.063 to 0.0815

¹ Change in HAM-D-15 score.

² Change in BPRS psychosis subscale score.

Table 3

Interaction terms (regression coefficients and their 95% confidence limits) for interactions between anxiety variables and treatment group adjusted for gender, age group, education and benzodiazepine prescription at baseline and at last visit.

	Tension behaviour by treatment group	Anxiety statements by treatment group	Somatic concern by treatment group	Composite anxiety score by treatment group
Linear regression Improvement in depressive symptoms ¹	1.309 (p = 0.033) 95% CI 0.105–2.514	0.397 (p = 0.562) 95% CI – 0.950 to 1.744	0.707 (p = 0.112) 95% CI –0.166 to 1.580	0.569 (p = 0.045) 95% CI 0.013–1.125
Improvement in psychotic symptoms ²	0.420 (p = 0.142) 95% CI –0.141 to 0.981	0.205 (p = 0.516) 95% CI – 0.416 to 0.826	–0.047 (p = 0.817) 95% CI –0.450 to 0.356	0.079 (p = 0.548) 95% CI –0.180 to 0.337
Logistic regression Probability of remaining in the trial for 12 weeks	0.356 (p = 0.028) 95% CI 0.039–0.674	0.169 (p = 0.483) 95% CI – 0.172 to 0.510	0.207 (p = 0.071) 95% CI –0.017 to 0.432	0.188 (p = 0.012) 95% CI 0.042–0.335

¹Change in HAM-D-15 score.

²Change in BPRS psychosis subscale score.

Table 4

Unadjusted and adjusted analyses for relation between anxiety diagnoses and outcome variables showing regression coefficients and their 95% confidence intervals (CI).

A. Unadjusted analyses		
	Panic Disorder	Generalized Anxiety Disorder
Linear regression Improvement in depressive symptoms ¹	-3.858 (p = 0.027) 95% CI -7.281 to -0.434	0.971 (p = 0.511) 95% CI -1.931 to 3.872
Improvement in psychotic symptoms ²	-0.419 (p = 0.602) 95% CI -2.000 to 1.162	0.129 (p = 0.848) 95% CI -1.200 to 1.459
Logistic regression Probability of remaining in the trial for 12 weeks	-0.131 (p = 0.752) 95% CI -0.945 to 0.682	-0.139 (p = 0.691) 95% CI -0.823 to 0.545
B. Analyses adjusted for gender, age group, education, and benzodiazepine prescription at baseline and at last visit		
	Panic Disorder	Generalized Anxiety Disorder
Linear regression Improvement in depressive symptoms ¹	-3.864 (p = 0.030) 95% CI -7.347 to -0.381	0.869 (p = 0.551) 95% CI -1.997 to 3.735
Improvement in psychotic symptoms ²	-1.396 (p = 0.088) 95% CI -3.003 to 0.211	-0.229 (p = 0.732) 95% CI -1.547 to 1.089
Logistic regression Probability of remaining in the trial for 12 weeks	-0.281 (p = 0.534) 95% CI -1.168 to 0.605	-0.103 (p = 0.780) 95% CI -0.823 to 0.618

¹ Change in HAM-D-15 score.

² Change in BPRS psychosis subscale score.

Table 5

Interaction terms (regression coefficients and their 95% confidence limits) for interactions between anxiety diagnoses and treatment group adjusted for gender, age group, education and benzodiazepine prescription at baseline and at last visit.

	Panic Disorder by treatment group	GAD by treatment group
Linear regression Improvement in depressive symptoms ¹	0.776 (p = 0.882) 95% CI -5.992 to 7.544	4.994 (p = 0.089) 95% CI -0.759 to 10.748
Improvement in psychotic symptoms ²	1.781 (p = 0.261) 95% CI -1.333 to 4.896	3.030 (p = 0.024) 95% CI 0.396-5.664
Logistic regression Probability of remaining in the trial for 12 weeks	-0.237 (p = 0.786) 95% CI -1.945 to -1.472	1.451 (p = 0.066) 95% CI 0.094-2.996

¹ Change in HAM-D-15 score.

² Change in BPRS psychosis subscale score.