ARTICOLE ORIGINALE

COMORBID ANXIETY DELAYS TREATMENT RESPONSE AND INCREASES RELAPSE RISK IN LATE-LIFE DEPRESSION: A CONTROLLED STUDY


INTRODUCTION

Co-morbid anxiety is common in depressive disorders, both in middle and later life. In community samples of younger depressed adults, the point prevalence of co-morbid anxiety disorders ranges from 33% (1) to 51% (2); with a 46% point-prevalence in a clinical sample (3). In community samples of older adults with late-life depression (LLD), the point prevalence of co-morbid anxiety disorders ranges from 26% (4) to 48% (5). In clinical samples of older patients with LLD, co-morbid anxiety disorders are diagnosed in 3% to 65% (6-8).

Beyond the high rates of coexistence, co-morbid anxiety has been often cited as a clinically relevant problem due to its impact on acute treatment response in LLD. Thus, several studies have found that greater severity of anxiety symptoms is associated with an increased risk of treatment dropout (9, 10), a decreased response to acute antidepressant treatment (9-11), or a longer time to both response (6, 12, 13) and remission (14, 15).

Although the impact of anxiety on response and recurrence of major depression has been previously studied extensively in general adult populations, its relevance to long term treatment response in late life depression has received much less attention (16, 17) and has not been examined in a controlled maintenance trial. Maintenance outcomes in LLD and the factors which moderate those outcomes are critical, given the brittle nature of response in this age group (18, 19).

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our knowledge, the only published data addressing these long-term outcomes were obtained during a 2-year naturalistic follow-up. In this uncontrolled study pretreatment anxiety symptoms were not related to time to recurrence during two years of open pharmacotherapy trial with nortriptyline (20).

Thus, given the high recurrence rate of LLD (21) and the increased morbidity and mortality risks associated with LLD (22-24) as well as the lack of controlled data regarding impact of pretreatment anxiety on long term treatment of LLD, further examination of anxiety as a predictor not only of response but of recurrence would greatly benefit clinicians in planning treatment. Accordingly, we conducted an analysis to assess whether pretreatment co-morbid anxiety predicts treatment outcomes during both acute and maintenance treatment of major depression in old age. We hypothesized that greater pretreatment severity of anxiety symptoms would predict poor treatment outcome, including both a longer time to response during acute treatment and an increased rate of and shorter time to recurrence during maintenance treatment.

**METHOD**

Data for this analysis were provided by the second study of Maintenance Therapies in Late Life Depression (MTLD-II) conducted at the University of Pittsburgh Intervention Research Center for the Study of Late-Life Mood Disorders between 1999 and 2004. Details of the study protocol are described elsewhere (19). In brief, participants were 70 and older, with a diagnosis per Structured Clinical Interview for DSM-IV (SCID) (25) of non-psychotic, non-bipolar major depressive disorder (single-episode or recurrent), a 17-item Hamilton Depression Rating Scale (HDRS) of >15, meeting DSM-IV criteria for a major depressive episode during a SCID interview, and having an independent geriatric psychiatrist confirm the diagnosis. Assessors were blind to treatment assignment. All patients provided written informed consent. For this data analysis, we collapsed the IPT and non-IPT groups because IPT was not shown to prevent recurrence in the primary outcome analysis, while paroxetine was (19).

Symptoms of anxiety were measured using the self-report anxiety scale from the Brief Symptom Inventory [BSI, (29)]. The BSI is a validated self-report scale developed from the SCL-90-R with strong test–retest and internal consistency reliabilities. Factor analytic studies of the internal structure of the scale have demonstrated its construct validity (29). The anxiety subscale consists of six items: “nervousness or shakiness inside”, “suddenly scared for no reason”, “feeling fearful”, “feeling tense or keyed up”, “spells of terror or panic”, and “feeling so restless you couldn’t sit still”. Each item is rated on a 5-point scale (0 = symptom not present, 4 = extremely severe). We used both a categorical and a continuous form of the BSI anxiety measure. We analyzed BSI scores (Cronbach’s alpha for the present sample = .84) on a continuum and also we dichotomized those with higher versus lower anxiety by using a median split (median value for the sample = 1.0). We present in this paper the results based on the categorical approach because it has more relevance to the categorical decisions clinicians are faced with in their practice.

The analyses included 181 subjects who participated in the acute treatment phase. Of these, 116 maintained response during continuation treatment and were randomly assigned to maintenance treatment. Pre-treatment BSI scores were available on 170 subjects entering the acute phase. Of these, 109 participated in randomly assigned maintenance treatment.

**Statistical analysis**

We used Kaplan-Meier survival analysis to assess the effect of pre-treatment anxiety symptoms (BSI scores) on time to response. In order to analyze the influence of lorazepam on time to response (30), we compared the time to response in the group receiving lorazepam versus the group not receiving lorazepam. Further, we stratified the sample based on presence or absence of lorazepam use. In order to control for other
potential confounders, we subsequently fit Cox proportional hazards models for each outcome, stratifying on severity of depression to estimate the unique effects of anxiety on acute treatment outcomes. We controlled for baseline depression severity as measured by the HDRS scores, with the four anxiety–related items –items 9, 10, 11 and 15— removed (12, 31, 32).

To assess the effect of co-morbid symptomatic anxiety on time to recurrence during maintenance treatment, we stratified the sample based on randomization to paroxetine or placebo and performed Kaplan-Meier analyses in four groups: 1) pharmacotherapy with lower BSI scores (N= 35); 2) pharmacotherapy with higher BSI scores (N=23); 3) placebo with lower BSI scores (N=31); 4) placebo with higher BSI scores (N= 20).

RESULTS

Participants’ baseline demographic and clinical characteristics are presented in Table 1.

Effect of Symptomatic Co-morbid Anxiety on Response during Acute Treatment

At baseline, 82 patients had higher BSI scores (above median split) and 88 had lower BSI scores. Among patients with higher BSI, 52% (43/82) achieved response and began maintenance treatment, while of those with lower BSI 75% (66/88) achieved response and began maintenance treatment (chi-square =6.09, df =1, p=0.01).

Patients with higher BSI had a median time to response significantly longer than those with lower BSI: 11.0 [95%CI: 7.7-13.9] vs. 6.7 [5.9-7.9] weeks (Wilcoxon chi square= 6.26, df =1, p=0.01).

Effects of adjunctive lorazepam

Patients who received adjunctive lorazepam (N=65) had a median time to response significantly longer than those who did not (N=120): 12.4 [95%CI: 8.4-14.7] vs. 6.9 [5.6-7.9] weeks (Wilcoxon = 16.81, df =1, p<0.0001). The mean (SD) dose of lorazepam received by patients with higher or lower BSI scores did not differ significantly: 1.03 (0.60) vs. 0.92 (0.44) mg/day (t=-0.75, df =61, p=0.45). However, as would be expected, lorazepam use was correlated with higher BSI scores (phi=0.31). Therefore, we analyzed post hoc the time to response separately in patients who received and did not receive lorazepam, contrasting those with higher BSI and lower BSI. Among patient who received lorazepam, those with higher BSI had a

### Table 1: Demographic and clinical characteristics of patients by level of Brief Symptom Inventory anxiety scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower BSI (N=88)</th>
<th>Higher BSI (N=82)</th>
<th>T/Chi-square</th>
<th>DF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of BSI Score Mean/Median</td>
<td>0.53/0.58</td>
<td>1.91/ 1.75</td>
<td>17.06</td>
<td>124</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current Age</td>
<td>76.3 (5.3)</td>
<td>77.1 (5.7)</td>
<td>-0.94</td>
<td>168</td>
<td>0.35</td>
</tr>
<tr>
<td>% Female (N)</td>
<td>57.9 (n=51)</td>
<td>71.9 (n=59)</td>
<td>3.64</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>% Caucasian (N)</td>
<td>93.2 (n=82)</td>
<td>91.4 (n=75)</td>
<td>0.18</td>
<td>1</td>
<td>0.67</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>12.9 (2.9)</td>
<td>13.0 (2.9)</td>
<td>-0.18</td>
<td>168</td>
<td>0.85</td>
</tr>
<tr>
<td>CIRS-G*</td>
<td>10.2 (3.6)</td>
<td>9.8 (4.4)</td>
<td>0.61</td>
<td>168</td>
<td>0.54</td>
</tr>
<tr>
<td>HDRS 17 **</td>
<td>19.2 (3.2)</td>
<td>22.2 (3.5)</td>
<td>-6.06</td>
<td>168</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDRS minus anxiety items (Q9, Q10, Q11, Q15)</td>
<td>14.2 (2.6)</td>
<td>16.1 (2.9)</td>
<td>-4.42</td>
<td>158</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at onset of first episode of depression</td>
<td>63.1 (17.8)</td>
<td>60.7 (19.4)</td>
<td>0.85</td>
<td>168</td>
<td>0.39</td>
</tr>
<tr>
<td>% patients with first episode (N)</td>
<td>61.3 (n=54)</td>
<td>45.1 (n=37)</td>
<td>4.50</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of current episode (weeks)</td>
<td>128.1 (230.4)</td>
<td>89.3 (174.7)</td>
<td>1.13</td>
<td>168</td>
<td>0.26</td>
</tr>
<tr>
<td>% receiving adjunct lorazepam during acute phase (N)</td>
<td>22.7 (n=20)</td>
<td>52.4 (n=43)</td>
<td>16.06</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lorazepam dose (mg/day)</td>
<td>0.92 (0.44)</td>
<td>1.03 (0.60)</td>
<td>-0.75</td>
<td>61</td>
<td>0.45</td>
</tr>
<tr>
<td>% with a co-morbid diagnosis of any anxiety disorder at baseline (N)</td>
<td>23.3 (n=20)</td>
<td>40.0 (n=32)</td>
<td>5.4</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Paroxetine Dose (at the end of acute phase), mg/day</td>
<td>24.2 (10.4)</td>
<td>26.3 (10.9)</td>
<td>-1.27</td>
<td>168</td>
<td>0.20</td>
</tr>
</tbody>
</table>

All results are mean (SD) unless indicated otherwise

*CIRS-G = Cumulative Illness Rating Scale for Geriatrics; **HDRS 17 = 17-item version of the Hamilton Depression Rating Scale; ***Natural Log used in the analyses. Means and standard deviations reported in their original units.
median time to response significantly longer than those with lower BSI: 13.9 [95%CI: 11.0-17.1] vs. 7.9 [95%CI: 5.9-13.6] weeks (Wilcoxon chi-square=4.48, df=1, p=0.03). Among patients who did not receive lorazepam, the difference in time to response between patients with higher versus lower BSI was not significant (Wilcoxon chi-square=0.0858, df=1, p=0.77).

The mean (SD) final dose of paroxetine received by patients with higher or lower BSI did not differ: 26.3 (10.9) vs. 24.2 (10.4) mg/day (t=-1.27, df =168, p=0.21).

The effect of symptomatic anxiety on time to response remained significant in our Cox model, stratifying on baseline HDRS score (minus anxiety items), (Hazard ratio= 0.65, 95% CI: 0.45-0.93, p=0.02).

Figure 1: Anxiety symptoms and time to response. Patients with higher severity of symptoms at baseline averaged 4.3 weeks longer response time.
(Wilcoxon chi-square=6.26, df =1, p=0.012)

Effect of Symptomatic Co-morbid Anxiety on Recurrence during Maintenance Treatment

A higher BSI predicted an increased rate of recurrence (Wald chi-square=7.05, df =1, p=0.008, 95% CI hazard ratio: 1.22-3.72).

Time to recurrence from randomization (see Figure 2) differed across the four groups, with the higher BSI group having a shorter time to recurrence (Log-Rank= 15.00, df=3, p=0.002). Recurrence rates (adjusting for censoring) were 29% (pharmacotherapy with lower BSI scores), 58% (pharmacotherapy with higher BSI scores), 54% (placebo with lower BSI scores) and 81% (placebo with higher BSI scores).

Among patients receiving pharmacotherapy, time to recurrence was significantly shorter for those with
higher BSI scores than those with lower BSI scores (Log-Rank= 5.66, df=1, p=0.02). Among patients on placebo, time to recurrence did not differ significantly between those with higher or lower BSI scores (Log-Rank = 2.54, df =1, p=0.11). Among patients with higher BSI scores, time to recurrence did not differ between those on placebo or paroxetine (Log-Rank=1.95, df =1, p=0.16). Among patients with lower BSI scores, time to recurrence was significantly shorter for those on placebo than on paroxetine (Log-Rank=5.28, df=1, p=0.02).

Because these findings suggested a moderator effect of anxiety, a separate Cox Regression examined the possible moderator effect of anxiety (measured by BSI) on maintenance treatment outcomes, by analyzing the interaction between BSI scores and pharmacotherapy. The results did not confirm a moderator effect (chi-square=0.49, df =1, p=0.48). The power to detect a moderator effect was low (0.22) and Hazard Ratio for the interaction was 1.5 (CI = 0.48-4.68).

We repeated the analysis for both acute and maintenance phases using the BSI as a continuous measure and the results were similar (data not shown but available upon request).

**DISCUSSION**

Our study is the first to show that high pretreatment anxiety symptoms increase not only the risk of non-response in acute treatment but also the risk of recurrence in the first two years after response to treatment in late life depression. In other words, elderly patients who start treatment with higher severity of anxiety have both a poorer acute response and a more brittle long-term response to pharmacotherapy. These results demonstrate a strong negative impact of anxiety symptoms on short- and long-term outcome of depression in old age, even with optimal treatment. These findings for acute treatment effects confirm previous reports (6, 10, 12) that greater pretreatment anxiety is associated with poorer response during acute treatment of LLD. We also found that these co-morbid anxiety symptoms increase the risk of recurrence. To our knowledge, only one previous uncontrolled follow-up study has examined the impact of co-morbid anxiety on long-term outcome of LLD. In this naturalistic study, pretreatment anxiety did not predict time to recurrence (20).

We found that patients with higher BSI scores and adjunctive lorazepam treatment had increased time to response. The use of lorazepam _per se_ probably did not prolong time to response, because patients receiving adjunctive lorazepam but having lower BSI scores had similar time to response as patients not receiving adjunctive lorazepam. This observation is consistent with our previous study (30) that reported that adjunctive lorazepam did not slow the antidepressant response in elderly depressed patients. However, patients with higher BSI not receiving adjunctive lorazepam had shorter time to response than those with higher BSI who received lorazepam. One possible explanation - that deserves further exploration - is that patients with higher BSI who needed adjunctive lorazepam differ clinically from patients with higher BSI who did not need adjunctive lorazepam. This difference might be related to a higher preponderance of GAD-like symptoms in the group who needed adjunctive lorazepam, as GAD more often than other anxiety disorders is associated with worse outcomes (5, 7).

Our study was limited in its power to detect a moderator effect, that is, interactions between treatment and co-existing anxiety. We were able to detect main effects of pharmacotherapy and of anxiety on recurrence, but lacked sufficient power to detect interaction between pharmacotherapy and anxiety.

This study is the first randomized controlled trial that demonstrates the limited efficacy of standard pharmacotherapy in LLD with coexisting anxiety to get and keep patients well. It is important to emphasize that patients treated in this study received very intensive management, with clinicians and psychiatrists reviewing cases weekly and refining treatment plans to minimize attrition and maximize response. Also, adjunctive pharmacotherapy strategies, which were instrumental in many patients achieving response and which were continued during the maintenance phase, were still not enough to protect most patients with co-morbid anxiety from recurring. Even under these intensive treatment conditions that go beyond regular clinical care, co-morbid anxiety had a prominent negative effect on acute and long-term outcomes.

Overall, our findings suggest limited efficacy of current medications with regard to mitigating the impact of co-morbid anxiety on response and recurrence, even though selective serotonin reuptake inhibitors (such as paroxetine, used in this study) are indicated for the treatment of both anxiety and depression. It is also worth noting that adding lorazepam to

**Table 2: Number of Subjects with higher versus lower BSI in each outcome group**

<table>
<thead>
<tr>
<th>Entered Maintenance Phase (Achieved Response)</th>
<th>Completed study (No recurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Medication (N)</td>
</tr>
<tr>
<td>Higher BSI at baseline (N=82)</td>
<td>43</td>
</tr>
<tr>
<td>Lower BSI at baseline (N=88)</td>
<td>66</td>
</tr>
</tbody>
</table>
paroxetine in patients with higher anxiety did not improve outcomes. Alternative treatment options should be considered for these patients.

Given the detrimental effect of anxiety on long-term course of depression and the limited benefit demonstrated here even with optimal treatment, clinicians are left with the challenge of what they can do to improve outcome in this group of patients (33). Expert consensus guidelines (34) recommend maximizing the antidepressant. It is possible that doses of paroxetine higher than those used in this study would have yielded better outcomes in anxious patients (35). However, older adults may not tolerate very high doses of antidepressants, given the frequent medical comorbidity and sensitivity to medications’ side effects in this population. Further research involving possible pharmacological alternatives [e.g. adjunctive use of second-generation antipsychotic agents (36, 37)] as well as learning-based psychotherapies (like problem-solving therapy and cognitive-behavioral therapy [38, 39]) is warranted.

In conclusion, replicating and extending the results of previous studies, our findings indicate a need for active identification and aggressive treatment of anxiety symptoms in late-life depression, as well as the need for further research to identify optimal treatment. In order to improve outcomes in elderly patients with anxious depression, we need to develop and test treatment algorithms that would involve both psychosocial and pharmacological alternative treatments.

REFERENCES

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