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Treatment resistant depression and Axis I co-morbidity

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ABSTRACT

Background. Treatment resistant depression (TRD) continues to present a formidable challenge to clinicians, accounts for over half of the annual costs associated with treatment for depression and causes great frustration to patients. Although there have been studies attempting to define TRD, little information is available as to the cause of TRD. One suggestion is that patients with TRD have a greater frequency of co-morbid psychiatric disorders, which explains their resistance to standard antidepressant treatments. The objective of this study was to compare the co-morbidity of Axis I disorders between a sample of TRD patients and a sample of non-TRD patients.

Methods. TRD and non-TRD patients, recruited from two separate antidepressant treatment studies, were assessed for Axis I co-morbidity using the SCID-P for the DSM-III-R. Patients for the two samples were then matched for baseline HAM-D-17 total score and gender.

Results. Results reveal that non-TRD patients had a higher rate of both lifetime and current generalized anxiety disorder co-morbidity than did the TRD patients. No other statistically significant differences in Axis I co-morbidity were found.

Conclusions. These findings do not support the idea that current or lifetime Axis I co-morbidity is more common in TRD than non-TRD patients. In fact, the only statistical difference showed non-TRD patients with higher co-morbidity rates.

INTRODUCTION

Despite efforts in recent years to formulate algorithms and guidelines for the treatment of patients with refractory, or treatment resistant, depression (TRD), this condition continues to present a formidable challenge to clinicians (Nierenberg & Amsterdam, 1990; Nierenberg & White, 1990). TRD patients account for only 15–30% of depressed patients undergoing psychiatric treatment, but represent over half of the total annual costs associated with the treatment of depression (Burrows *et al*. 1994). Because clinicians typically use multiple mono- and polypharmacological strategies over long time periods, great frustration can develop when patients demonstrate no or partial response.

To date, the majority of the research on TRD has focused on how to define treatment-resistance (Nierenberg & White, 1990; Phillips & Nierenberg, 1994; Fava *et al*. 1996). Initial concerns included the possibility that many patients labelled as treatment resistant were simply treated with inadequate dosages of antidepressants or took these medications for an insufficient length of time. Greater consensus, however, has been reached recently with respect to defining treatment-resistance. Phillips & Nierenberg (1994) provide dosage and plasma levels that should be used and sustained before considering a trial as being adequate. In addition, the same authors suggest that a medication trial of 4 to 6 weeks may not be of sufficient duration to assess response/non-

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response. Trials of medications should be conducted for a minimum of 6 weeks, and up to 12 weeks if a partial response is detected. There is less consensus, however, with respect to the number of failed medication trials necessary before a patient can be defined as resistant. Some argue that failing one adequate trial constitutes treatment-resistance, whereas others believe multiple failed trials are necessary before reaching this conclusion (Nierenberg, 1990).

Prior to efforts dedicated to defining TRD, many researchers examined variables that may be predictive of response to antidepressant treatment. Among the factors found to be associated with poorer outcome included: longer current episodes, a greater level of self-reported *versus* clinician-rated symptom severity, somatization symptoms, certain co-morbid personality and Axis I disorders, the melancholic depressive subtype, low pre-treatment cortisol levels, blunted prolactin response to fenfluramine challenge, concurrent substance abuse, lack of social support, neuroticism, high reward dependence, lower levels of education, psychomotor retardation and higher initial symptom severity (Rush *et al.* 1983; Frank *et al.* 1984; Joyce & Paykel, 1989; Kocsis *et al.* 1989; Nierenberg, 1990; Goodwin, 1993; Popescu *et al.* 1993; Schmauss & Erfurth, 1993; Hoencamp *et al.* 1994; Nelson *et al.* 1994; Phillips & Nierenberg, 1994; Burns *et al.* 1995; Nelson & Cloninger, 1995; Fava *et al.* 1996; Spillman *et al.* 1997; Cleare *et al.* 1998; Flory *et al.* 1998; Hirschfeld *et al.* 1998). In a study based on the NIMH Collaborative Research Program, cognitive, social, and work dysfunction were all predictive of poorer outcome in one or more of the treatment groups (Sotsky *et al.* 1991). Hirschfeld *et al.* (1998) found that living with a partner or spouse, having more education and having a higher quality of life were all associated with better outcome.

Two distinct limitations do not allow the above findings to be extrapolated for the question of what contributes to treatment resistance. First, the finding that the above variables are predictive of poorer response to treatment has not been uniformly replicated. In fact, some researchers have found that the same factors bear no relation to treatment response (Joyce & Paykel, 1989; Kocsis *et al.* 1989; Hirschfeld *et al.* 1998). Secondly, none of these studies examined patients who had been identified as treatment resistant prior to the onset of treatment. Rather, status as a non-responder was based only on the medication trial pertinent to the prospective study in the reports.

Some researchers have argued that, at a conceptual level, the most logical explanation for treatment resistance is co-morbidity of other disorders, which compromises the effectiveness of standard antidepressant treatments (Nierenberg & Amsterdam, 1990). For example, if a patient suffers from both depression and OCD, certain antidepressant treatments may be ineffective in alleviating the entire constellation of symptoms. In such cases, what are actually symptoms of the co-morbid condition can appear as unresolved depressive symptoms. This problem is compounded by the tendency for clinicians to overlook co-morbid conditions, especially outside of research settings where time and resource constraints may not allow for formal, structured diagnostic interviews. To test such a model formally, a comparison would have to be made between TRD and non-TRD patients.

There exists a clear need for a better understanding of what factors are associated with TRD, especially compared with depression that does not exhibit resistance to treatment. Are there certain factors that help separate TRD as a distinct subtype? If so, then improvements could be made to customize treatments for this population of patients. To this end, the objective of this study was to compare a sample of patients formally defined as treatment resistant with a sample of patients not having experienced treatment resistance. In particular, we were interested in rates of Axis I co-morbidity between these two samples. Our hypothesis was that treatment resistant patients would experience higher rates of Axis I co-morbidity, possibly explaining their resistance to standard antidepressant treatments.

METHOD

TRD and non-TRD participants were recruited through respective out-patient antidepressant clinical trials at the Massachusetts General Hospital's Depression Clinical and Research Program (DCRP). Common exclusion criteria

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Table 1. *Demographic and clinical data*

Characteristic	TRD sample	Non-TRD sample
Gender, *N*		
Male	39	78
Female	31	61
Age of 1st onset	23·2 years	27·3 years
Duration of current episode, mean	46·5 months	35·0 months
Prior episodes, mean	0·97	1·08

for both trials were: a history of organic mental or seizure disorder, serious or unstable medical illness, substance abuse disorders active within the past 12 months, acute suicidal risk (as assessed through clinical interview and using the HAM-D-17 and BDI), pregnancy, lactation, bipolar disorder, psychotic disorders, history of adverse reaction or allergy to study medications, concomitant use of psychotropic medications, and clinical or laboratory evidence of thyroid abnormalities. Participants in both studies signed Institutional Review Board (IRB) approved informed consent immediately prior to the initial study visit.

Enrolment in the two out-patient studies was as follows: 92 patients were enrolled between 1993 and 1999 in the TRD study and a total of 378 patients between 1989 and 1994 were enrolled in the non-TRD study. Because of non-completers and insufficient data, only 70 of the TRD patients were used in the analysis. For the non-TRD patients 139 were used in analysis, as two non-TRD patients were matched to each TRD patient (process is described below). From the available non-TRD sample, patients were randomly selected as representative matches for each TRD patient. Inclusion criteria for the TRD study were as follows: men and women ages 18 to 70 with major depressive disorder (MDD) as diagnosed using the Structured Clinical Interview for the DSM-III-R (SCID-P) (Spitzer *et al.* 1989); a score on the 17-item Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1960) of $\geqslant 18$; and at least one, but no more than five, adequate failed medication trials during the current episode of MDD. 'Adequacy' was assessed using the McLean Hospital Antidepressant Treatment Record (McATR) (Nierenberg, 1992), which, providing specific criteria for adequate dosage and duration for a trial, defines an 'adequate trial' as maintaining a significant dosage level (which varies from medication to medication) of medication for at least 6 weeks. This study was designed specifically for patients with TRD. Clinicians conducting patient interviews were formally trained in the use of the above instruments and scales. Inter-rater reliability, for the use of the SCID-P in our group of clinicians across a wide range of studies, was recently estimated as kappa = 0·80 (Fava *et al.* 2000).

Inclusion criteria for the non-TRD protocol included: men and women ages 18 to 65 meeting criteria for current MDD as defined by the SCID-P (Spitzer *et al.* 1989); a HAM-D-17 score of $\geqslant 16$ at baseline; and being completely free of psychotropic medications for at least 2 weeks before the baseline visit. Additional specific exclusion criteria for this study include a past history of failure of 60 to 80 mg of fluoxetine per day and a failure of the combination of fluoxetine and desipramine or lithium. All patients entering this trial did not meet criteria for treatment-resistance during the current episode of MDD as defined in the TRD study.

Participants from both studies were matched for baseline HAM-D-17 total score and gender in order to minimize the effect of these variables on comparisons of Axis I co-morbidity. Each of the 70 TRD patients was matched as above with two non-TRD patients, with the exception of one TRD patient for whom only one match could be identified in the non-TRD sample. HAM-D-17 total scores were matched within one point of each other (i.e. a total score of 19 for a TRD patient was matched to a non-TRD patient total score of 18–20). The investigators felt that given the limited number of study subjects available in the TRD study, this was the most effective way to detect differences between the study groups. This method not only allowed for comparisons between like subjects, but also increased the overall statistical power of the analyses.

Multiple chi-square analysis was used to compare frequencies of Axis I disorders between TRD and non-TRD patients as well as to compare categorical baseline demographic and clinical variables for which patients in the two samples were not matched (see Table 1). Unpaired *t* tests were used to compare baseline demographic and clinical variables measured in a continuous manner.

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RESULTS

Mean age for the TRD sample was 41·8 years and for the non-TRD sample was 39·3 years ($t = 1{\cdot}531$, $P = 0{\cdot}1273$). Table 1 depicts gender distribution and other clinical data for both TRD and non-TRD samples. No significant differences were found between study groups for any of the variables listed in Table 1. As described previously, TRD and non-TRD patients were matched at baseline for HAM-D-17 total score and gender. Table 2 presents frequency of types medications failed by the patients in the TRD sample. Table 3 presents Axis I lifetime co-morbidity data, as well as chi-square analyses, which evaluated differences in co-morbidity between the two groups. As can be seen from Table 3, only one statistically significant difference existed between the two groups – non-TRD patients had a significantly higher rate of lifetime GAD co-morbidity than the TRD patients. No other differences were found to be statistically significant. Range of Axis I lifetime co-morbidity was 4·3–30·0% for TRD patients and 5·0–34·5% for non-TRD patients. Table 4 presents Axis I current co-morbidity data, as well as chi-square analyses,

Table 2. *Frequency of medications failed in the current depressive episode by TRD patients*

Medication(s)	Received	Not received
SSRI	88	4
Effexor	26	66
MAOI	16	76
Bupropion	26	66
Tricyclic	26	66
Trazodone	16	76
Nefazodone	15	77
Remeron	14	78
Lithium augmentation	19	73
Thyroid augmentation	0	92
SSRI combination	19	73

Table 3. *Lifetime Axis I co-morbidity*

DSM diagnosis	TRD sample Frequency (%)	Non-TRD sample Frequency (%)	χ^2	P
Alcohol abuse	21/70 (30·0)	47/139 (33·8)	0·308	0·6404
Other substance abuse	10/70 (14·3)	30/139 (21·6)	1·602	0·2642
Panic disorder	12/70 (17·1)	17/139 (12·2)	0·940	0·3970
OCD	7/70 (10·0)	7/139 (5·0)	1·836	0·2398
Agoraphobia	8/70 (11·4)	9/139 (6·5)	1·529	0·2831
Social phobia	19/70 (27·1)	48/139 (34·5)	1·167	0·3464
Simple phobia	9/70 (12·9)	19/139 (13·7)	0·026	> 0·9999
GAD	3/70 (4·3)	22/139 (15·8)	0·589	0·014*
Somatoform disorders	6/70 (8·6)	7/139 (5·0)	0·998	0·3672
Eating disorders	6/70 (8·6)	12/139 (8·6)	0·002	0·9999

OCD, Obsessive–compulsive disorder; GAD, generalized anxiety disorder.
For all χ^2 comparisons df = 1.
* $P < 0{\cdot}05$.

Table 4. *Current Axis I co-morbidity*

DSM diagnosis	TRD sample Frequency (%)	Non-TRD sample Frequency (%)	χ^2	P
Alcohol abuse	2/70 (2·9)	8/139 (5·8)	0·858	0·5010
Other substance abuse	1/70 (1·4)	8/139 (5·8)	2·115	0·2775
Panic disorder	6/70 (8·6)	10/139 (7·2)	0·125	0·7849
OCD	4/70 (5·7)	4/139 (2·9)	1·018	0·4458
Agoraphobia	4/70 (5·7)	7/139 (5·0)	0·043	> 0·9999
Social phobia	15/70 (21·4)	42/139 (30·2)	1·812	0·1923
Simple phobia	6/70 (8·6)	19/139 (13·7)	1·149	0·3685
GAD	3/70 (4·3)	22/139 (15·8)	5·889	0·0137*
Somatoform disorders	4/70 (5·7)	6/139 (4·3)	0·200	0·7348
Eating disorders	2/70 (2·9)	1/139 (0·7)	1·504	0·2603

OCD, Obsessive–compulsive disorder; GAD, generalized anxiety disorder.
* $P < 0{\cdot}05$.

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which evaluated differences in co-morbidity between the two groups. As can be seen from Table 4, one statistically significant difference existed between the two groups – non-TRD patients had a significantly higher rate of current GAD co-morbidity than TRD patients had. No other differences were found to be statistically significant. Range of Axis I current co-morbidity was 1·4–21·4% for TRD patients and 0·7–30·2% for non-TRD patients.

DISCUSSION

To our knowledge, this is the first study to compare Axis I co-morbidity between two samples of depressed out-patients who had been formally defined as treatment resistant and non-treatment resistant. We found only one significant difference between the two groups – non-TRD patients had significantly higher rates of current and lifetime GAD than the TRD patients. Rates of Axis I lifetime co-morbidity were found to range from 4·3–30·0% for TRD patients and 5·0–34·5% for non-TRD patients. Not only are these rates lower than found previously in a sample of treatment resistant unipolar patients, but they also do not support the idea that higher rates of Axis I co-morbidity contribute to treatment-resistance (Sharma *et al*. 1995).

It is important to note that some research has been conducted to examine what factors are associated with Axis I co-morbidity in depressed out-patients. Recent research indicates that Axis I co-morbidity in depressed patients may vary with gender. Fava *et al*. (1996) and Carter *et al*. (1999) both found that women were more likely than men to have a lifetime history of bulimia nervosa, while men were more likely than women to have a history of substance abuse and dependence. Alpert *et al*. (1999) found that patients with early-onset depression had a greater number of Axis I co-morbid conditions when compared to patients with late-onset depression. Tedlow *et al*. (1999) demonstrated that depressed patients with anger attacks did not differ from those without anger attacks with respect to Axis I co-morbidity. However, the above studies did not focus on the association between co-morbidity and treatment-resistance.

Strengths of our study include using formal criteria to define treatment-resistance and matching patients for gender and baseline depression severity. Using formal TRD criteria is especially critical given recent debate concerning what constitutes treatment-resistance. Our use of matching patients for gender and initial symptom severity is also critical, as these two variables have been found to be associated with differing rates of co-morbidity and response to treatment. In addition, the documented inter-rater reliability between the physicians at the center where the studies were conducted also adds significant validity to the study results.

There are several possible limitations to our study. The first is a sampling bias resulting from respective exclusion criteria of the studies from which patients were drawn. For example, both studies excluded patients with concurrent substance abuse. Perhaps this led to rates of co-morbid substance abuse disorders that were lower than what would be found in general practice. Sampling bias in a study population also tends to lead to a sample having more prominent occurrence of specific conditions and characteristics than in the normal population. Study subjects are specifically seeking out help and may therefore present with different severity and prevalence of symptoms and co-morbid conditions than subjects not seeking help. In addition, the severity of the patient's depressive state may have affected his/her ability to report co-morbid symptoms. It is possible that symptoms of MDD could influence the accuracy of a patient's account and recall of current or lifetime symptomatology. We also do not know to what extent our findings may have differed if we had examined only chronic TRD patients as opposed to acute TRD patients. Our sample of TRD patients was experiencing an acute major depressive episode, but not necessarily a chronic condition. We must also note that the fact that the subjects were from two different studies is in itself a shortcoming. The variety of methods and procedures used in the two studies could have in itself caused variability in the measures used or it could have prevented differences from being detected. It should also be noted that treatment resistance was determined retrospectively rather than prospectively. More statistical power could be achieved in future studies by prospectively identifying treatment resistance. The obvious difficulty in using a retrospective analysis is the possible bias inherent in a patient's reporting of

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failed trials, especially during an acute major depressive episode.

There are some further limitations that are worth noting. Given the small sample size of the TRD patients, attempts were made to increase statistical power by matching TRD subjects with non-TRD subjects; however, we would suggest that further studies be done using larger sample sizes before fully interpreting the differences found here between TRD and non-TRD patients in regards to lifetime and current rates of GAD co-morbidity. Small sample sizes could have resulted in differences in Axis I co-morbidity rates that appear clinically meaningful (e.g. TRD OCD co-morbidity rate of 10% *v.* non-TRD OCD co-morbidity rate of 5%), but in fact are not statistically significant. With such low rates of prevalence, it is possible that even a larger sample would not increase the importance of this finding. In addition, the TRD subjects had a varying number of failed trials to a variety of different medications. Because there was no way of controlling for this variability, we do not know what effect it may have had on the ability of subject to report co-morbid symptoms. Often a medication will alleviate one or more symptoms that may or may not be related to the depression; these symptoms can be related to the comorbid condition, but are often easily confused with symptoms of depression. Because of the small sample size of TRD patients, we were unable to examine the effect of number of failed trials on outcome. It is possible that a group of TRD patients with a more homogeneous and large number of failed trials would experience higher rates of Axis I co-morbidity. We should note also that although we did match patients on two important variables – age and initial severity of depression, this study would have been strengthened by matching on additional clinical variables, including number of prior treatments, duration of the current episode, first age of onset, and number of prior episodes. Future studies should attempt to broaden matching criteria, which will strengthen any conclusions reached regarding differing rates of Axis I co-morbidity.

A final issue, briefly touched on earlier, concerns the interplay of co-morbid condition, the treatment(s) to which a patient was resistant, and the distinction between recovery from depression and improvement in the co-morbid condition(s). There is the possibility that treatments to which a given patient was resistant in his/her current major depressive episode had an effect on symptoms of a co-morbid condition. For example, despite lack of an antidepressant response to fluoxetine, a given patient's co-morbid OCD may have improved during the course of using this medication. Similarly, a different co-morbid condition (e.g. PTSD) may not have improved at all under the same scenario. It is difficult, if not impossible, to assess the effects of such relationships between co-morbid conditions and antidepressant medications that patients were resistant to. This is due to the complex permutations of such relationships, which are beyond the scope of this paper to formally evaluate. However, a limitation of this study is that our ability to measure prevalence of co-morbid conditions may have been affected by such factors.

A related issue concerns the degree to which depression and other co-morbid conditions are related. Is panic disorder more closely related to depression that PTSD? What about OCD and social phobia? From a theoretical standpoint, one could argue that certain conditions share more in common (i.e. avoidant behaviour in social phobia and withdrawn behaviour in depression). For this reason, it is difficult to assess whether an improvement in depressive symptoms is because of a change in a co-morbid condition and vice versa. Again such relationships could have affected our ability to measure rates of co-morbidity in the current study.

The current study adds to the body of literature concerning TRD. As reviewed by Nierenberg & White (1990), Phillips & Nierenberg (1994) and Fava *et al.* (1996), methodology of past TRD studies varies somewhat. The most important distinction between studies concerns whether treatment-resistance was determined prospectively or retrospectively. In the current study, we did so in a retrospective fashion, to which there are obvious disadvantages that were mentioned earlier. The other two most important factors that distinguish TRD studies from each other are type of exclusion criteria and definition of what constitutes a failed trial. In the current study, patients were excluded for reasons common to drug trials and a failed trial was formally defined using the McATR. In previous studies of TRD,

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patients were not always drawn from drug trials, but from a variety of sources. Thus exclusion criteria varied, which can have an effect on study outcomes. In addition, a failed trial is defined in a much looser fashion in most previous TRD studies, therefore creating the possibility that such trials do not actually represent treatment resistance.

In summary, findings from this study do not support the idea that current or lifetime Axis I co-morbidity occurs at higher rates in TRD *v.* non-TRD patients. In fact, the only statistically significant difference found between the two groups was that GAD occurred at higher rates in the non-TRD sample when compared with the TRD sample. These findings are important as they contribute to our knowledge base of what factors cause or are associated with resistance to treatment. Through better understanding of these factors, treatments can be tailored for this sub-population of depressed patients.

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