The Treatment of Nonmelancholic Depression: When Antidepressants Fail, Does Psychotherapy Work?

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Objective: Treatment-resistant depression (TRD) is used as a descriptive or diagnostic term and has generated many management guidelines weighting antidepressant (AD) therapy, but which may be an inappropriate paradigm for the nonmelancholic disorders where psychotherapy may be a more salient modality. This study sought to evaluate the effectiveness of psychological therapy in patients whose nonmelancholic depressive condition had been resistant to at least 2 ADs.

Method: Principal analyses compared 32 patients, diagnosed with a nonmelancholic depression who received 12 weeks of psychological therapy, with a small control group. Comparative analyses failed to find a distinct therapeutic effect, leading to an extension study pursuing candidate explanatory factors for this lack of response, including psychosocial factors.

Results: While our sample showed a 41% response and 22% remission rate to psychotherapy, their improvement pattern was similar to the control group, thus arguing against any specific therapeutic benefit. Explanatory factors nominated by the treating psychologist weighted personality issues for 35% of the patients, distal stressors for 22%, and comorbid anxiety conditions for 18%. When sample members were compared with an age- and sex-matched sample of patients with nonmelancholic depression who improved distinctly during a similar 12-week period, rates of such putative personality, stress, and anxiety risk factors did not differ, arguing against the likelihood of these factors compromising improvement.

Conclusions: Patients with nonmelancholic TRD also failed to demonstrate a clear response to a psychotherapeutic approach, while our pursuit of clinically explanatory variables was not supported empirically.

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Treatment-resistant depression remains a clinical conundrum in terms of identifying underlying mechanisms and formulating management options. A recent review highlighted the keen interest in the topic illustrated by more than 2600 published articles reviewing TRD and related constructs during the preceding 5 years. Despite such a wealth of publications, Möller et al stated that there is neither an agreed on operational definition of TRD nor has any distinct phenotypic pattern been identified. TRD is sometimes positioned as synonymous with chronic depression, although the latter refers more to a prolonged and enduring depressive condition and the former weights failure to respond to multiple strategies and with minimal or no emphasis on its duration. Other overlapping terms consistently used are refractory depression, difficult to treat depression, and residual depression. Therefore, TRD may overlap conceptually and clinically with other terms, and there is no universally accepted definition.

Despite such ambiguities, TRD is a common clinical phenomenon. An early report quantified that one-third of depressed patients fail to respond to an initial AD, while an additional 50% partially respond. The more recent STAR*D study quantified remission rates across the first 4 treatment steps (with a complete description of the treatment steps provided in Rush et al) of 37%, 31%, 14%, and 13%, respectively. STAR*D treatment steps principally involved differing ADs, although a percentage received CBT, either alone or in combination with an AD. If patients did not achieve remission or could not tolerate a treatment step, they were encouraged to proceed to the next acute treatment step. The cumulative remission rate after those 4 steps was 67%, indicating that one-third were nonremitters after that fourth stage—a nonremission rate consistent with the earlier estimate.

While TRD is sometimes applied as a diagnosis, it may be better positioned as a descriptor—capturing treatment nonresponse across heterogeneous unipolar and bipolar depressive disorders and reflecting multiple possible determinants. Determinants may be biological (for example, rapid metabolizing status), psychological (for example, a personality contribution), social (for example, SLEs), or reflect the differential effectiveness and salience of drug and nondrug treatment modalities across constituent depressive conditions.

An operational model was proposed by Thase and Rush that defines TRD by weighting response to ADs, and where they detailed a 4-item staging model, progressing across nonresponse from no medication having been tried; an adequate trial of 1 or 2 differing and adequate ADs; failure

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**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| AD           | antidepressant |
| BDI          | Black Dog Institute |
| CBT          | cognitive-behavioural therapy |
| CCDAS        | Costello and Comrey Depression and Anxiety Scale |
| ECT          | electroconvulsive therapy |
| IPT          | interpersonal therapy |
| MDD          | major depressive disorder |
| QIDS-SR      | Quick Inventory of Depressive Symptomatology—Self-Report |
| RCT          | randomized controlled trial |
| SAS-SR       | Social Adjustment Scale—Self-Report |
| SLE          | stressful life event |
| STAR*D       | Sequenced Treatment Alternatives to Relieve Depression |
| T & P        | Temperament and Personality |
| TAU          | treatment as usual |
| TRD          | treatment-resistant depression |
to respond to 2 differing augmentation strategies; and failure
to respond to ECT. Such a model has strongly influenced
the conceptualization and management of TRD, with the
now commonly accepted definition being failure to respond
to 2 or more AD trials of adequate dose and duration.7 Such
a definition weights resistance only in relation to physical
treatments, such as ADs and ECT, and effectively ignores
causal or diagnostic factors. In fact, psychotherapy is
generally positioned as an adjunct treatment rather than a
primary treatment option for TRD. Despite some indication
from a small RCT that CBT may be more effective for
primary treatment option for TRD. Despite some indication
of a nonmelancholic depression may reflect
resistance—but more a paradigm failure, with treatment
situations, failure to respond may not reflect treatment
effectively create a (false-positive) TRD scenario. In such
or SLE precipitants, the role of ADs may be limited and
TRD emerges from personality-based predispositions
and seek to address the principal cause. A quintessential
biological condition is melancholic depression, where
its treatment ascriptions include a preferential response
to physical treatments, such as drugs and ECT, a poorer
response to psychotherapy, and a low placebo response.11
By contrast, CBT and IPT assume an etiological
predisposition emerging from the individual’s personality
style and psychosocial stressors, respectively, and weight
interventions targeting such causal factors. If, in fact,
TRD emerges from personality-based predispositions
or SLE precipitants, the role of ADs may be limited and
effectively create a (false-positive) TRD scenario. In such
situations, failure to respond may not reflect treatment
resistance—but more a paradigm failure, with treatment
choice not matched to causal factors.12 Our model of
the nonmelancholic depressive disorders is that they are
principally a consequence of antecedent stressors and
(or) a vulnerable personality style, as detailed by Parker
and Manicavasagar.10 Assuming that a diagnosis of TRD
in people with a nonmelancholic depression may reflect
failure to provide a cogent nondrug therapy designed to
address these factors, we designed a study to determine the
impact of a paradigm change to management. We report
key study analyses and undertook an extension study to
determine possible explanatory factors.

Methods

Intervention Study and Control Groups

We sought to recruit patients receiving a clinical diagnosis
of a nonmelancholic depression who had failed to report
any distinct improvement to 2 or more adequately trialled
ADs during their lifetime and who had not received
psychological treatment in the preceding 3 months.
Eligible patients (treatment group) were invited to receive
psychotherapy from an experienced clinical psychologist.
People unable to attend weekly treatment sessions owing
to geographical reasons were assigned to a control group.

Recruitment and Assessment

The sample was derived during the 2009 to 2012 period
from patients (over 18 years) attending the BDI Depression
Clinic, a state-wide tertiary service for patients with a
primary mood disorder. Clinic patients were referred by
their managing doctor for diagnostic and management
advice in relation to persisting and (or) severe depressive
conditions.

All patients received a detailed clinical assessment by a
BDI psychiatrist. A clinical diagnosis of nonmelancholic
depression required the absence of any prototypic13
melancholic features (for example, psychomotor
disturbance, a nonreactive and anhedonic mood, energia,
and diurnal variation of mood and energy) and the presence
of putative nonmelancholic features, such as mood
reactivity and increased appetite and (or) food cravings.
Study exclusions were excessive drug or alcohol use, a
primary medical problem or contributory organic condition,
or a substantive alternative primary diagnosis. We viewed
the psychotherapeutic intervention as primary (and under
evaluation), and therefore did not exclude patients if their
managing therapist changed their medication and (or)
dosage during the study course.

Prior to clinical assessment, patients completed the
computerized Mood Assessment Program, which generates
sociodemographic and clinical information, including
age at depression onset, current length of depressive
episode, medical history, number of previous medications
trialed, impact of current and SLEs, family history of
mood disorders, history of anxiety disorders or use of
illicit drugs and alcohol, medications (past and present),
organic and medical conditions, and personality styles.
The last was assessed by the T & P Questionnaire,14 which
generates 10 scale scores, with 8 (that is, social avoidance,
irritability, perfectionism, anxious worrying, personal
reserve, self-criticism, interpersonal sensitivity, and self-
focused) assessing at-risk temperament and personality
styles to depression and 2 (that is, cooperativeness and
effectiveness) assessing disordered personality function.
The measure is psychometrically sound, with high
internal consistency, test–retest reliability, and concurrent
validity.\textsuperscript{14} All patients provided informed consent and the study was approved by the University of New South Wales Ethics Committee.

We aimed to quantify 12-week progress between people who accepted the psychotherapeutic intervention and those in an adequately sized TAU comparison group who were unable to attend the clinic for various reasons. Recruitment proved extremely difficult, and, during the 3-year period, only 41 patients met both eligibility criteria and consented to be in the treatment or control group. Therefore, we elected to cease recruitment after enrolment and 12-week completion of at least 30 patients, and with our final treatment sample totalling 32 patients, while our TAU control group had only 8 patients. Despite limited comparison sample sizes, analyses (as shown below) allow interpretation of progress in the treatment group to be offered with some degree of confidence.

**Primary and Secondary Study Measures**

A battery of questionnaires were completed by participants in both groups at study commencement (baseline), weekly intervals, and at 12-week study completion. The measures completed at these 2 time points are outlined in the following section.

**Weekly Measures**

Our primary measure was the 16-item, self-report version of the QIDS-SR,\textsuperscript{15} measuring depression severity. The QIDS-SR has been shown to be sensitive to change to medications and psychotherapy treatments, and has adequate reliability and validity scores.\textsuperscript{16} Secondary weekly measures included the 14-item anxiety subscale of the Depression Anxiety Stress Scales\textsuperscript{17} and the 6-item Work Productivity and Activity Impairment Questionnaire,\textsuperscript{18} measuring work and activity impairment—with both measures having sound psychometric properties.\textsuperscript{18,19} Life enjoyment and satisfaction was measured by the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire,\textsuperscript{20} which has been shown to have acceptable reliability and validity in the development study.

**Measures Completed at Baseline and 12-Week Study Completion**

In addition to the weekly measures, all patients completed 3 additional measures at baseline and 12-week study completion: the 54-item, self-report version of the SAS-SR,\textsuperscript{6} the anxiety scale of the CCDAS,\textsuperscript{22} and a clinic-developed, 6-item Overall Functioning Assessment (based on the Work and Social Adjustment Scale\textsuperscript{23}), which measures global impairment during the preceding month. The SAS-SR is a widely used measure of social adjustment, with various studies attesting to its acceptable psychometric properties.\textsuperscript{24,25} The CCDAS is a measure of trait anxiety and has been shown to have acceptable reliability and concurrent validity.\textsuperscript{26} All measures were computer-completed, with the control group receiving an email with a link to the questionnaires at weekly intervals. Patients also underwent a structured diagnostic interview administered by a trained research assistant, involving mood disorder modules and the psychotic disorders section of the Mini International Neuropsychiatric Interview,\textsuperscript{27} to ascertain the presence of a major depressive episode at baseline and at study completion.

**Therapeutic Intervention**

Patients receiving psychological treatment from our BDI Depression Clinic psychologist received 10 sessions conducted during a 12-week period—the first 8 were weekly sessions, followed by 2 sessions conducted 2 weeks apart. The BDI psychologist had a formal clinical psychology degree and 10 years’ experience in providing psychological therapies to patients with depression. The treatment model was broadly based on our theoretical formulation of etiological and maintaining factors contributing to nonmelancholic depression, but was tailored to meet the particular needs of each patient. The treatment plan had some consistent components, including an initial focus on psychoeducation about nonmelancholic depression, the identification of short- and long-term stressors, and an examination of coping styles. Subsequent sessions focused more on individual personality characteristics, cognitions, and schemas that were formulated as contributing to the persistence of the patient’s depression. Although a range of psychological approaches were used, the main ones were CBT (n = 27), IPT (n = 8), schema therapy (n = 5), acceptance and commitment therapy (n = 2), dialectical behavioural therapy (n = 2), and mindfulness training (n = 2).

**Statistical Analysis**

Principal analyses involved independent Student $t$ test and chi-squared analyses of all study variables compared from baseline to the final therapeutic session after 12 weeks. Data management and analyses were conducted using SPSS, version 20.0 (SPSS Inc, Chicago, IL).

**Results**

**Comparison of Principal Study Groups**

The treatment (n = 32) and control (n = 8) groups did not differ by mean age (mean 43.2, SD 13.7 and mean 49.0, SD 8.3, respectively; $t$ = 1.07, $df$ = 38, $P$ = 0.29), marital status ($\chi^2 = 0.98$, $df$ = 2, $P$ = 0.61 across 3 categories), employment status ($\chi^2 = 5.31$, $df$ = 4, $P$ = 0.26 across 5 categories), or education level ($\chi^2 = 2.54$, $df$ = 4, $P$ = 0.64 across 5 categories). The female preponderance was lower in the treatment group (51.5%) than the control group (62.5%) but nonsignificant ($\chi^2 = 0.31$, $df$ = 1, $P$ = 0.58).

The treatment and control groups reported a similar age of depression onset (21.0 and 25.0 years), and current depressive severity (QIDS-SR = 15.6 and 14.6), although the treatment group reported a nonsignificantly shorter current depressive episode (74.4 and 81.4 days). The treatment group had previously trialled (over their lifetime) fewer ADs for their depression than the control group (3.6 and 5.9, respectively; $t$ = 3.06, $df$ = 38, $P$ = 0.004).
Table 1 reports baseline and study completion data for the patients receiving treatment. There was a significant improvement on our primary measure of depression severity (the QIDS-SR) and on all secondary measures other than the work productivity and quality of life measures, and the trait anxiety subscale. The responder rate (that is, at least a 50% reduction in QIDS-SR scores) was 40.6%, while remission (that is, a QIDS-SR score of 5 or less) was achieved by 21.9%.

Table 2 reports change scores on all study measures by patients in the treatment and control groups, with analyses failing to quantify any significant differences on any study measure. While patient numbers in the control group were low, the parallel changes in study measure scores across the 2 groups were quite striking. As an illustration, we plot only weekly scores on our primary QIDS-SR measure (Figure 1). Seemingly identical trajectories of improvement in QIDS-SR scores are evident in both groups. This suggests that any improvement in people receiving psychotherapy likely reflects a natural remission or related phenomenon rather than any specific therapeutic effect. Thus our hypothesis that provision of an active psychotherapeutic intervention would be a more salient and effective treatment modality in patients with a nonmelancholic TRD was not supported. Subsequent analyses explored possible explanations.

Qualitative Analyses

We invited our study psychologist to provide a formulation for treatment group participants of contributory factors, to both onset and depression persistence, as identified at initial assessment and during the therapy course. The psychologist was required to select the relative contribution for each patient (from 5 a priori options and with multiple options allowed) of the explanatory factors judged as potentially compromising any distinct therapeutic response—whether or not the patient actually improved across the intervention period. The most commonly nominated factor (mean 35%, SD 13.7) was the patient’s personality style (for example, rejection sensitivity, self-criticism, and anxious worrying) or the presence of a personality disorder (for example, rejection sensitivity, self-criticism, and anxious worrying).
avoidant, narcissistic, and borderline). Next (mean 22%, SD 12.9) was the impact of distal childhood stressors, such as childhood sexual abuse or absent and (or) limited parental attachment bonds. Other commonly selected factors included the presence of a comorbid anxiety condition (mean 18%, SD 11.4), enduring stressors, such as financial or employment issues (mean 12%, SD 9.6), and recent stressors, such as a marital breakdown or the loss or death of a significant other (mean 12%, SD 12.7).

In relation to depression persistence, personality style or personality disorder nuances were nominated for 18 patients (55%). Other factors included the continuing impact of distal stressors, such as childhood abuse (n = 8 or 24%), comorbid factors, such as anxiety (n = 4 or 12%), recent severe stressors (n = 2 or 6%), and enduring or chronic stressors (n = 1 or 3%).

Subsidiary Quantitative Analyses

We subsequently undertook a quantitative study to examine the potential salience of the factors identified in the qualitative analyses to compromising response to therapy. Such an objective required a comparison with a patient sample, whose members had, by contrast, shown a substantive therapeutic response. Therefore, we derived an adequately sized age- and sex-matched group of independent patients (improver sample) diagnosed with a nonmelancholic depression at the BDI Depression Clinic and reported a 50% or more improvement on our primary study measure of depression severity (the QIDS-SR) at 12-week review—and with group inclusion, irrespective of the receipt of any new or modified (drug or nondrug) treatment regime. We hypothesized that our treatment sample would have higher rates of predisposing personality styles, anxiety conditions, and distal and proximal stressors than those in the improver sample.

The treatment (n = 32) and improver (n = 53) samples did not differ by mean age (43 years, SD 13.9 and 41 years, SD 12.6, respectively; t = 0.44, df = 82, P = 0.40), female preponderance (52% and 53%, respectively), marital status (χ² = 2.42 df = 2, P = 0.30 across 3 categories), employment status (χ² = 4.24, df = 4, P = 0.37 across 5 categories), or education level (χ² = 1.73, df = 4, P = 0.78 across 5 categories)—suggesting adequate matching. The 2 groups did not differ by age at their initial depressive episode (21 and 22 years, respectively), but the treatment group had experienced a slightly (nonsignificant) longer current depressive episode (74 and 67 weeks, respectively). People in the treatment and improver groups had previously received a comparable number of ADs (3.6 and 3.2, respectively), but our treatment group tended to be more likely to have received 5 or more ADs (38% and 22%, respectively). They did not differ in number of current or past significant medical conditions (3.1 and 2.2, respectively), presence of anxiety disorders (generalized anxiety, social phobia, panic disorder, and obsessive–compulsive disorder), current number of stressors (3.0 and 2.7, respectively), rejecting parents (50% and 46%, respectively), and a family history of alcoholism (40.6% and 40.0%, respectively). However, the treatment group were more likely (than the improver group) to report a greater number of SLEs (5.5 and 3.8, respectively; t = 2.4, df = 832, P < 0.02) and did show a nonsignificant trend to be more likely to report a family history of depression (72% and 58%, respectively). On all T & P Questionnaire items, the groups returned comparable mean scores and without any indicative trend differences. Thus analyses suggested that people in the treatment group had experienced a somewhat longer current depressive episode and were somewhat more likely to have received at least 5 ADs, but did not differ on personality, anxiety, and stress constructs that we positioned as accounting for their TRD.
Discussion

Study Overview
We postulated that people with a nonmelancholic TRD who had received several ADs (quantified mean 3.6, SD 1.6) may not reflect true treatment resistance but more of a paradigm failure, and where a psychotherapeutic intervention addressing psychosocial determinants would be salient. If confirmed, this may lead to broader models for conceptualizing TRD and management algorithms for separate melancholic and nonmelancholic depressive disorders.

Main Findings
The provision of psychotherapy by a highly trained psychologist to our sample of patients with nonmelancholic TRD was encouraging of our hypothesis, in that we quantified a 41% responder and a 22% remission rate on our primary measure of depressive severity. However, and despite having few control patients, the trajectory in weekly QIDS-SR scores in the treatment and control groups were strikingly similar, and therefore argued against a true therapeutic effect and more for a nonspecific therapeutic or even a nontherapeutic contribution to improvement (for example, regression to the mean and vicissitudes in life improving). The suggested failure of our treatment group to evidence any true therapeutic responsiveness argues for their having a depressive state resistant to both medication and psychotherapy and inviting the question as to why. Our qualitative analyses indicated numerous plausible candidates—such as the presence of a significant personality style or disorder, exposure to severe distal and (or) recent stressors, and the presence of a comorbid anxiety condition. However, the prevalence of such factors did not differ across our sample and a comparison sample that had shown substantive improvement during a similar 12-week interval.

Study Limitations
Our analyses again argue the need (if not the necessity) for therapeutic studies having appropriate comparison or control groups, and we acknowledge that the small sample sizes (particularly in the control group) leads to a need to interpret these results with caution. In their absence, we might have argued that psychotherapy was a more cogent treatment model in that recipients showed a modest response to psychotherapy and imputed key determinants of treatment resistance (for example, personality style, stress, and anxiety) in our patients with nonmelancholic TRD. Our comparison groups effectively disallowed either conclusion to be made. In addition, while a study aim was to examine the effectiveness of changing the paradigm from a pharmacological to a psychological approach, most patients remained on ADs, which may have confounded persistence, which, being subjectively based, may or may not have been valid in their identification and weighting.

Conclusions
Sample numbers suggest that our study is best viewed as a pilot one, while findings invite more questions than provide clarity. If nonmelancholic depression is largely a consequence of debilitating SLEs interacting with a vulnerable and predisposing personality style, then it remains unclear as to why a percentage of people are resistant to drug and nondrug therapies, and particularly to the psychotherapy provided to our sample, which was designed to specifically address these factors. Possible explanations include the short therapy duration (in that such patients may need a longer period of psychotherapy to establish a therapeutic alliance and [or] obtain benefit), or a need for another paradigm rather than psychotherapy. In the introduction, we noted that TRD is a conundrum. Most treatment studies have focused on biological explanations and drug treatments. Our study explored the effectiveness of psychological therapy in a group of patients diagnosed with nonmelancholic depression and examined whether psychotherapy was effective when previous AD diagnoses were not. Our results appear to broaden, rather than narrow, the conundrum, but suggest the need for future studies exploring a wide set of possible explanatory factors.

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