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Reliability and validity of the difficult to treat depression questionnaire (DTDQ)

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ABSTRACT

It has recently been recommended that treatment resistant depression be reconceptualized and renamed as difficult to treat depression (DTD). A consensus statement by an expert panel identified multiple variables associated with DTD and emphasized the importance of conducting a comprehensive evaluation of patients to identify predictors of inadequate treatment response. For practical reasons, it would be desirable to develop a self-report scale that can be incorporated into clinical practice that identifies patient, clinical, and treatment risk factors for DTD. Nine hundred twenty depressed patients completed the Difficult to Treat Depression Questionnaire (DTDQ). A subset of patients completed the scale a second time and completed the Remission from Depression Questionnaire at admission and discharge from a partial hospital program.

The DTDQ demonstrated excellent internal consistency and test-retest reliability. Both the total DTDQ and the number of prior failed medication trials, the metric primarily relied upon to classify treatment resistant depression, predicted outcome. However, the DTDQ continued to be significantly associated with outcome after controlling for the number of failed trials, whereas the number of failed trials did not predict outcome after controlling for DTDQ scores. The DTDQ is a reliable and valid measure of the recently discussed concept of DTD.

1. Introduction

During the past two decades there has been intense interest in defining, identifying, and investigating treatments for depressed patients with treatment resistant depression (TRD) (Carter et al., 2020; Li et al., 2021; Scott et al., 2022). While there has been variability in the definition of TRD (Gaynes et al., 2019; Sforzini et al., 2022), the concept generally refers to depression that has not fully responded to multiple pharmacological treatment efforts.

More recently, it has been recommended by experts in depression treatment research that TRD be reconceptualized and renamed as difficult to treat depression (DTD) (Rush et al., 2019). Multiple reasons were given for the recommended change in terminology, including the DTD label being less stigmatizing than TRD. A limitation of the TRD construct is its exclusive focus on acute treatment trial failures without consideration of longer-term course (e.g., relapse after a transient remission). Also, TRD definitions are often dichotomous determinations based on the number of failed pharmacological treatments without consideration of the type of treatment failure (e.g., 3 medications or 2 medications and ECT) or without consideration of treatments other than medication (McAllister-Williams, 2022; Rush et al., 2019). The broader conceptualization of DTD attends to longitudinal course, both the number and types of treatments to which the patient did not respond, and the possibility of identifying patients with DTD prior to initiating treatment based on clinical, social, and biological factors (Rush et al., 2019). Most importantly, the advocates of the DTD concept recommended shifting the focus of treatment from a curative/remission model to a disease management model that emphasizes improved functioning and quality of life while also striving for optimal symptom control (though not necessarily complete symptom elimination).

In fact, replacing the term TRD with DTD is not a new proposal. A conference entitled *Difficult to Treat Depression* was held 20 years ago during which it was suggested that DTD was a more appropriate name than TRD (Kupfer and Charney, 2003). However, for the most part during the past 20 years, the term DTD has been used synonymously with TRD insofar as discussions of DTD have simply made reference to patients who have not adequately responded to one or more pharmacologic interventions (Casey et al., 2013; Chan et al., 2013; Conway et al., 2020; Fabbri et al., 2021; Fetzer et al., 2021; Fleck and Horwath, 2005; Gaynes, 2009; Riveros et al., 2022; Young et al., 2020). Studies of

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patients with DTD have based the definition solely in terms of inadequate response to pharmacotherapy (e.g., Grudet et al., 2022; Keitner et al., 2009).

A recent consensus statement identified multiple variables that are associated with DTD and emphasized the importance of conducting a comprehensive evaluation to identify possible contributors to inadequate treatment response (McAllister-Williams et al., 2020). Some of the patient and disorder characteristics that predict poorer outcome in the treatment of depression include prior nonresponse to treatment, symptom chronicity, personality pathology, comorbid disorders, childhood trauma, suicidality, substance misuse, psychosocial stress, social isolation, and early age of onset (McAllister-Williams et al., 2020). DTD has been conceptualized as a dimensional construct, and a specified, criteria-based, definition to distinguish patients who did and did not have DTD was not described. Nor did the consensus statement identify an assessment tool to identify patients who are more likely to have DTD.

Comprehensive evaluations are time-consuming and expensive, and thus unlikely to be conducted in routine clinical practice. For practical reasons, it would therefore be desirable to develop a self-report scale that can be easily incorporated into clinical practice that identifies the patient, clinical, and treatment risk factors for DTD.

In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we describe the reliability and validity of a self-report measure to identify patients with possible DTD. Consistent with the concept of DTD, we predicted that patients scoring higher on the DTD Questionnaire (DTDQ) would have a less favorable response to treatment.

2. Method

2.1. Patients

The study was conducted in the Rhode Island Hospital Department of Psychiatry partial hospital program, a 5-day per week intensive treatment program. The length of treatment is flexible, based on patients' symptoms, functioning, and engagement in treatment. Patients meet with a therapist and psychiatrist daily or nearly every day for individual sessions, as well as attend multiple group therapy sessions. The program serves a range of presenting concerns and patients are referred from various clinical settings. Nine hundred twenty patients with DSM-IV/DSM-5 major depressive disorder (MDD) are the focus of the present analysis. Patients who were admitted multiple times during the duration of the study only had the data from their first admission included.

A minority of the patients in the PHP were interviewed by a diagnostic rater who administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). Most patients who presented for treatment were not evaluated with the SCID due to a lack of available interviewers but were instead diagnosed by board-certified psychiatrists.

The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed consent.

2.2. Measures

The assessment battery has changed through the duration of the MIDAS project, with some questionnaires added and others removed. The focus of the present study is the 920 patients with MDD who completed the treatment program and completed the DTDQ at admission. A subset of 45 patients completed the DTDQ twice, the second time 1–2 days after the first administration.

The items of the DTDQ were derived from reviews of the literature of the factors predicting poorer outcome in the treatment of depression (Kim et al., 2021; Perlman et al., 2019; Tanguay-Sela et al., 2022; Tunvirachaisakul et al., 2018) and the factors identified as characteristic of difficult to treat depression (Mcallister-Williams et al., 2020). Each item is rated on a 5-point scale (0–4), with greater scores reflecting greater levels of pathology/severity (e.g., higher scores on the depression severity item reflect greater levels of depression; higher scores on the financial strain item reflect greater financial difficulty). Anchor point descriptions for each level are provided. For example, the item on depression chronicity is: What percent of the past 5 years have you been depressed? Less than 10%; 10–24%; 25–49%; 50–90%; More than 90%. On average, the measure took approximately 20 min to complete. The scale is included in the Appendix. Copies of the scale are available from the first author.

Because the outcome of DTD should consider both symptom and nonsymptom domains, the broad-based Remission from Depression Questionnaire (RDQ) (Zimmerman et al., 2013) was the outcome measure. The domains covered on the RDQ were based on a literature review, our previous study of depressed patients' ratings of the relative importance of 16 factors in determining remission from depression (Zimmerman et al., 2006a), and two focus groups. The depression subscale includes 14 items assessing the DSM-5 symptom criteria of MDD. As previously reported, the depression subscale had high internal consistency and test-retest reliability (Zimmerman et al., 2013). We modified the RDQ to enhance its applicability to a diagnostically heterogeneous sample as seen in the PHP. Symptom items were added assessing anxiety, anger, and physical pain, as well as adding items to the coping, functioning, and well-being subscales. Nineteen items were added to the original 41-item scale. The modified 60-item measure (RDQ-M) included 14 depressive symptoms, 11 nondepressive symptoms, 5 coping ability/stress tolerance items (e.g., I easily got overwhelmed by stress.), 12 positive mental health items (e.g., I felt confident.), 10 functioning items (e.g., I did not do my work (at a paid job, at home, or at school) as well as usual.), and 8 general well-being/life-satisfaction items (e.g., I was satisfied in my relationships.). Patients are asked to rate each item on a 3-point rating scale ranging from 0 to 2 (not at all or rarely true; sometimes true; often or almost always true), with higher item values reflecting greater pathology over the past week. Thus, higher scores indicated greater symptomatology, poorer coping, more impaired functioning, fewer positive mental health indicators, and less life satisfaction. A study of 274 depressed outpatients demonstrated that the RDQ had excellent internal consistency (Cronbach's $\alpha = 0.97$ for the total scale and above 0.80 for each of the subscales) and test-retest reliability (total scale $r = 0.85$, and above 0.60 for each subscale) (Zimmerman et al., 2013). In the present study the scale had excellent internal consistency (admission: Cronbach's $\alpha = 0.92$ for the total scale and above 0.65 for each of the subscales; discharge: Cronbach's $\alpha = 0.97$ for the total scale and above 0.80 for each of the subscales).

2.3. Data analyses

All analyses were conducted using SPSS, version 27.0. We undertook a sequence of eight analyses. First, we examined the correlation matrix of the DTDQ items to determine the amount of shared variance between items. To reduce item redundancy, we retained only one item of a pair that overlapped in content and that correlated greater than 0.70 with another item. Second, we examined the distribution of item ratings and computed kurtosis and skewness. Because the scale is intended as a prognostic measure it is important that item ratings are not overly skewed. We a priori determined that items on which more than 75% of the patients had the same rating would be deleted from the scale. Third, we examined two types of reliability of the DTDQ—test-retest reliability and internal consistency. We examined the test-retest reliability of the total scale as well as the individual items, and we also examined the correlation of each item with the total scale score (without that item contributing to the total score). Fourth, we examined the correlation between the DTDQ and the pre-treatment total RDQ score and RDQ subscales. We predicted that higher scores on the DTDQ would be associated with greater symptom severity, poorer coping ability, greater impairment in functioning, fewer indicators of positive mental health,

and poorer quality of life. Fifth, we examined the correlation between the DTDQ and end of treatment scores on the RDQ. We hypothesized that higher scores on the DTDQ would predict higher discharge symptom levels, and poorer functioning, coping and quality of life. Sixth, we re-examined the correlation between the DTDQ and discharge scores on the RDQ after controlling for pre-treatment scores on the RDQ. Seventh, to determine if the DTDQ captured important prognostic information beyond a simple count of the number of failed medication trials, we examined the correlation between the DTDQ and the discharge RDQ controlling for the number of failed medication trials. The number of failed trials was assessed with the question "How many times have you stopped or switched medication because it did not help?"0; 1; 2; 3–4 times; 5 or more times." We also examined the correlation between the number of failed medication trials and the discharge RDQ while controlling for the DTDQ score. And eighth, we examined the distribution of DTDQ scores to select a cutoff point to dichotomize patients into 2 groups reflecting lesser and greater difficulty to treat. The pre-treatment RDQ scores, and the discharge RDQ controlling for pre-treatment RDQ scores, were then compared across these two groups. We used t-tests to determine whether RDQ scores were significantly higher in patients who scored above and below the cutoff score. Levene's test for Equality of Variances was used to examine homogeneity of variance of the two samples, and when significant we used separate variance estimates with adjusted degrees of freedom. An analysis of covariance (ANCOVA) was used to compare the 2 groups on the discharge RDQ scores while controlling for the differences in pretreatment values.

3. Results

3.1. Description of sample

The 920 patients included 648 (70.4%) cisgender female, 232 (25.2%) cisgender male, and 36 (3.9%) gender diverse individuals. Data on gender was missing for 4 patients. The patients ranged in age from 18 to 83 years (M = 38.4, SD = 14.3). Approximately two-fifths of the patients were never married (40.4%, n = 372); the remainder were married (25.1%, n = 231), cohabitating (13.2%, n = 121), divorced (14.3%, n = 132), separated (4.3%, n = 40), or widowed (2.5%, n = 23). Over one-third of the patients completed at least a 4-year university degree (37.5%, n = 345). The majority of the sample identified as White (72.1%, n = 663). A minority of patients identified as Black (7.0%, n = 64), Hispanic (11.8%, n = 109), Asian (2.1%, n = 19), or from another or a combination of racial/ethnic backgrounds (6.8%, n = 63).

3.2. Elimination of items

Before examining the psychometric performance of the scale we first examined the inter-item correlation matrix of the items. To reduce redundancy, we retained only one item of a pair that was similar in content and that correlated higher than 0.70. One item was eliminated. ("How many times in your life have you taken medication for your psychiatric symptoms?." was eliminated because it correlated highly with the item "How many times have you stopped or switched medication because it did not help?").

Next, we examined the distribution of scores for each item. No item was eliminated because more than 75% of the sample selected the same item value.

3.3. Descriptive statistics of the items

The means of the items were between 0.55 (drug use) and 3.32 (self-criticism) (Table 1). Only 3 items had a mean score below 1, and 2 items had a mean above 3. The skew values of 38 of the 39 items were between −2 and +2; thus, only 1 item (drug use) was highly skewed. This item was maintained despite the skewness due to its potential relevance to predicting DTD.

Table 1
Descriptive statistics of the Difficult to Treat Depression Questionnaire (DTDQ) items in depressed patients (n = 920).

DTDQ Items	Mean	SD	Kurtosis	Skew
Depression chronicity	2.71	1.04	0.20	−0.81
Anxiety chronicity	2.89	1.09	0.16	−0.92
Anger chronicity	1.45	1.34	−1.03	0.46
Usual hedonic capacity	2.29	0.86	−0.36	−0.28
Depression severity	2.84	0.91	−0.40	−0.39
Anxiety severity	2.93	0.94	−0.19	−0.60
Anger severity	1.87	1.16	−0.68	0.26
Severity of recent stressors	2.88	0.89	0.30	−0.59
Anticipated stressor chronicity	2.18	1.05	0.39	−0.20
Number of medication failures due to lack of efficacy	2.31	1.46	−1.26	−0.37
Number of medication failures due to side effects	1.46	1.37	−1.06	0.49
Overall benefit of medication	1.63	1.38	−0.71	−0.06
Overall benefit of psychotherapy	1.36	1.33	−0.70	0.18
Hopefulness of treatment benefit	1.65	0.91	0.62	0.22
Deserve to feel better	0.88	1.00	0.88	1.14
Stress at home	2.44	1.06	−0.63	−0.21
Stress at work (or school)	1.45	2.11	−1.71	−0.10
Disability payments	1.19	1.77	−1.54	−0.10
Impaired days past month	2.21	1.37	−1.31	−0.04
Financial stress	2.28	1.26	−0.91	−0.26
Introversion	2.49	1.14	−0.69	−0.44
Perception of childhood	2.53	1.25	−1.01	−0.30
Childhood trauma	2.09	1.71	−1.70	−0.14
Adult trauma	1.73	1.71	−1.68	0.23
Physical health	2.02	0.89	−0.49	0.17
Physical pain	1.57	1.07	−0.47	0.26
Social support	1.64	1.15	−0.70	0.31
Alcohol use	1.12	1.19	−0.22	0.87
Drug use	0.55	1.05	3.33	2.06
Coping ability with stress	3.16	1.01	1.14	−1.26
Coping ability with daily hassles	2.58	0.92	−0.42	−0.20
Usual level of self-esteem	2.92	1.03	−0.25	−0.71
Self-criticism	3.32	0.86	1.00	−1.23
Suicide attempts	0.87	1.22	0.27	1.21
Self-harm	1.61	1.71	−1.58	0.40
Psychiatric hospitalizations	1.06	1.34	−0.17	1.07
Partial hospitalizations	1.13	1.33	−0.69	0.82
Emergency room visits	1.14	1.30	−0.34	0.91
Age onset psychiatric treatment	1.33	1.20	−0.52	0.62

3.4. Item-scale correlations, internal consistency, and test-retest reliability of the DTDQ

The DTDQ demonstrated excellent test-retest reliability (r for total scale = 0.94). The test-retest reliability of each item was significant (median r = 0.83) (Table 2).

The DTDQ also had very good internal consistency, with Cronbach's α of 0.83. All item-scale correlations except the item for alcohol use were significant (median = 0.35) (Table 2).

3.5. Association between the DTDQ and baseline symptom severity, functional impairment and other nonsymptom domains

The correlation between the DTDQ and the total RDQ score was significant at admission (r = 0.54, p<.001) and discharge (r = 0.28, p<.001). Because of the significant pre-treatment correlation, we computed a partial correlation between the DTDQ and the post-treatment RDQ total while controlling for the pre-treatment RDQ total. The partial correlation was also significant (partial r = 0.18, p<.001) indicating that greater DTDQ scores predicted poorer outcome, even after accounting for admission symptoms and functioning.

We repeated the analysis examining the individual RDQ domains. At both admission and discharge, higher DTDQ scores were associated with higher levels of depressive and nondepressive symptoms, poorer coping, greater impairment in functioning, reduced positive mental health, and lower quality of life (Table 3). Again, because of the significant pre-

Table 2
Test-retest reliability and item-total correlations of the individual items of the Difficult to Treat Depression Questionnaire (DTDQ) .

DTDQ Items	Test-retest Reliability	Item-Total Correlations
Depression chronicity	.89	.52
Anxiety chronicity	.82	.45
Anger chronicity	.90	.40
Usual hedonic capacity	.87	.50
Depression severity	.74	.30
Anxiety severity	.67	.37
Anger severity	.53	.39
Severity of recent stressors	.83	.32
Anticipated stressor chronicity	.71	.30
Number of medication failures due to lack of efficacy	.71	.43
Number of medication failures due to side effects	.86	.35
Overall benefit of medication	.84	.27
Overall benefit of psychotherapy	.67	.21
Hopefulness of treatment benefit	.44	.31
Deserve to feel better	.83	.33
Stress at home	.88	.31
Stress at work (or school)	.78	.08
Disability payments	.85	.13
Impaired days past month	.68	.27
Financial stress	.90	.32
Introversion	.86	.23
Perception of childhood	.92	.41
Childhood trauma	.87	.42
Adult trauma	.79	.37
Physical health	.83	.32
Physical pain	.81	.29
Social support	.70	.29
Alcohol use	.94	−0.02
Drug use	.74	.08
Coping ability with stress	.75	.37
Coping ability with daily hassles	.70	.44
Usual level of self-esteem	.85	.46
Self-criticism	.78	.36
Suicide attempts	.98	.43
Self-harm	.90	.40
Psychiatric hospitalizations	.97	.27
Partial hospitalizations	.90	.35
Emergency room visits	.97	.39
Age onset psychiatric treatment	.95	.21

Note. All test-retest reliability correlations are significant at $p <$. 001. All item-total correlations where $r > 0.08$ are significant at $p < 0.001$; if $r = 0.08$, $p =$ .02, $r < 0.08$, $p =$ ns.
Note 2. The sample size for the test-retest reliability analysis was 45.

Table 3
Correlation between the Difficult to Treat Depression Questionnaire (DTDQ) and symptom and nonsymptom domains on the Remission from Depression Questionnaire (RDQ) at admission and discharge in depressed patients.

RDQ Subscale	Admission	Discharge	Discharge control for Admission
Total RDQ score	.54	.28	.18
Depressive symptoms	.41	.28	.20
Non-depressive symptoms	.45	.38	.27
Coping ability	.38	.20	.15
Positive mental health	.35	.19	.12
Functional impairment	.38	.17	.09
Quality of life	.39	.19	.10

Note. For $r <= 0.10$, $p < 0.05$. For 0.10 to 0.12, $p <$ .01. For $r > 0.12$, $p <$ .001.
Note. At admission the sample sizes varied from 869 to 889 due to missing data. At discharge the sample sizes varied from 557 to 559, and the sample sizes for the partial correlations varied from 510 to 538.

treatment correlations, we computed partial correlations with the post-treatment RDQ scores while controlling for pre-treatment scores. The pattern of findings remained identical, with all partial correlation coefficients being statistically significant (Table 3).

3.6. Predicting outcome—DTDQ scores vs. number of failed medication trials

TRD is typically defined by the number of failed medication trials. However, DTD expands upon this conceptualization to assess a more complex phenomenon; it includes a count of number of failed trials, as well as other factors demonstrated to be associated with more chronic courses of MDD including depression severity and chronicity, other domains of mental health, physical health, coping, and recent and past trauma. An important question is whether the DTDQ better predicts outcomes than a simple count of number of failed medication trials. Indeed, the DTDQ item assessing the number of failed medication efforts correlated significantly with the DTDQ total score ($r = 0.43$, $p<.001$) and the discharge RDQ total score ($r = 0.18$, $p<.001$). However, when controlling for the DTDQ total score (minus this item), the number of failed medication trials was no longer significantly correlated with the discharge RDQ total (partial $r = 0.06$, n.s.). By contrast, the DTDQ total score remained significantly correlated with the discharge RDQ total after controlling for the number of failed medication trials (partial $r =$ 0.22, $p<.001$).

We repeated this analysis focusing specifically on the depressive symptoms subscale of the RDQ and the pattern of results was identical. That is, the number of failed medication trials was significantly correlated with the discharge RDQ depression score ($r = 0.15$, $p<.001$); however, the partial correlation, controlling for the DTDQ total, was no longer significant (partial $r = 0.02$, n.s.). By contrast, the DTDQ total score remained significantly correlated with the discharge depression subscale after controlling for the number of failed medication trials (partial $r = 0.25$, $p<.001$).

3.7. Distribution of DTDQ scores, deriving a cutoff, and outcome in patients with higher and lower DTDQ scores

DTD has been conceptualized as a dimensional variable rather a categorical variable (Rush et al., 2019). However, just as treatment resistance is dimensional with levels of severity, though it is usually defined categorically, we anticipate that DTD will also be examined from a categorical perspective. We therefore conducted an exploratory analysis to identify a cutoff score to distinguish patients with higher and lower DTDQ scores.

We examined the distribution of DTDQ scores and identified a point of rarity at a score of 88 (possible scores range from 0 – 156). This characterized approximately 25% of our sample as having DTD. At admission, the DTD group reported significantly higher levels of

Table 4
Remission from Depression Questionnaire (RDQ) scores at admission in patients with and without Difficult to Treat Depression (DTD).

RDQ-M Subscale	No DTD Mean (SD)	DTD Mean (SD)	*t*-test
Total RDQ score	80.9 (16.6)	94.4 (11.9)	$t = 11.3$, $p < .001$
Depressive symptoms	18.4 (4.5)	21.0 (3.4)	$t = 8.2$, $p < .001$
Non-depressive symptoms	13.6 (2.4)	17.0 (3.8)	$t = 9.8$, $p < .001$
Coping ability	6.8 (2.1)	8.0 (1.8)	$t = 7.7$, $p < .001$
Positive mental health	17.8 (4.8)	20.0 (3.6)	$t = 6.3$, $p < .001$
Functional impairment	11.9 (4.0)	14.3 (3.3)	$t = 8.0$, $p < .001$
Quality of life	12.3 (3.4)	14.1 (2.4)	$t = 7.4$, $p < .001$

Note. Due to missing data the sample size in the no DTD group was total RDQ (N = 654), depressive symptoms (n = 660), non-depressive symptoms (n = 659), coping ability (n = 653), positive mental health (n = 656), impaired functioning (n = 645) and well-being (n = 652).In the DTD group, total RDQ, depressive symptoms, non-depressive symptoms, and positive mental health (n = 229), coping ability (n = 228), impaired functioning (n = 224) and well-being (n = 228).

depressive and non-depressive symptoms (Table 4). The DTD patients also reported poorer coping ability, less positive mental health, greater impairment in functioning, and poorer quality of life.

The patients with DTD responded less well to treatment. Even after controlling for the differences in baseline scores on the RDQ, the patients with DTD reported significantly greater severity of depressive and non-depressive symptoms and poorer coping at discharge (Table 5). The trends for poorer outcome in the DTD group on the positive mental health, functioning and quality of life subscales were in the same direction but failed to reach significance.

4. Discussion

The landmark National Institute of Mental Health Collaborative Study of the longitudinal course of depressed patients found that depression was often more chronic than had been previously believed (Keller et al., 1984). The more recent milestone STAR*D treatment study confirmed that depression is often difficult to treat, even when the dose and duration of treatments are optimized (Rush et al., 2006). During the past two decades, numerous efforts have been directed towards developing treatments for patients who have failed to adequately respond to multiple courses of treatment, and the search for novel interventions continues (Carter et al., 2020; Li et al., 2021; Scott et al., 2022).

Prior studies have examined predictors of poorer outcome and course, and a number of variables have been identified to be associated with worse prognosis. Often, these variables are studied in isolation. For example, there are multiple studies of personality and personality disorders (Bock et al., 2010; Ceresa et al., 2021; Grilo et al., 2005; Newton-Howes et al., 2014), trauma (Klein et al., 2009; Miniati et al., 2010; Nanni et al., 2012), pain (Ang et al., 2009; Leuchter et al., 2010), and co-occurring anxiety (Coryell et al., 2012; Fava et al., 2008; Papakostas and Larsen, 2011; Russell et al., 2001; Wiethoff et al., 2010) as individual factors that are associated with a more chronic course or poorer response to treatment. Based on reviews of the factors associated with poorer outcome, including the review in the consensus statement on DTD, our goal was to develop an instrument that incorporated these various elements. The DTD expert group described a comprehensive assessment that includes a thorough evaluation of clinical, biological, cognitive, and medical factors. While such a detailed assessment would be ideal, we are skeptical that outside of specialized programs at large medical centers such a comprehensive evaluation protocol will be adopted in routine practice. Indeed, multiple studies have found that unstructured diagnostic interviews markedly underdiagnose the breadth of psychopathology compared to semi-structured diagnostic interviews (Kashner et al., 2003; Miller et al., 2001; Shear et al., 2000; Zimmerman and Mattia, 1999), yet semi-structured interviews are rarely utilized in clinical practice. Even in clinical research settings, the cost of a comprehensive interview-based semi-structured evaluation might preclude its adoption unless research funds covered the cost. In combination with the wide breadth of factors identified as predicting poorer outcome in the treatment of depression, we considered a self-report scale to be preferable to a semi-structured interview to identify DTD.

Relatedly, most of the constructs assessed by the DTDQ are measured by a single question. While it may be preferable to assess constructs with multi-item scales, if each construct was assessed with an average of only 3 items the measure would be over 100 items in length, which would likely impede its use in clinical settings. Moreover, we have previously demonstrated the reliability and validity of single item scales for some of the items on the questionnaire (Zimmerman and Becker, 2022; Zimmerman et al., 2006b).

In describing the advantages of transitioning from a TRD to a DTD approach, Rush et al. (Rush et al., 2019) suggested that it may be possible to identify patients as more or less difficult to treat before they initiate treatment. Variables such as the presence of childhood trauma and neglect, poor social support, and medical illness are likely to make depression more difficult to treat in previously untreated patients. Thus, it may be possible to identify DTD before treatment failures have accumulated. We administered the DTDQ to all patients (i.e., treatment naive and those who have not responded to prior treatment attempts), and in a future analysis we will examine the scale's prognostic utility specifically in patients who did not report having failed a previous treatment effort.

Both the total DTDQ and the number of prior failed medication trials predicted outcome. However, the DTDQ continued to be significantly associated with outcome after controlling for the number of failed trials, whereas the number of failed trials did not predict outcome after controlling for DTDQ scores. This suggests that the DTDQ captures important prognostic information beyond that accounted for by the number of medication trial failures. A caveat, though, is that the number of failed trials was assessed by a single self-report question assessing a lifetime history of failed trials in contrast to a more detailed assessment of treatment history of failed trials during the current episode that it typically done in TRD studies. Of course, the criticism of assessing somewhat complex constructs with single questions would also apply to the other constructs assessed by the DTDQ.

To date, an operational definition of DTD has not been described. Cosgrove and colleagues (Cosgrove et al., 2020) expressed concern that DTD is loosely defined and such imprecision in its definition could be exploited in studies examining the efficacy of new treatments for this subgroup of patients. While we derived a cutoff to dichotomize patients into DTD and non-DTD groups, we do not view this cutoff as definitive. Future research, particularly in outpatient settings, should examine the validity of this and other possible cutoffs.

The DTDQ assesses most, but not all, factors that have been consistently associated with poorer response to treatment. For example, the consensus statement on DTD listed older age, family history of affective disorders, and pharmacokinetics as prognostic factors that are not assessed on the DTDQ. On the other hand, the scale includes some variables associated with prognosis such as perceived social support, recent life events, anhedonia, financial insecurity, hopefulness of treatment benefit, perception of current physical health, and physical pain that were not included in the table of prognostic factors in the consensus statement.

The present study was conducted in a partial hospital program where illness severity, chronicity, diagnostic comorbidity, and prior treatment failure is generally greater than outpatient settings. This may therefore be a particularly appropriate setting to develop and study a measure of DTD. Conversely, given that the study was conducted in a single setting, the extent to which the results are generalizable needs to be demonstrated. While the generalizability of any single site study is limited, a strength of the study was that the patients were unselected with regards to meeting any inclusion or exclusion criteria outside of the presence of MDD and completion of the DTDQ. The MIDAS project does not select

Table 5
Remission from Depression Questionnaire (RDQ) scores at discharge in patients with and without Difficult to Treat Depression (DTD).

RDQ-M Subscale	No DTD Mean (SD)	DTD Mean (SD)	ANCOVA
Total RDQ score	46.5 (23.6)	56.7 (26.6)	$F = 5.00$, $p = .03$
Depressive symptoms	9.5 (5.4)	11.8 (6.0)	$F = 7.46$, $p < 0.01$
Non-depressive symptoms	7.0 (4.6)	10.2 (5.3)	$F = 17.17$, $p < 0.001$
Coping ability	4.2 (2.4)	4.9 (2.5)	$F = 4.42$, $p = .04$
Positive mental health	10.8 (6.2)	12.2 (6.6)	$F = 1.52$, $p = .22$
Functional impairment	7.4 (4.6)	8.8 (4.7)	$F = 2.59$, $p = .22$
Quality of life	7.5 (4.4)	8.5 (4.8)	$F = 0.69$, $p = .44$

Note. Due to missing data the sample size in the no DTD group was total (n = 419), depressive symptoms (425), non-depressive symptoms (424) coping ability (n = 414), positive mental health (n = 421), impaired functioning (n = 401) and well-being (n = 418). In the DTD group total, depressive symptoms, non-depressive symptoms, and positive mental health (n = 120), coping ability (n = 118), impaired functioning (n = 112) and well-being (n = 119).

cases that are prototypic, and thus more severe variants, of any diagnostic construct. Nonetheless, replication of the results in samples with different demographic characteristics is warranted. It will also be important to replicate these findings in an outpatient sample.

The DTDQ was administered to patients prior to beginning treatment. While the test-retest reliability of the assessment was high, both assessments were conducted at the beginning of treatment. Therefore, we were unable to determine if DTDQ scores changed as a result of treatment. However, given that the measure is designed as a prognostic tool, we believe that it is essential to administer the scale early during treatment in order for its predictive utility to be adequately evaluated.

Another limitation of the study was the reliance on a self-report measure to assess the outcome variables. However, an advantage of the RDQ is that is assesses both symptom and nonsymptom domains. An assessment of functioning, quality of life, coping ability, and positive mental health, along with symptoms, is consistent with recommendations of the consensus statement on DTD to expand outcome evaluations beyond symptoms, and consistent with surveys of depressed patients regarding the primary goals of treatment (Baune and Christensen, 2019; Grosse Holtforth et al., 2009; Morton et al., 2022). Nonetheless, replication of the results using clinician administered symptom and nonsymptom outcome measures is warranted.

In conclusion, the results of the present study suggest the DTDQ is a reliable and valid measure of the recently discussed concept of difficult to treat depression. The identification of depression that is difficult to treat has clinical and research significance. Foremost is the potential shift in the primary target of treatment from symptom elimination to improved functioning and quality of life for those patients whose symptoms are less likely to remit. Such a paradigm shift in the goals of treatment would be consistent with results of the aforementioned surveys of depressed patients regarding the primary goals of treatment (Baune and Christensen, 2019; Grosse Holtforth et al., 2009; Morton et al., 2022). From a research perspective, the development of standardized, quantifiable, approaches towards identifying DTD could address concerns about manipulating the criteria for patient recruitment into treatment studies of DTD (Cosgrove et al., 2020) by providing a metric to enhance transparency in patient selection.

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Contributors

Mark Zimmerman designed the study, wrote the first draft of the manuscript, and directed the data analysis. Daniel Mackin managed and analyzed the data and reviewed the draft of the manuscript and provided feedback to Dr. Zimmerman that was incorporated into the final submission.

Declaration of Competing Interest

None.

Acknowledgments

None.

Appendix

Name: Date: ID #:

INSTRUCTIONS: The following questions are about various factors important to consider in patients presenting for the treatment. After each question there are 5 statements. Read all statements carefully. Then decide which one best describes you or your history

(1) What percent of the past 5 years have you been depressed?

a Less than 10%
b 10–24%
c 25–49%
d 50–90%
e More than 90%

(2) What percent of the past 5 years have you had problems with anxiety?

a Less than 10%
b 10–24%
c 25–49%
d 50–90%
e More than 90%

(3) What percent of the past 5 years have you had problems with anger?

a Less than 10%
b 10–24%
c 25–49%
d 50–90%
e More than 90%

(4) Please complete the following **sentence: "Usually.."**

a I fully enjoy life.
b For the most part I am able to enjoy life.
c I get only some enjoyment from life.
d I get little enjoyment or satisfaction from life.
e I get no enjoyment or satisfaction from life.

(5) How depressed have you been feeling during the past week?

a Not at all
b Mildly
c Moderately
d Severely
e Extremely

(6) How anxious have you been feeling during the past week?

a Not at all
b Mildly
c Moderately
d Severely
e Extremely

(7) How angry or irritable have you been feeling during the past week?

a Not at all
b Mildly
c Moderately
d Severely
e Extremely

(8) **Please rate the** severity **of recent stressors.**

a Minimal
b Mild
c Moderate
d Severe
e Extreme

(9) **How likely do you think it is that recent stressors will resolve**

over the next 2–3 months?

☐ Check here if you have not experienced any recent stressors

a Very likely
b Likely
c Not sure
d Unlikely
e Very unlikely

(10) **How many times have you stopped or switched medication because it did not help?**

a 0 times
b 1 time
c 2 times
d 3–4 times
e 5 or more times

(11) **How many times have you stopped or switched medication due to side effects?**

a 0
b 1
c 2
d 3–4 times
e 5 or more times

(12) **In general, how helpful have medications been for you?**

☐ Check here if you have never taken a medication for psychiatric symptoms

a Very helpful most or all the time
b Somewhat helpful most or all the time
c Helpful some of the time but not at other times
d A little helpful some of the time
e Minimal or no benefit

(13) **If you have been in counseling before, how helpful has counseling been?**

☐ Check here if you have never been in counseling

a Very helpful most or all the time
b Somewhat helpful most or all the time
c Helpful some of the time but not at other times
d A little helpful some of the time
e Minimal or no benefit

(14) **How likely do you think it is that with treatment you will feel significantly better 2–3 months from now?**

a Very likely
b Likely
c Not sure
d Unlikely
e Very unlikely

(15) **Do you deserve to feel better?**

a Yes, absolutely
b I think so
c I am not sure
d Probably not
e Definitely not

(16) **How are things at home?**

a Excellent
b Very good
c Not too bad
d Stressful
e Very stressful

(17) **How are things at work (or school if full-time student)?**

☐ Check here if you are not currently working or in school

a Excellent
b Very good
c Not too bad
d Stressful
e Very stressful

(18) **If you are *not* currently working (or in school), the reason is:**

☐ Check here if you are working or in school

a I am retired or staying at home to raise my children.
b I have not been able to find a job.
c I am on disability for medical reasons or I have been feeling too depressed or anxious to work or look for a job.
d I am on temporary disability or leave due to psychiatric reasons.
e I am on long-term disability for psychiatric reasons.

(19) **How much time during the past month were you** COMPLETELY **UNABLE to perform your usual daily responsibilities (at a paid job, at home, or at school) because of your psychiatric symptoms?**

a 0 days
b 1 day up to a week
c 1–2 weeks
d 2–3 weeks
e nearly the entire month

(20) **How would you describe your current financial situation?**

a Not currently a problem
b A minor stressor
c A moderate stressor
d A severe stressor
e An extreme stressor

(21) **How extraverted (outgoing) or introverted (shy) are you?**

a Much more extraverted (outgoing) than others
b Somewhat more extraverted than others
c About the same as most people
d Somewhat more introverted than others
e Much more introverted (shy) than others

(22) **How would you describe your childhood?**

a Excellent
b Pleasant
c Difficult at times
d Often difficult
e Traumatic

(23) **Did you experience any trauma growing up (before age 18) such as physical or sexual abuse?**

a No such traumatic events
b Traumatic event(s) with minimal impact

c Traumatic event(s) with mild impact
d Traumatic event(s) with moderate impact
e Traumatic event(s) with major impact

(24) **Have you had any traumatic experiences as an adult (age 18 and older) such as physical or sexual abuse?**

a No such traumatic events
b Traumatic event(s) with minimal impact
c Traumatic event(s) with mild impact
d Traumatic event(s) with moderate impact
e Traumatic event(s) with major impact

(25) **How would you rate your current physical health?**

a Excellent
b Good
c Fair
d Poor
e Very poor

(26) **How much physical pain have you been feeling during the past week?**

a None
b Mild
c Moderate
d Severe
e Extreme

(27) **How would you describe your support network?**

a Excellent
b Good
c Fair
d Poor
e Very poor

(28) **Which of the following statements is most accurate regarding your use of alcohol?**

a I do not drink alcohol.
b I drink but never excessively.
c I only rarely drink more than I should.
d I sometimes drink more than I should.
e I often drink more than I should.

(29) **Which of the following statements is most accurate regarding your use of drugs?**

a I do not use street drugs.
b I use drugs but never excessively.
c I only rarely use drugs more than I should.
d I sometimes use drugs more than I should.
e I often use drugs more than I should.

(30) **Which of the following statements is most accurate about how you generally handle stress?**

a I handle stress much better than most people.
b I handle stress somewhat better than most
c people.
d I handle stress about as well as most people.
e I do not handle stress as well as most people.
f I am frequently overwhelmed by stress.

(31) **How would you rate your usual ability to cope with the daily hassles of life?**

a Excellent Fix alignment in this item
b Good
c Fair
d Poor
e Very poor

(32) **How would you rate your usual level of self-esteem?How would you rate your usual level of self-esteem?**

a Excellent
b Good
c Fair
d Poor
e Very low

(33) **How critical of yourself do you tend to be?**

a Not at all
b A little bit
c A moderate amount
d Quite a bit
e Extremely

(34) **How many times in your life have you attempted suicide?**

a 0 times
b 1 time
c 2 times
d 3–4 times
e 5 or more times

(35) **How many times in your life have you deliberately hurt yourself?**

a 0 times
b 1 time
c 2 times
d 3–4 times
e 5 or more times

(36) **How many times in your life have you been hospitalized for psychiatric reasons?**

a 0
b 1
c 2
d 3–4 times
e 5 or more times

(37) **How many times in your life have you been in a partial hospital program?**

a 0
b 1
c 2
d 3–4 times
e 5 or more times

(38) **How many times have you been seen in an emergency room for psychiatric reasons?**

a 0
b 1

c 2
d 3–4 times
e 5 or more times

(39) **How old were you the first time you received psychiatric treatment?**

a less than 8 years old
b 8–12
c 13–17
d 18–25
e older than age 25

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