Predicting clinical course in major depressive disorder

Received: 2 June 2018 | Revised: 27 October 2018 | Accepted: 6 November 2018

DOI: 10.1002/da.22865

RESEARCH ARTICLE

WILEY ADAA ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

Predicting clinical course in major depressive disorder: The association between DM-TRD score and symptom severity over time in 1115 outpatients

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Background: The Dutch Measure for Quantification of Treatment Resistance in Depression (DM-TRD) is a promising prediction tool for major depressive disorder (MDD) based on variables associated with treatment outcome. The objective of our study was to examine the association between the DM-TRD and clinical course in a large cohort of MDD outpatients receiving treatment as usual. Furthermore, we examined whether the addition of an item measuring the presence of childhood adversity improved this association.

Methods: We included 1115 subjects with MDD (according to the DSM-IV) who were naturalistically treated at seven outpatient departments of a secondary mental healthcare center in the Netherlands. Data on subjects who had a diagnostic work-up between June 2014 and June 2016 were analyzed. Multilevel analyses were performed to examine the association between the DM-TRD score at baseline and clinical course, defined by symptom severity according to scores on the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) over time. We also investigated whether an extra item measuring *childhood adversity* improved the model.

Results: The model including the DM-TRD and its interaction with time was superior to previous models. The addition of *childhood adversity* and its interaction with time did not improve the model.

Conclusions: In depressed outpatients receiving treatment as usual, the solid longer-term association between higher DM-TRD scores and worse clinical course supports its usefulness in clinical practice. Childhood adversity did not improve the model value indicating that—counterintuitively—this parameter offers no additional predictive power to the variables included.

KEYWORDS

ambulatory care, clinical course, cohort studies, depression, major depressive disorder, multilevel analysis, outpatients, prediction, psychiatric status rating scales, the Netherlands, treatment outcome

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the most common disorders in psychiatry with an adult lifetime prevalence of almost 20% (Kessler et al., 2005). It has a considerable social and economic impact and MDD is currently ranked fourth worldwide in terms of disease burden (Kassebaum et al., 2016; Mathers & Loncar, 2006). Individuals with MDD show marked heterogeneity in symptomatology, natural course, and treatment response. Although antidepressant medication and psychotherapy show clear efficacy (Cipriani et al., 2018; Cuijpers, Dekker, Hollon, & Andersson, 2009; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004), a substantial number of patients remains symptomatic and responses to different treatments for MDD vary widely between patients (Spielmans, Berman, & Usitalo, 2011). In addition, depressive episodes that need multiple treatment steps are associated with poorer outcomes and higher relapse rates (Fava, 2003; Judd et al., 1998; Ruhe, Huyser, Swinkels, & Schene, 2006; Rush et al., 2006).

Planning of MDD treatment may become more efficient if, instead of applying a "one size fits all" concept, clinicians could predict which patients will need routine or specialized care. Patients can be referred accordingly and the treatment-plan can be better adapted to the individual needs. Different approaches to personalized treatment planning of psychiatric disorders have recently been advocated (Chekroud, Lane, & Ross, 2017; Hetrick et al., 2008; van Os et al., 2017).

One of the instruments with the ability to improve treatment planning in MDD is the Dutch Measure for Quantification of Treatment Resistance in Depression (DM-TRD), developed by Peeters et al. (2016). It is based on the Maudsley Staging Method (MSM) (Fekadu, Wooderson, Markopoulou, & Cleare, 2009); a tool developed to predict treatment outcome in clinical samples characterized by advanced stages of treatment resistance. The MSM was the first TRD-measure that added factors known to predict the prognosis or course of the disease (e.g., severity and duration of the index episode) to information about failed treatments for the index episode within one instrument (Fekadu et al., 2009; van Belkum et al., 2018). The DM-TRD is a feasible instrument to assess failed biological, psychotherapeutic, and supportive treatments (Peeters et al., 2016). In addition to the MSM, it assesses other factors known to potentially influence treatment outcome, for example, as the presence of ongoing psychosocial stressors (Brown et al., 2010) and comorbid anxiety symptoms or personality disorders (Fava et al., 2008). First results with the DM-TRD in depressed inpatient/outpatient samples of modest size with a significant range in treatment resistance suggested that the DM-TRD may be a useful instrument to predict treatment outcome (Peeters et al., 2016). However, the DM-TRD needs to be studied in a larger sample.

Furthermore, the DM-TRD might be improved. For example, although childhood adversity is known to be negatively associated with clinical course and treatment response of MDD (Nanni, Uher, & Danese, 2012; Tunnard et al., 2014; Wiersma et al., 2009), it was not included in the DM-TRD. This negative association can be explained by the hypothesis that childhood adversity may cause neurobiological changes that result in a range of potentially negative long-term neurological effects, such as changes in neuroendocrine signaling and neuronal plasticity (van Bodegom, Homberg, & Henckens, 2017). In addition, childhood adversity influences the development of maladaptive personality traits that are associated with anxiety and mood disorders (Rosenman & Rodgers, 2006; Spinhoven, Elzinga, Van Hemert, de Rooij, & Penninx, 2016).

The objectives of this study were twofold. First, we investigated the association between the DM-TRD score and clinical course in a large, depressed outpatient population, independent from previous samples. Second, we examined whether the addition of a question addressing childhood adversity would enhance the association of the DM-TRD score with clinical course.

2 | MATERIAL AND METHODS

2.1 | Design and participants

This study was conducted at PsyQ, a nationwide organization providing outpatient secondary mental healthcare in the Netherlands. Seven PsyQ locations[1] participated in this study. Because we only used information that was routinely collected, without any intervention, the Medical Research Ethics Committee of the Leiden University Medical Center waived formal informed consent for this study. Only anonymized data retrospectively extracted from the electronic patient record (EPR) were used. Data from individuals who used the possibility to object to the use of their information for scientific purposes at the start of or during their treatment were not included.

Individuals 18 years or older were included in the study if they met the DSM-IV-TR (APA, 2000) criteria for MDD or dysthymic disorder according to their EPR. We included data of subjects who had a diagnostic work-up between June 2014 and June 2016. Excluded from the study were data from subjects with bipolar disorder, psychotic disorder or substance dependence (except for nicotine). In these secondary care settings, all subjects received treatment as usual; this implies treatment according to the Multidisciplinary Guideline for Depression and may include psychotherapy, pharmacotherapy, or both (Spijker et al., 2013).

Extracted from the EPR were demographic and diagnostic information, the DM-TRD score and baseline and follow-up scores on the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003). The last time point for obtaining follow-up data from the EPR was May 4th 2017, that is 46 weeks from the last inclusion. Baseline QIDS-SR was defined as the QIDS-SR obtained $\pm$45 days from filling in DM-TRD. Subjects without at least one (follow-up) QIDS-SR-measurement were defined as drop outs. The parameter *Time* was defined as the difference in weeks between the assessment of the DM-TRD and the assessment of the last QIDS-SR within a subject. The outcome variable was defined as the course of symptom severity over time according to the consecutive QIDS-SR measurements.

2.2 | Measures

The Dutch Measure for Quantification of Treatment Resistance in Depression: The DM-TRD is an 11-item questionnaire assessing information about clinical condition, psychiatric comorbidity, and failed treatments for the current episode: scores range from 2 to 27, with higher scores indicating worse treatment outcome (Peeters et al., 2016). In the present study, the DM-TRD was administered by a mental health professional during diagnostic work-up. In the original DM-TRD, establishing the presence of a comorbid personality disorder was based on global routine clinical information in cases where no formal structured information (e.g., SCID-II) was available. To address the presence of a (suspected) personality disorder in subjects without a formally assessed SCID-II classification, a brief personality screener was used, that is the Standardized Assessment of Personality–Abbreviated Scale (SAPAS) (Bukh, Bock, Vinberg, Gether, & Kessing, 2010; Moran et al., 2003). The DM-TRD item concerning comorbid personality pathology was scored 0.5 if the SAPAS was $\geq$3 (suspected to have personality disorder). If the SAPAS score was $<$3, comorbid personality disorder was scored 0 on the DM-TRD. This adjustment had no effect on the original total DM-TRD score of 27 points.

The original DM-TRD was expanded by adding a dichotomous question pertaining to the presence of childhood adversity. Childhood adversity was questioned as follows: "Have you had to deal with severe affective neglect, (repeated) sexual abuse, or psychological or physical threats during your youth (before the age of 16 years)?" where an affirmative answer scores 1 point. This modification led to a total maximum score of 28.

The Quick Inventory of Depressive Symptomatology-Self Report (Rush et al., 2003): The QIDS-SR is a 16-item self-report depression symptom severity measure derived from the 30-item Inventory of Depressive Symptoms (IDS) (Rush, Gullion, Basco, Jarrett, & Trivedi, 2009) with adequate psychometric properties shown by its Cronbach's α ranging from 0.69 to 0.89 (Reilly, MacGillivray, Reid, & Cameron, 2015). It was used to evaluate symptom severity of the depressive episode at both baseline and follow-up. The QIDS-SR score ranges from 0 to 27, where a score ≤5 is defined as "no depression" (or "remission" if the subject previously suffered from depression) and 27 as "very severe depression." The QIDS-SR was assessed routinely every 3 months and at the end of treatment.

2.3 | Statistical analyses

Data were analyzed using SPSS version 23. The clinical and demographic characteristics of subjects and differences between drop-outs and nondrop-outs were assessed using descriptive statistics, Chi-square tests and *t*-tests, as appropriate. Linear mixed models were performed to examine the association between the DM-TRD score and QIDS-SR scores over time (Twisk, 2003). Different models were compared using the Akaike's Information Criterion (AIC); a lower AIC-value shows a better model fit penalized for the number of variables used (Akaike, 1974). The AIC is asymptotically equivalent to cross-validation in linear mixed models (Fang, 2011), which means that the final model (i.e., the model with the lowest AIC) has the best generalization in the presence of new data. We examined whether the model with the interaction between the DMTRD score and the time interval (weeks between DM-TRD-assessment and last QIDS-SR-measurement) had improved (i.e., had a lower AIC) compared to the model without this interaction. The model included main effects for time, a quadratic time effect and the DM-TRD score. The quadratic time effect was added to investigate whether the time effect was nonlinear (Twisk, 2003), which indicates that the greatest improvement occurs during the primary phase of treatment. The linear mixed models had a random intercept and random effects for the linear and quadratic time effects. For the secondary research question, the item on childhood adversity was added as a fixed parameter to the model and improvement was determined based on the AIC. Finally, the interaction between childhood-adversity and time was added to examine the effect of childhood adversity on clinical course.

3 | RESULTS

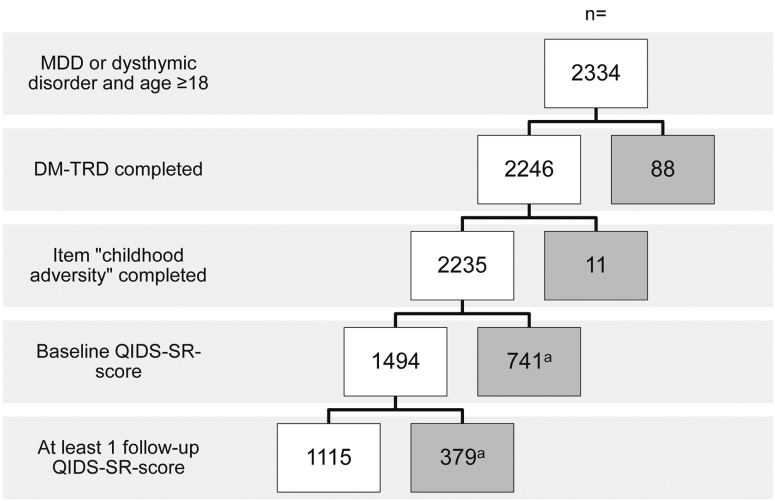
3.1 | Participants

According to the EPR, 2334 subjects met our primary inclusion criteria; of these 2246 had a completed DM-TRD. Excluded were 11 subjects due to a childhood adversity score. Another 1120 subjects were excluded due to the lack of baseline and/or follow-up QIDS-SR scores (Figure 1). No significant differences were found between study dropouts ($n = 1120$) and those who were analyzed ($n = 1115$) regarding gender, age, symptom severity, and duration of episode (according to the DM-TRD-items), total DM-TRD scores, and the score on the "childhood-adversity"-item (all p-values > 0.2). Although there were statistically significant differences between the seven locations regarding baseline symptom severity and duration of follow-up (all p-values < 0.05), the effects of these differences were small ($r = 0.03$–0.25 and Cohen's $d = 0.24$, respectively) and therefore not included in further analyses.

Table 1 presents the demographic and clinical characteristics of the study population. According to the baseline-QIDS-SR, most subjects were suffering from severe depression and many reported childhood adversity (Table 1). The mean interval between DM-TRD assessment and the last QIDS-SR measurement was 48 ($SD = 28.9$) weeks. The average difference between the baseline and final QIDS-SR score was a decrease of 5.1 ($SD = 6.3$) points. The endorsed frequencies for all DM-TRD item categories including the scoring are listed in Table 2.

3.2 | Association between DM-TRD scores and clinical course

Table 3 presents the results of the final model, after the model selection procedure, including the main effects for DM-TRD and time, as well as



[a]No clinical or demographic differences were found between the analyzed sample (n=1115) and dropouts (n=1120).

FIGURE 1 Flow chart of the study population 182 × 140 mm (300 × 300 DPI)

TABLE 1 Characteristics of the sample ($n = 1115$)

Demographics	
Age, years *mean* (*SD*)	**40.3** (12.5)
Female gender *n* (%)	**734** (65.8)
Clinical characteristics	
Score DM-TRD *mean* (*SD*)	**9.2** (*2.9*)
Baseline QIDS-SR score *mean* (*SD*)	**16.9** (*4.5*)
Number of QIDS-SR per subject *mean* (*SD*)	**4.2** (*2.2*)
Childhood adversity "yes" *n* (%)	**410** (*36.7*)
Current episode > 12 months *n* (%)	**579** (*51.9*)

their interaction. The model including this interaction had a lower AIC (26,847.2) compared to the model without this interaction (26,857.2) and to the model without the DM-TRD main effect (26,970.9). These findings confirm a negative association between the DM-TRD score and symptom severity according to the QIDS-SR scores over time. The results from the optimal model were used to demonstrate various courses with different DM-TRD scores. These estimated courses start at the similar baseline QIDS-SR score of 16.9 (the mean of our sample) during 48 weeks (the mean duration of follow-up) and are shown in Figure 2. The results of the quadratic time effect indicate a significant nonlinear relation and this effect is discernible in this figure as well.

3.3 | Childhood adversity

For the subgroups with ($n = 410$) and without ($n = 705$) childhood adversity, no significant differences were found in baseline QIDS-SR score, the number of QIDS-SR measurements and duration of follow-up in weeks (all p values > 0.1). The DM-TRD score for the group with childhood adversity ($M = 9.49$, $SD = 1.94$) was slightly higher than for the group without childhood adversity ($M = 9.10$, $SD = 1.93$), $t(1113) = -3.23$, $p = 0.001$, $d = 0.2$.

The AICs of the models including childhood adversity as a fixed parameter and its interaction with time (26,847.6 and 26,848.2, respectively) increased in comparison to previous AICs. This higher AIC indicated that the childhood adversity item does not improve our model.

4 | DISCUSSION

The main objective of this study was to examine the association between the DM-TRD and clinical course in a large, depressed outpatient population. Similar to an initial report (Peeters et al., 2016), higher DM-TRD scores were associated with poorer outcomes during follow-up. Given the positive interaction effect between the DM-TRD and the duration of follow-up, the DM-TRD is suggested to be associated with a solid longer-term prediction of symptom severity over time.

The second objective was to examine whether adding an item addressing the presence of childhood adversity improved the predictive property of the DM-TRD on clinical course. Contrary to our expectation, this extension of the DM-TRD did not add to the predictive power of the original model.

Severity of depressive symptoms prior to treatment is one of the most solid predictors of treatment outcome (Fekadu et al., 2009; Friedman et al., 2012). In the present study and a previous one in an independent sample (Peeters et al., 2016), the DM-TRD added prognostic factors that are associated with clinical course above and beyond baseline severity thereby illustrating its utility for clinical practice.

The prediction of symptom severity over time by the use of the DM-TRD can offer several advantages in clinical practice. First, as previously shown for the MSM (Fekadu et al., 2009; van Belkum et al., 2018), it can provide additional information concerning the expected course of illness. Moreover, the DM-TRD can potentially enhance adequate treatment planning, for example, by determining a cut-off score from which treatment planning is intensified compared to treatment as usual because of the expected difficulties. In agreement with Peeters et al. (2016), the DM-TRD is a feasible tool for this purpose. The information collected by the DM-TRD will usually be a part of the diagnostic interview and filling out the instrument will take only a few extra minutes. Its feasibility is confirmed by the large amount of completed DM-TRD-questionnaires in our study population.

Second, on a more detailed level of treatment planning, it may help to find optimal treatment (monotherapy, combined therapy or intensified treatment) based on future studies that are more controlled than the present one.

The addition of an item assessing childhood adversity did not improve the predictive value of the DM-TRD in our study. In a recent meta-analysis, Nanni et al. (2012) found that childhood adversity increased the risk of recurrence and persistence of MDD episodes twofold. Childhood adversity is also associated with an early illness onset (Nanni et al., 2012; Tunnard et al., 2014; Wiersma et al., 2009).

There are several explanations for our unexpected null-finding. First, we used a dichotomous way to address the presence of childhood adversity by asking just one question which may have led to under- or over reporting and thereby influencing our results in unknown ways. Additionally, the dichotomous format of the question does not allow to report on type (e.g., physical abuse, single traumatic events, emotional abuse or bullying), severity, duration, and current psychological burden of the experienced adversity. The subtype of the abuse is known to have a strong influence on the course of MDD. For example, emotional abuse is associated with longer index episodes and physical abuse is associated with greater episode recurrence (Tunnard et al., 2014). However, adding a standardized trauma questionnaire, for example, the Childhood Trauma Questionnaire (Bernstein & Fink, 1998; Spinhoven et al., 2014) to the DM-TRD would decreased the clinical feasibility.

Second, the presence or absence of childhood adversity was added to a model consisting of variables known to influence clinical course and whose elements may also serve as a proxy for childhood adversity. The resulting collinearity easily obscures a possible association between adversity and clinical outcome. Another explanation may be that the presence of adversity was awarded with only one additional point in the DM-TRD, thereby potentially downplaying its relevance

TABLE 2 The endorsed frequencies of the DM-TRD items including the childhood adversity item and the scoring of the items

Item	Specification	Scoring	*n* (%)
Episode duration	Acute (<12 months)	1	536 (48)
	Subacute (≥12 and <24 months)	2	235 (21)
	Chronic (≥24 months)	3	344 (31)
Symptom severity	Subsyndromal	1	41 (4)
	Mild	2	129 (12)
	Moderate	3	675 (60)
	Severe without psychosis	4	247 (22)
	Severe with psychosis	5	23 (2)
Functional impairment	No impairment (GAF90–100)	0	4 (<1)
	Mild (GAF60–90)	1	135 (12)
	Moderate (GAF30–60)	2	955 (86)
	Severe (GAF0-30)	3	21 (2)
Comorbid anxiety symptoms	Not present	0	449 (40)
	Present, but not fulfilling DSM-IV-criteria	0.5	442 (40)
	Fulfilling criteria DSM-IV	1	224 (20)
Comorbid personality disorder	Present, based on formal interview	1	28 (3)
	No formal interview:		
	SAPAS ≥ 3	0.5	697 (62)
	SAPAS < 3	0	390 (35)
Psychosocial stressors	No psychosocial stressor	0	233 (21)
	>1 Psychosocial stressor	1	882 (79)
Treatment failures	*Antidepressants*		
	Level 0: not used	0	631 (57)
	Level 1: 1–2 medications	1	468 (42)
	Level 2: 3–4 medications	2	15 (1)
	Level 3: 5–6 medications	3	1 (<1)
	Level 4: 7–10 medications	4	0 (0)
	Level 5: >10 medications	5	0 (0)
	Augmentation/combination		
	Level 0: not used	0	970 (87)
	Level 1: 1–2 medications	1	131 (12)
	Level 2: 3–4 medications	2	9 (1)
	Level 3: 5–6 medications	3	5 (<1)
	Electroconvulsive therapy		
	Not used	0	1106 (99)
	Used	1	9 (1)
	Psychotherapy		
	Not used	0	639 (57)
	Supportive therapy	0.5	360 (33)
	Empirically supported psychotherapy 1	1	103 (9)
	>2 empirically supported psychotherapies	2	13 (1)
	Intensified treatment		
	Not used	0	1087 (98)
	Day patient treatment	1	5 (<1)
	Inpatient treatment	2	23 (2)
Childhood adversity	Yes	1	410 (37)
	No	0	705 (63)
Total score		**2–28**	

TABLE 3 Results of the linear mixed models summarizing the association between DM-TRD and QIDS-SR scores during follow-up (final model)

	DM-TRD score				
	Fixed effect			Random effect	
Parameter	Est.	St. Error	Sig.	Var.	SE.
Intercept	10.926	0.602	<0.0001	10.17	0.784
Time[a]	−0.216	0.016	<0.0001	0.026	0.003
Time × time	0.001	<0.0001	<0.0001	<0.0001	<0.0001
Total DM-TRD score	0.623	0.064	<0.0001		
Total DM-TRD score × time	0.005	0.0015	0.001		
Level 1 residual				10.27	0.309

[a]Interval in weeks between assessment of the DM-TRD and assessment of the last QIDS-SR.

in the model in comparison to the contribution of other variables that were also awarded one point. Third, in the present sample, the duration of follow-up was lower compared to previous studies in depressed patients which may have obscured differences in long-term outcome (Nanni et al., 2012; Wiersma et al., 2009). Fourth, the interval between the consecutive follow-up measurements was considerably long (3 months) which may have left differences in time course undetected. Fifth, in this naturalistic study, it is unclear if patients with childhood adversity were treated differently than those without adversity. During an initial diagnostic work-up, if severe childhood adversity is assessed this may result in different treatment planning, such as referral to specialized trauma treatment unit (selection bias) or differences in the treatments applied for depression (e.g., monotherapy vs. combination therapy or intensified psychotherapy).

Despite the large sample, the naturalistic treatment setting and the state of the art statistical analyses, some limitations need to be discussed. First, this naturalistic study was carried out in routine clinical practice without control of or information on applied treatments. However, it can be stated that all participants were treated according to current, relevant clinical guidelines. Treatment outcome may have been influenced by unknown differences in treatment (e.g., psychotherapy, pharmacotherapy or both) thereby leaving significant differences in DM-TRD elements between subjects undetected. Nevertheless, and as a first step, the DM-TRD showed an association with the clinical course across the whole range of provided treatments. Second, the weights of the DM-TRD-items (for both the categories per item and for the items relative to each other) were determined by clinical face-validity instead of an empirical approach to balance weights. This might have underestimated the predictive value of the DM-TRD in our study. Therefore, future studies should attempt to optimize scaling and weighing of the different items. Third, although the item on childhood adversity was introduced as a revision of the

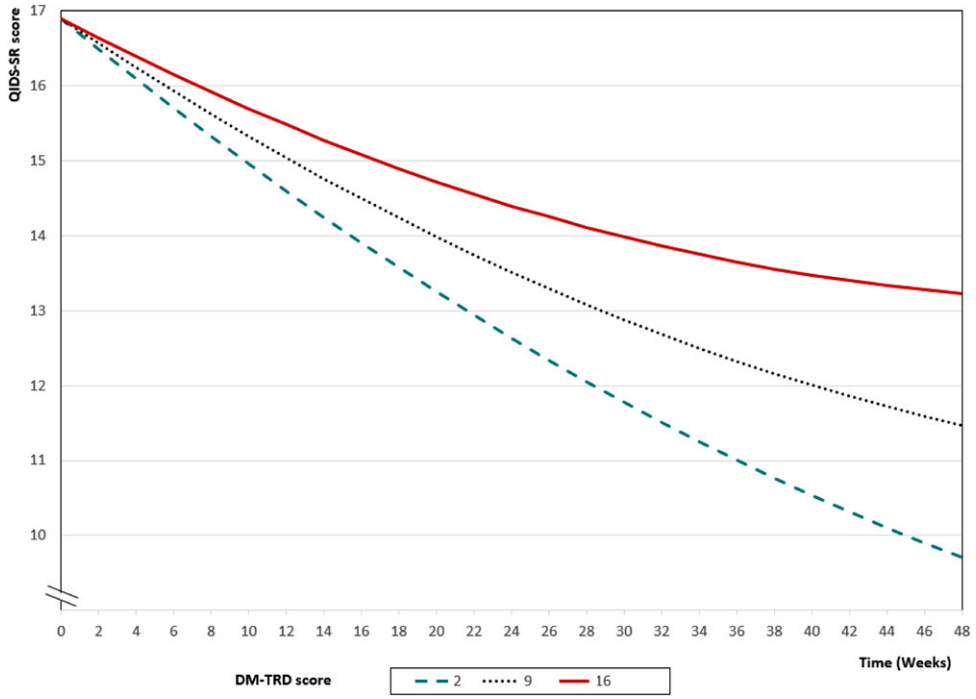


FIGURE 2 Estimated course of the QIDS-SR scores for three assumed DM-TRD scores when baseline QIDS-SR scores are equal (mean of the sample, 16.9) 169 × 127 mm (300 × 300 DPI)

DM-TRD, other factors susceptible to influence treatment course, for example, age of onset of the first episode (Lamers et al., 2011), somatic comorbidity (Milligen, Vogelzangs, Smit, & Penninx, 2012) or psychotic features (Perlis, 2011; Wigman et al., 2014), were not included.

As a next step, the DM-TRD needs evaluating for its properties to assist in treatment planning, by defining cut-off scores for specific indications (if possible), and ultimately using the DM-TRD in a randomized-controlled trial to assist treatment indication, thereby enabling advanced personalized treatment planning.

5 | CONCLUSION

The DM-TRD is a practical and valid instrument that is associated with symptom severity over time in patients with MDD. It can be easily incorporated in the context of diagnostic work-up procedures and with its present items does not require childhood adversity as an additional source of information.

CONFLICTS OF INTERESTS

This research was performed without additional funding. The authors report no financial or other relationship relevant to the subject of this article. Mrs. E.J.M. Huijbens has no conflicts of interest to declare.

ACKNOWLEDGMENTS

The authors thank Mrs. E.J.M. Huijbens, BSc, for her contribution to the development of the dataset.

NOTE

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REFERENCES

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, *19*(6), 716–723. https://doi.org/10.1109/TAC.1974.1100705

APA. (2000). *Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.

Bernstein, D. P., & Fink, L. (1998). Childhood Trauma Questionnaire: A retrospective self-report. Manual. San Antonio, TX: The Psychological Corporation, Harcourt Brace & Company.

Brown, G. W., Harris, T. O., Kendrick, T., Chatwin, J., Craig, T. K., Kelly, V., … Thread Study Group. (2010). Antidepressants, social adversity and outcome of depression in general practice. *Journal of Affective Disorders*, *121*(3), 239–246.

Bukh, J. D., Bock, C., Vinberg, M., Gether, U., & Kessing, L. V. (2010). Clinical utility of Standardised Assessment of Personality-Abbreviated Scale (SAPAS) among patients with first episode depression. *Journal of Affective Disorders*, *127*(1–3), 199–202. https://doi.org/10.1016/j.jad.2010.05.023

Chekroud, A., Lane, C., & Ross, D. (2017). Computational psychiatry: Embracing uncertainty and focusing on individuals, not averages. *Biological Psychiatry*, *82*(6), e45–e47. https://doi.org/10.1016/j.biopsych.2017.07.011

Cipriani, A., Furukawa, T., Salanti, G., Chaimani, A., Atkinson, L., Ogawa, Y., … Higgins, J. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, *391*(10128), 1357–1366.

Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. *Journal of Clinical Psychiatry*, *70*(9), 1219–1229. https://doi.org/10.4088/JCP.09r05021

Fang, Y. (2011). Asymptotic equivalence between cross-validations and Akaike information criteria in mixed-effects models. *Journal of Data Science*, *9*(1), 15–21.

Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, *53*(8), 649–659. https://doi.org/10.1016/S0006-3223%2803%2900231-2

Fava, M., Rush, A. J., Alpert, J. E., Balasubramani, G. K., Wisniewski, S. R., Carmin, C. N., … Trivedi, M. H. (2008). Difference in treatment outcome in outpatients with anxious versus nonanxious depression: A STAR*D report. *American Journal of Psychiatry*, *165*(3), 342–351.

Fekadu, A., Wooderson, S., Donaldson, C., Markopoulou, K., Masterson, B., Poon, L., & Cleare, A. J. (2009). A multidimensional tool to quantify treatment resistance in depression: The Maudsley staging method. *Journal of Clinical Psychiatry*, *70*(2), 177–184. https://doi.org/10.4088/JCP.08m04309

Fekadu, A., Wooderson, S., Markopoulou, K., & Cleare, A. J. (2009). The Maudsley staging method for treatment-resistant depression: Prediction of longer-term outcome and persistence of symptoms. *Journal of Clinical Psychiatry*, *70*(7), 952–957. https://doi.org/10.4088/JCP.08m04728

Friedman, E. S., Davis, L. L., Zisook, S., Wisniewski, S. R., Trivedi, M. H., Fava, M., & Rush, A. J. (2012). Baseline depression severity as a predictor of single and combination antidepressant treatment outcome: Results from the CO-MED trial. *European Neuropsychopharmacology*, *22*(3), 183–199.

Hetrick, S., Parker, A. G., Hickie, I., Purcell, R., Yung, A., & McGorry, P. (2008). Early identification and intervention in depressive disorders: Towards a clinical staging model. *Psychotherapy and Psychosomatics*, *77*(5), 263–270. https://doi.org/10.1159/000140085

Judd, L. L., Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., … Keller, M. B. (1998). A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Archives of General Psychiatry*, *55*(8), 694–700. https://doi.org/10.1001/archpsyc.55.8.694

Kassebaum, N., Arora, M., Barber, R., Bhutta, Z., Brown, J., Carter, A., … Collaborators H. A. L. E. (2016). Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1603–1658. https://doi.org/10.1016/S0140-6736%2816%2931460-X

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, *62*, 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Lamers, F., Van Oppen, P., Comijs, H., Smit, J., Spinhoven, P., Van Balkom, A., … Penninx, B. (2011). Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depres-

sion and Anxiety (NESDA). *Journal of Clinical Psychiatry*, *72*(3), 342–348. https://doi.org/10.4088/JCP.10m06176blu

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, *3*(11), 2011–2030. https://doi.org/10.1371/journal.pmed.0030442

Milligen, v. B. A., Vogelzangs, N., Smit, J. H., & Penninx, B. W. J. H. (2012). Physical function as predictor for the persistence of depressive and anxiety disorders. *Journal of Affective Disorders*, *136*(3), 828–832. https://doi.org/10.1016/j.jad

Moran, P., Leese, M., Lee, T., Walters, P., Thornicroft, G., & Mann, A. (2003). Standardised Assessment of Personality-Abbreviated Scale (SAPAS): Preliminary validation of a brief screen for personality disorder. *British Journal of Psychiatry*, *183*(SEPT.), 228–232. https://doi.org/10.1192/bjp.183.3.228

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*(2), 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: A systematic review. *Archives of General Psychiatry*, *61*(7), 714–719. https://doi.org/10.1001/archpsyc.61.7.714

Peeters, F. P. M. L., Ruhe, H. G., Wichers, M., Abidi, L., Kaub, K., van der Lande, H. J., … Schene, A. H. (2016). The Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD): An extension of the Maudsley Staging Method. *Journal of Affective Disorders*, *205*, 365–371. https://doi.org/10.1016/j.jad.2016.08.019

Perlis, R. H., Uher, R., Ostacher, M., Goldberg, J. F., Trivedi, M. H., Rush, A. J., & Fava, M. (2011). Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Archives of General Psychiatry*, *68*(4), 351–360. https://doi.org/10.1001/archgenpsychiatry.2010.179

Reilly, T., MacGillivray, S., Reid, I., & Cameron, I. (2015). Psychometric properties of the 16-item Quick Inventory of Depressive Symptomatology: A systematic review and meta-analysis. *Journal of Psychiatric Research*, *60*, 132–140. https://doi.org/10.1016/j.jpsychires.2014.09.008

Rosenman, S., & Rodgers, B. (2006). Childhood adversity and adult personality. *Australian & New Zealand Journal of Psychiatry*, *40*(5), 482–490. https://doi.org/10.1080/j.1440-1614.2006.01826.x

Ruhe, H. G., Huyser, J., Swinkels, J. A., & Schene, A. H. (2006). Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: A systematic review. *Journal of Clinical Psychiatry*, *67*(12), 1836–1855.

Rush, A., Trivedi, M., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/appi.ajp.163.11.1905

Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B., & Trivedi, M. H. (2009). The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychological Medicine*, *26*(03), 477–486. https://doi.org/10.1017/s0033291700035558

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., … Keller, M. B. (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573–583. https://doi.org/10.1016/S0006-3223%2802%2901866-8

Spielmans, G. I., Berman, M. I., & Usitalo, A. N. (2011). Psychotherapy versus second-generation antidepressants in the treatment of depression: A meta-analysis. *Journal of Nervous and Mental Disease*, *199*(3), 142–149. https://doi.org/10.1097/NMD.0b013e31820caefb

Spijker, J., Bockting, C., Meeuwissen, J., Van Vliet, I., Emmelkamp, P., Hermens, M., & van Balkom, A. (2013). *Multidisciplinaire richtlijn Depressie (Derde revisie): Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een depressieve stoornis [Multidisciplinary guidelines for depression (third revision): Guideline for the diagnosis, treatment and guidance of adult patients with a depressive disorder]*. Utrecht: Trimbos Institute.

Spinhoven, P., Elzinga, B. M., Van Hemert, A. M., de Rooij, M., & Penninx, B. W. (2016). Childhood maltreatment, maladaptive personality types and level and course of psychological distress: A six-year longitudinal study. *Journal of Affective Disorders*, *191*, 100–108.

Spinhoven, P., Penninx, B., Hickendorff, M., van Hemert, A., Bernstein, D., & Elzinga, B. (2014). Childhood trauma questionnaire: Factor structure, measurement invariance, and validity across emotional disorders. *Psychological Assessment*, *26*(3), 717–729. https://doi.org/10.1037/pas0000002

Tunnard, C., Rane, L. J., Wooderson, S. C., Markopoulou, K., Poon, L., Fekadu, A., … Cleare, A. J. (2014). The impact of childhood adversity on suicidality and clinical course in treatment-resistant depression. *Journal of Affective Disorders*, *154*, 122–130.

Twisk, J. W. R. (2003). *Applied longitudinal data analysis for epidemiology: A practical guide*. Cambridge, United Kingdom: Cambridge University Press.

van Belkum, S. M., Geugies, H., Lysen, T. S., Cleare, A. J., Peeters, F., Penninx, B., … Ruhe, H. G. (2018). Validity of the Maudsley staging method in predicting treatment-resistant depression outcome using the Netherlands study of depression and anxiety. *The Journal of Clinical Psychiatry*, *79*(1):17m11475. https://doi.org/10.4088/JCP.17m11475

van Bodegom, M., Homberg, J. R., & Henckens, M. J. A. G. (2017). Modulation of the hypothalamic–pituitary–adrenal axis by early life stress exposure. *Frontiers in Cellular Neuroscience*, *11*(87). https://doi.org/10.3389/fncel.2017.00087

van Os, J., Verhagen, S., Marsman, A., Peeters, F. P. M. L., Bak, M., Marcelis, M., … Delespaul, P. (2017). The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. *Depression and Anxiety*, *34*(6), 481–493. https://doi.org/10.1002/da.22647

Wiersma, J. E., Hovens, J. G., van Oppen, P., Giltay, E. J., van Schaik, D. J., Beekman, A. T., & Penninx, B. W. (2009). The importance of childhood trauma and childhood life events for chronicity of depression in adults. *Journal of Clinical Psychiatry*, *70*(7), 983–989.

Wigman, J., van Os, J., Abidi, L., Huibers, M. J. H., Roelofs, J., Arntz, A., … Peeters, F. P. M. L. (2014). Subclinical psychotic experiences and bipolar spectrum features in depression: Association with outcome of psychotherapy. *Psychological Medicine*, *44*(2), 325–336.

How to cite this article: van Dijk DA, van den Boogaard TM, Deen M, Spijker J, Ruhé HG, Peeters FPML. Predicting clinical course in major depressive disorder: The association between DM-TRD score and symptom severity over time in 1115 outpatients. *Depress Anxiety*. 2019;36:345–352. https://doi.org/10.1002/da.22865