A Multidimensional Tool to Quantify Treatment Resistance in Depression: The Maudsley Staging Method

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Objective: Treatment resistance is a common clinical phenomenon in depression. However, current unitary models of staging fail to represent its complexity. We aimed to devise a model to stage treatment-resistant depression, taking into account the core factors contributing to treatment failure.

Method: We reviewed the literature to identify factors consistently associated with treatment resistance. We also analyzed data from a subgroup of patients discharged from a specialist inpatient unit for whom adequate data were obtainable.

Results: We present a points-based staging model incorporating 3 factors: treatment, severity of illness, and duration of presenting episode. In this model, the rating of symptom severity ranges from subsyndromal depression (score 1) to severe syndromal depression with psychosis (score 5). Antidepressant treatment is rated on a 5-point subscale based on number of medications used, while duration of the presenting episode is rated on a 3-point subscale. The overall level of resistance estimated using this model varies from minimal resistance (score of 3) to severe resistance (score of 15). The rating system allows the overall severity of treatment resistance to be summarized either as a single numeric score or under a single descriptive category. It may also be possible to specify categories (mild, moderate, and severe) based on severity of resistance. Analysis of inpatient data indicates that the factors incorporated in the model and the model itself have some predictive validity.

Conclusion: This staging model has reasonable face and predictive validity and may have better utility in staging treatment resistance than currently available methods.

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Recent studies have consistently demonstrated the serious public health impact of depression. It is the fourth leading cause of global disease burden[1] and affects about 15% of the general population.[2–6] It is also associated with considerable economic burden. For the year 2000, the estimated cost of depression in England was over £9 billion,[7] while in the United States, it was over $81 billion.[8]

Almost 50% of the cost and disease burden caused by depression is likely to be attributable to treatment-resistant depression (TRD).[9–11] Such a high burden is due to a combination of factors. First, TRD itself is common, affecting about 30% of those with major depression[12,13] and may even be as high as 60% if TRD is defined as absence of remission.[10,13] Second, duration and severity of illness, both of which are higher in TRD, are important considerations in computing disease burden.[14] Third, patients with TRD are more likely to suffer from comorbid physical and mental disorders, to experience marked and protracted functional impairment, and to incur significantly higher medical and mental health care costs.[15–19] Thus TRD is common and presents a significant personal and public health problem. However, the lack of a uniformly accepted and valid definition of, and staging method for, TRD has hampered progress in the study of this important domain of depression.

In this article, we propose a multidimensional staging model for TRD based on a conceptual framework formulated from existing knowledge supplemented by empirical data drawn from a sample of patients with TRD.

CONCEPT DEVELOPMENT

Definition

Whereas the phenomenon of clinical resistance is common in medical practice, the conceptual underpinning of resistance in psychiatric disorders may be more complex. In general, treatment resistance may be modeled on the basis of the responsiveness of the causative pathogenic agent to treatment, the underlying pathologic process, or the extent of disease process. For depression, the limited knowledge regarding these factors makes staging resistance modeled on these factors less viable. Instead, attempts to conceptualize and quantify treatment resistance in depression have relied on number and type of treatments used to relieve depression. However, the lack of a universally accepted staging model that adequately describes treatment failure and resistance has led to extensive variations in the definition of TRD.

This variation was highlighted in a recent review of controlled treatment trials.[20] The review demonstrated that the variability in the methodological and conceptual issues in TRD were due to the lack of consensus in how the underlying depressive syndrome and treatment responsiveness were defined. For example, although treatment failure is a frequently used criterion, the number of unsuccessful trials required to indicate treatment resistance varied across studies. Fourteen of the studies included in the Berlim and Turecki review[20] defined treatment resistance as failure to improve after the use of at least 1 antidepressant medication, while 24 studies defined it as failure to respond to at least 2 antidepressant medications. In terms of defining the depressive syndrome, some studies used rating scales (for example, the Hamilton Rating Scale for Depression [HAM-D][21]) while others relied on standard operationalized diagnostic systems, such as the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[22] Treatment nonresponse was characterized either in terms of failure to achieve a specified percentage reduction in the score of a dimensional rating scale or the continuation of a major depressive episode despite treatment. Most studies defined treatment failure only in relation to the presenting episode while a few also included treatment failures in previous episodes.

Challenges in Current Definitions of TRD

Despite the aforementioned variations in the definition of treatment resistance, a few methods of staging have come to prominence. The Thase and Rush model[23] is one example. This is a hierarchical model[24] of staging in which medications used at the higher order of treatment resistance are implicitly assumed to have superior efficacy. The hierarchical assumptions and limited flexibility to accommodate the potentially numerous medications that may be deployed to treat a resistant episode are its major drawbacks. Additionally, the hierarchical model assumes that medication would be given in a certain sequence, progressing from single medication to augmentation strategy and culminating in the use of electroconvulsive therapy (ECT). However, in clinical practice, treatment is prescribed in an individualized way with informed negotiation rather than in a predetermined sequence in which ECT is the treatment of last resort. Furthermore, in current practice, restrictions applied in some countries[25–27] favor the use of ECT in life-threatening emergencies. Additionally, there is no clear evidence supporting the superiority of switching within antidepressant class as opposed to switching to different antidepressant class,[18,28] as implied in the model. Neither are there clear provisions for combination or augmentation strategies.[18]

In the Massachusetts General Hospital staging method (MGH-S),[18] the staging of treatment resistance is primarily based on the number of antidepressant medications used, and a special weight is given for failure of treatment with ECT, which receives a score of 3. There is some limited evidence for the utility of this model.[29] The model allows flexibility to incorporate as many medications as required in gauging degree of treatment resistance. However, with the potential for the large number of treatment options currently available, the system may be less efficient and less discriminating. Thus, data obtained may not inform intervention strategies or enhance understanding and communication. There is also no clear evidence supporting the magnitude of the special weight given to treatment with ECT.

The European method of staging relies on matching treatment resistance to specific class of medication used combined with duration of treatment trials.[30] This method is useful insofar as it recognizes the role of duration of illness in treatment resistance. However, its assumption regarding the differential effectiveness of antidepressant medications is without a clear evidence base. The model is also limited in scope.

One further staging model was recently explored. This model was based on depressive subtypes on a dimension of severity (psychotic, melancholic, and nonmelancholic).[11] This approach has been shown to have some convergent validity with clinician impressions of resistance on a cross-sectional assessment.[11] Again this model is of limited scope.

In addition to what has been discussed so far, the key shortcoming of these staging models is their reliance on a single criterion, mainly treatment response.[23,30]

Lack of efficacy of medication to produce improvement is the essential and core element of treatment resistance. However, basing staging methods solely on medication use to the exclusion of other relevant factors such as duration and severity of illness, type of depression, and the role of psychosocial stressors has been criticized.[31] A set of useful proposals that clarify assessment of TRD,

dubbed "paradigm failures," has been proposed.[24] Failure to adequately establish the severity or type of depression and to "identify organic determinants" of depression were considered to be the main causes of misclassification of a mood state unresponsive to treatment as TRD.[24] It is important to emphasize that these failures are primarily diagnostic, although discussion of TRD often confuses these paradigm failures with TRD.

Considering these shortcomings in the available staging methods, we aimed to develop a staging model taking advantage of the improved understanding regarding the treatment of depression and responsiveness.[13,28] Once this model was developed, we tested the predictive validity of the model on prospective data extracted from case notes.

Considerations in Proposed Staging

Multidimensional nature of resistance. Resistance is not an all-or-nothing phenomenon. It exists as a continuum, and various dimensional factors contribute to its occurrence and maintenance. The core assumption in treatment resistance is the failure of adequate treatment (given at adequate dose and duration) to lead to improvement, irrespective of how improvement may be defined. Treatment resistance also occurs in a context of a depressive illness of quantifiable severity and a specifiable duration, with certain factors playing a role in its maintenance. We therefore propose that a model of staging of treatment resistance should incorporate severity and duration of depressive illness and the required level of intervention before improvement is gained.

Treatment failure. Treatment resistance can be considered only in the context of adequate treatment trials (in terms of adequate dose and duration). Once the first treatment trial fails, response to successive treatments declines. This phenomenon was demonstrated in the recent STAR*D study, in which failure of the first treatment step led to a lowering of the level of response and remission in all subsequent treatment steps.[28] This effect implies that failure of the first treatment is influential in treatment resistance and may be a useful starting point in any measure of this conceptual continuum. However, there is no clear evidence-based guidance as to how the subsequent hierarchies in the continuum should be composed. Currently there is no evidence supporting the superiority of employing switching or augmentation strategies in subsequent stages of treatment resistance.[13,28] Therefore, this approach cannot form the basis for staging resistance. Furthermore, formulating a hierarchy of treatment resistance based on the type of treatment used[23] has limited support.[29] However, number of treatments sequentially failing to produce improvement has some supportive evidence[11,29] and may form the basis for a staging criterion. But the number of medications that may be used is potentially endless, rendering a counts-based system less efficient and less helpful in estimating the level of resistance. We therefore classified antidepressant counts into 5 levels, as shown in Table 1. Antidepressant treatment counted only if treatment was given for 6 weeks at adequate doses. We employed the Maudsley Prescribing Guidelines for estimating the minimum effective doses of antidepressants.[32] For example, a dose of 20 mg of fluoxetine or citalopram, 30 mg of mirtazapine, and 60 mg of duloxetine would count as adequate doses, according to the guideline. We also added separate scores for adequate treatment trials with ECT and augmentation strategies. Adequate trial of ECT was considered to be at least an 8 session course. Additional medications that are not primarily antidepressants, such as lithium, anticonvulsants, thyroid hormones, pindolol, and buspirone, which are used to enhance the efficacy of antidepressant, counted as augmentation.[32,33] These medications received a score if they were given at adequate doses for at least 6 weeks.

Severity of depression. Staging treatment resistance only in relation to number of medications used says little about the specific nature of the depression itself. Moderately severe depression that is resistant to treatment is distinct from a severe psychotic depression that is also resistant to treatment. Inclusion of severity of depression as a staging criterion not only makes clinical sense, but severity of illness has also been consistently associated with nonresponse in numerous treatment[34–37] and follow-up studies.[38–42] Severity of symptoms is the best predictor of persistence of depressive symptoms[43] and occurrence of residual symptoms and relapse.[34,44] Conversely, early remission or less-severe depression predicted maintenance of remission in the longer term.[36,39,45]

The association of severity of illness with outcome has been demonstrated for both severity determined by diagnosis according to specified criterion[46,47] or measured by dimensional scales, such as the HAM-D.[39] The relationship was also shown for medication treatment, ECT, and psychotherapy.[35,48] It is therefore reasonable and relevant to incorporate severity of illness to model treatment resistance.

We base our recommendation for modeling depression severity on the Mental and Behavioral Disorders section of the 10th revision of the *International Classification of Diseases* (ICD-10).[49] The ICD-10 uses dimensional subtyping to classify depression, and its accessibility and common use in clinical practice make such modeling attractive. These severity subtypes in the ICD-10 system range from mild depression to severe depression with psychosis. Despite some uncertainties as to whether depression with psychotic symptoms may be a distinct disorder,[50–52] we have included it as the most severe form of depression, as it is presented in both ICD-10 and DSM-IV. We have further tested this approach using an empirical data set. We add another level, a subsyndromal severity, to the ICD-10 severity subtypes. The inclusion of this additional level of severity is based on the accumulating

evidence that substantiates the role of depression at the subsyndromal level as a cause of disability[53] and poor quality of life.[54] Subsyndromal symptoms also predispose to relapse.[53,55] We omit the ICD-10 somatic syndrome subgrouping, which we incorporate within the main severity dimensions, partly for simplicity. We also omit the issue of mood-congruence in the psychotic end of the spectrum.

Duration. Duration of illness, both before and after an adequate treatment trial, is also an important consideration in treatment resistance. Again, studies have consistently demonstrated that the longer the duration of illness, the poorer the response to treatment. Longer duration of illness predicts poor response to acute treatment[46,47,56,57] and to augmentation with lithium.[58] Chronicity also predicted poorer relapse-free survival.[34,59]

We based our model on the duration of the presenting depressive episode, irrespective of treatment experience. We classified duration into 3 categories. Duration of 1 year or less was considered acute, between 1 and 2 years subacute, and anything longer than 2 years chronic. The cutoff of 2 years for chronic depression was based on the criterion of the DSM-IV Text Revision (DSM-IV-TR) diagnostic system.[60]

Empirical Evidence

Empirical evidence to test this model was derived by extracting data from case notes of patients with TRD (N = 88) discharged from an inpatient unit specializing in the treatment of resistant mood disorders. Cases were selected on the basis of having adequate information to test the hypothesized model. Data were extracted on ICD-10 diagnosis, severity of illness, full prior treatment history, outcome at discharge (score on HAM-D), and sociodemographic information. Severity of illness was categorized into 5 groups to fit the severity classes identified a priori according to ICD-10 groupings. The subsyndromal subtype was a residual group including patients who were symptomatic but did not fulfill the diagnostic criteria for any of the other diagnostic subtypes. Duration of illness was also input as defined a priori in the model. We used logistic regression to determine the power of the proposed staging model and its components (number of medications, duration of presenting episode, and severity of illness) to predict failure to achieve remission at discharge. This was defined as a HAM-D_{21} score of 11 and above (i.e., a score of 10 or less was considered remission). Independent variables included all factors proposed in this report. We also attempted to assess the impact of various weights given for ECT by varying the score for ECT (1, 2, or 3). The role of augmentation strategies was explored using both a continuous variable (based on the number used) and as a categorical variable (yes or no). We also explored the Thase and Rush hierarchies.[23] Finally, we looked for the presence of significant linear trend for the main components of the model and the final model, as well as for the Thase and Rush stages. In other words, we explored whether an increasing score in the component subscales and final model score was associated with a corresponding increase in the likelihood of being a nonremitter or treatment resistant.

Table 1. Maudsley Staging Parameters and Suggested Scoring Conventions

Parameter/Dimension	Parameter Specification	Score
Duration	Acute (≤ 12 months)	1
	Sub-acute (13–24 months)	2
	Chronic (> 24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1–2 medications	1
	Level 2: 3–4 medications	2
	Level 3: 5–6 medications	3
	Level 4: 7–10 medications	4
	Level 5: > 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		(15)

RESULTS

Staging

The details of the proposed staging model and scoring system are shown in Table 1. Three main conventions of presenting or communicating the stages of resistance are suggested. The simplest is to use a single numerical score. This normally should be between 3 and 15. Staging of resistance can also be presented in 3 severity categories—mild (scores = 3–6), moderate (scores = 7–10), and severe (scores = 11–15). Finally, resistance may be presented descriptively and easily communicated incorporating all the main factors in the description. This presentation will help specify the duration, severity, and number of treatment failures, e.g., *moderate, subacute level 2 resistance* would correspond with failure of 3 to 4 antidepressants, and a moderately severe depression with a presenting episode of illness lasting between 1 and 2 years.

Results From Empirical Data

Characteristic of sample. Main characteristics of the sample are depicted in Table 2. Most of the cases were women, and about 85% of cases had at least moderately severe depressive disorder on admission. The median duration of the presenting episode was 3 years, with a range of 23.9 years. Most patients had received at least 3 antidepressant medications prior to admission (87.5%), and a

Table 2. Demographic and Clinical Characteristics of Sample

Characteristic	N	%
Sex		
Male	21	23.9
Female	67	76.1
Marital status		
Single	26	29.5
Married	50	56.8
Postmarital[a]	12	13.6
Remission status at discharge		
Remission	33	37.5
Resistance	55	62.5
Severity		
Subsyndromal	3	3.4
Mild	9	10.2
Moderate	29	33.0
Severe	31	35.2
Severe with psychosis	16	18.2
Duration		
Acute	14	15.9
Subacute	20	22.7
Chronic	54	61.4
Antidepressant medication		
Level 1	11	12.5
Level 2	20	22.7
Level 3	16	18.2
Level 4	31	35.2
Level 5	10	11.4
Augmentation		
Yes	77	87.5
No	11	12.5
Electroconvulsive therapy		
Yes	62	70.5
No	26	29.5
Model summary		
Mild resistance	5	5.7
Moderately severe resistance	30	34.1
Severe resistance	53	60.2

[a]Includes separated, divorced, and widowed.

similar proportion had received medication augmentation. The proportion of cases with a history of ECT use was also quite high (N = 62; 70.5%). At admission, the mean severity score on the staging model of treatment resistance was 10.7 (SD = 2.3), with a minimum score of 5 and maximum of 15. Based on the 3 severity categories proposed, 5.7% (N = 5) had mild, 34.1% (N = 30) had moderate, and 60.2% (N = 53) had severe treatment resistance. Patients were treated for a mean of 26 weeks (SD = 16 weeks).

Predictive validity. All factors in the model (treatment failure and severity and duration of illness) independently predicted resistance (defined as failure to achieve remission) at discharge (Tables 3 and 4). On its own, treatment with ECT was marginally predictive of resistance. However, use of augmentation strategies (entered both as a categorical [yes, no] and continuous [number of augmentation medications] variable) was not predictive of resistance. We tested the prediction of treatment resistance by excluding psychotic depression from the model. The precision of estimate deteriorates with this exclusion, and we used the original 5 levels of severity for fitting the final model.

Table 3. Independent Predictive Power of Individual Model Components and (unadjusted) Final Model

Variable	Adjusted Odds Ratio	95% CI	Significance
Severity	2.27	1.35 to 3.82	.002
Duration	2.14	1.07 to 4.29	.030
Treatment	1.43	1.05 to 1.95	.024
Final model	1.67	1.29 to 2.16	< .001

The model also demonstrated significantly positive test for trend (Table 5). The highest values were identified for the proposed staging model, both with continuous and ordinal scores (mild, moderate, and severe). The final model correctly predicted treatment resistance in 85.5% of cases.

Staging based on the Thase and Rush model[23] has some predictive power for treatment resistance, albeit with lower precision. The Thase and Rush model also shows a positive trend, but much lower compared with the proposed multidimensional model.

DISCUSSION

Model Characteristics

This study presents the first multidimensional staging model for TRD. The proposed model incorporates the relevant factors that should be considered in planning intervention. The model appears to have reasonable face validity and predictive validity. The model also has adequate flexibility and can be easily used by clinicians. The model can potentially facilitate better communication among clinicians and researchers.

The factors included are independently associated with treatment resistance, thus justifying their inclusion.

In relation to the specific factors, the model fit for antidepressant treatment appears to be best when antidepressants are categorized as suggested in our model than when used as continuous count. However, these groupings are pragmatic, aimed at providing an efficient classification method. Thus, there is room for error. Our model indicates that a special weight should not be given for ECT. The model fit deteriorates with increased weight. We therefore limited the score for ECT to 1. This result may partly be because our sample consisted of a more severely treatment-resistant group of patients.

Understandably, it was difficult to specify duration criteria. We have partly relied on the DSM-IV-TR criteria to specify chronic resistance and have included an additional category. Duration may also be partly confounded by treatment history, as most patients with longer history of treatment are more likely to receive more treatment. However, in our sample, independence of association was confirmed.

Although the Thase and Rush model[23] was also found to be a useful predictor of treatment resistance, the

Table 4. Prediction of Treatment Resistance for Individual Variables or Combination of Variables Considered in Model and Fitness of Model

Variable	Odds Ratio	95% Confidence Interval	p Value	Model Fit (p Value)[a]
Electroconvulsive therapy (ECT)	2.64	1.03 to 6.77	.043	NA[b]
Augmentation (yes)[c]	3.43	0.92 to 12.80	.070	NA[b]
Augmentation, number	1.00	0.71 to 1.40	.997	.08
Antidepressants, number	1.17	1.01 to 1.33	.040	.49
Antidepressant[d]	1.50	1.04 to 2.16	.030	.13
Antidepressant[d] + Augmentation[c] + ECT1[e]	1.41	1.08 to 1.85	.013	.12
Antidepressant[d] + Augmentation[c] + ECT2[e]	1.34	1.07 to 1.68	.012	.06
Antidepressant[d] + Augmentation[c] + ECT3[e]	1.27	1.06 to 1.54	.012	.10
Severity of illness	2.17	1.32 to 3.55	.002	.85
Duration	2.37	1.30 to 4.31	.005	.49
Final model[f]	1.67	1.29 to 2.16	< .001	.26
Thase and Rush model[23]	1.60	1.09 to 2.36	.017	.84

[a]Hosmer and Lemeshow test for goodness of fit.
[b]Binary variables.
[c]Augmentation, binary (yes/no) categories.
[d]Antidepressant medications classified as in proposed staging model.
[e]ECT given a score of 1, 2, or 3.
[f]Final model = severity, antidepressant,[d] ECT,[b] augmentation,[c] and duration of current episode together.
Abbreviation: NA = not applicable.

Table 5. Linear Trend for Association With Nonremission at Discharge Using Final Model, Individual Model Components, and the Thase and Rush Model

	Linear Trend	
Variable	χ^2	Significance
Duration	8.80	.003
Severity	9.63	.002
Antidepressant medication	4.12	.042
Proposed model	16.12	< .001
Proposed model (3 severity categories)	10.72	.001
Thase & Rush model[23]	6.14	.013

coefficients of prediction were not as strong as in our model. The linear trend in the Thase and Rush model was also fairly modest. Although we did not specifically attempt to test the validity of the other staging models, the MGH-S was highly dependent on total antidepressant count and special weighting of ECT. Antidepressant count was not a stable predictor of resistance in our sample, and the staging model failed to improve with higher weight for ECT.

Model Omissions

We have not incorporated functional impairment into the staging model. This omission was because functional impairment is one step removed from the actual psychopathology of depression and is also determined by factors that may not be directly related to depression. Thus, individuals with a given level of psychopathology may exhibit different levels of disability due to physical fitness, physical ill health, past level of social function, demoralization, level of social support, and illness behavior. We also planned to incorporate some etiological factors, notably the presence of psychosocial stressors, as their omission in other staging models of treatment resistance has been criticized.[31] However, this factor is difficult to quantify and adds more subjectivity and complexity to the model. Nevertheless, both functional impairment and psychosocial stressors may be considered and assessed in future modifications. The place of psychotherapy is also not clear. Although we obtained information on use of psychotherapy, it was extremely difficult to be certain if psychotherapy was used adequately. We thus omitted psychotherapy from our model. The role of psychotherapy can be evaluated in future studies.

Model Limitations

Construction of the model, to some extent, relies on retrospective data gathering. Specifically, at initial assessment, staging treatment resistance may be mostly based on retrospective data. However, for patients already within services, the stage of resistance can be estimated more reliably in collaboration with the patient and information collected prospectively during service contacts. In our case, we relied on extracting information from detailed clinical records. Although this approach minimizes error, it does not entirely remove it. We also had a very special patient group with more severe treatment resistance; to some extent this characteristic could compromise the generalizability of our findings. Nevertheless, the model was prepared with less severely resistant patients in mind as well. Therefore, the continuum of resistance in the final model has wide variability, providing the opportunity for staging both mild and more severe cases of treatment resistance. We should acknowledge that, as well as representing the more severe end of the spectrum, we have only been able to enter a modest sample size to test the validity of the model. We would now encourage the model to be tested on larger groups, including the less severely treatment-

resistant patients, as well as the more severe patients included here.

CONCLUSION

We have here attempted to provide an alternative staging model of treatment resistance in depression. Clearly, the treatment of depression is far more complex than indicated in the commonly used method of staging, the Thase and Rush model.[23] Treatment resistance in depression is also less well understood than in oncological conditions from which the Thase and Rush staging model was adapted. By incorporating the various factors known to be involved in treatment resistance, our proposed model better embraces the complexity of treatment resistant depression. But by restricting the options for completing the staging, our model provides an efficient alternative to the currently available models of staging.

Drug names: buspirone (BuSpar and others); citalopram (Celexa and others); duloxetine (Cymbalta); fluoxetine (Prozac and others); lithium (Eskalith, Lithobid, and others); mirtazapine (Remeron and others); pindolol (Visken and others).

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