CHAPTER 1

Definitions and Predictors of Treatment-resistant Depression

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Summary

Treatment-resistant depression (TRD) remains a common condition, with 50–60% of patients not achieving meaningful response following antidepressant treatment. The huge complexity of the phenomenon and the wide variety of parameters that must be taken into account make creating a definition possible, but several attempts have been proposed over the last 30 years. Many TRD staging models have been suggested, all of them intended to clarify the concept of TRD, but the lack of consensus represents an ongoing clinical and nosological controversy. In parallel, efforts towards a more accurate definition are aimed at proposing clear-cut criteria for clinical trials and research to evaluate specific treatment strategies and biological factors in TRD.

Treatment-resistant Depression, First Edition. Edited by Siegfried Kasper and Stuart Montgomery.

Beyond a definition, efforts have been made to identify key clinical factors associated with TRD.

The purpose of this chapter is to review current available definitions and predictors of TRD originating from different fields and to discuss their usefulness in clinical practice and clinical research.

Introduction

Although TRD appears to be relatively common in clinical practice, the inconsistent way in which it has been characterized and defined remains a real problem, limiting systematic research. From a clinical point of view, TRD usually refers to an inadequate response to at least one antidepressant trial of adequate dose and duration. It is estimated that 50–60% of patients do not achieve meaningful response following antidepressant treatment (Souery *et al*., 1999). This conception may include a variety of clinical situations, from uncomplicated failure to one course of antidepressant to multiple failures with long-term persistence of depressive symptoms despite more complex treatments. The term *treatment refractoriness* is generally used in these circumstances. While this approach corresponds to the clinical reality, it doesn't help to define TRD and to predict which depressive episode will be resistant to treatment. The huge complexity of the phenomenon and the wide variety of parameters that must be taken into account make creating a definition possible, but several attempts have been proposed over the last 30 years. Misdiagnosis ('pseudoresistance'), comorbidities, definition of treatment response, treatment duration and compliance and the number of treatment failures are among the more difficult variables which need to be integrated in any attempt to characterize or define TRD, making this a real challenge (Fornaro *et al*., 2010).

Definitions of TRD have been considered from different perspectives and with diverse objectives. The available

definitions are mostly proposed by clinicians who have in mind a direct benefit for difficult-to-treat patients. The identification of predictors for TRD shares the same concern. In parallel, efforts at providing a more accurate definition aim to propose clear-cut criteria for clinical trials and research in order to evaluate specific treatment strategies and biological factors in TRD.

The purpose of this chapter is to review current available definitions and predictors of TRD originating from different fields and to discuss their usefulness in clinical practice and clinical research.

Definition of TRD: historical perspective

The basic question that needs to be addressed in the proposed definitions remains the threshold at which we define 'treatment resistance'. This threshold is composed of multiple complex variables, foremost among which is the number of antidepressant failures. Historically, two distinct periods can be recognized in the attempt to define TRD. The poor level of attention paid to conceptual examination in the 1970s and 1980s resulted in unsystematic research and uncontrolled clinical trials, which in turn led to a degree of confusion. An analysis of the existing publications on TRD highlights a long misty period; in a review of a 10-year period of the literature covering 1985–1995, more than 15 separate definitions were proposed (Ayd, 1983; Fawcett & Kravitz, 1985; Feigner *et al*., 1985; Fink, 1991; Links & Akiskal, 1987; McGrath *et al*., 1987; Montgomery, 1991; Nelsen & Dunner, 1993; Roose *et al*., 1986; Schatzberg *et al*., 1983, 1986; Thase & Rush, 1995). This *first wave* of definitions was influential in introducing key parameters such as dose (a minimal adequate dose equivalent of 200 mg of imipramine per day), duration of treatments and number of failures, but all of the definitions differed with respect to quantification of these parameters and the hierarchy of treatment types and sequences. At this time, tricyclic antidepressants

(TCAs), monoamine oxidase inhibitors (MAOIs), lithium and electroconvulsive therapy (ECT) were among various treatments incorporated in any TRD definition, but all in different sequences and with various durations based on empirical assumptions. Feigner *et al*. (1985) proposed defining TRD as a failure to respond to either TCAs or MAOIs plus a duration of episode of at least 2 years; Links & Akiskal (1987) considered TRD a failure to respond to two TCAs, one MAOI, one ECT, one lithium and one heterocyclic trial; Fawcett & Kravitz (1987) introduced the need to apply various combinations of adequate trials of TCA, MAOI and ECT. Montgomery (1991) was the first to recommend a pragmatic approach of two antidepressant failures, anticipating the current most accepted description.

These proposals had the merit of setting the stage and emphasizing the need to propose a systematic approach in TRD. The challenge at that time was to propose clinical guidelines and treatment strategies and to initiate clinical and biological research in the field. The concept of TRD was not ready and mature enough to be considered for recognition by regulatory authorities in Europe or the USA, and no official indication for TRD was possible.

A new era opened with the emergence of more structured and practical definitions of TRD, giving priority to a descriptive approach that led to the *staging models* of TRD. Thase & Rush (1997) were the first to publish a comprehensive staging model, taking into account the number and class of treatments received in order to indicate the level of resistance. Lately, in response to the need to validate treatment strategies or specific medications in TRD, regulatory authorities in Europe and the USA have elaborated their own recommendations for use in clinical trials.

Besides the development of descriptive definitions, recent progress has been made in the identification of predictive factors for TRD. Combining such variables with the proposed definitions and staging models will certainly help to validate the concept of TRD.

TRD staging models

Several staging models have been proposed, all of them intended to clarify the concept of TRD. Although some overlap exits between these models, they mainly differ in the weight of quantitative and qualitative parameters considered. The current proposals have undoubtedly contributed to a better assessment of TRD, but the lack of consensus represents an ongoing clinical and nosological controversy (Fornaro *et al*., 2010).

Thase and Rush model (1997)

Faced with the heterogeneity of TRD, Thase & Rush (1997) proposed applying the concept of illness classification used in oncology. Their starting point was the most common situation: the failure of a selective serotonin reuptake inhibitor (SSRI) chosen as first-line treatment. More than a simple descriptive staging model, their guideline suggested a series of sequential strategies for each stage of resistance. The recommendations were primarily based on the available publications on the management of treatment nonresponse to SSRIs. Antidepressant nonresponders are classified along a five-stage continuum according to the number and class of antidepressants that have failed to provide a response. In the final algorithm, *stage I resistance* is considered a failure of at least one adequate trial of one major class of antidepressant.

The proposed model is then built based on the assumption that switching to an alternative medication with a different mechanism of action is appropriate. A hierarchy of treatments is implied with the statement that MAOIs are more effective than TCAs, and TCAs are superior to SSRIs. The authors also discuss the use of combination and/or augmentation strategies in the most difficult-to-treat situations, after more than two failures, but do not include these strategies in the staging model.

Stage II resistance is defined as a failure of at least two adequate trials of at least two distinct classes of antidepressant. *Stage III* is

stage II resistance plus failure of an adequate trial of a TCA, *stage IV* corresponds to stage III plus failure of an adequate trial of an MAOI and *stage V* is stage IV plus a course of bilateral ECT.

Trying to integrate the simple descriptive approach of the level of treatment resistance to sequential treatment strategies is useful but raises important methodological issues. It is subject to discussion or controversy over the validity of the existing data on the efficacy of the treatment strategies; this is particularly illustrated by the issue of the current and more recent data not supporting the use of antidepressants from two different classes. However, this approach is commonly used in clinical practice and is recommended in several treatment guidelines (Bauer *et al*., 2007). The results of a recent meta-analysis comparing two switch strategies for depressed patients failing to respond to an SSRI, a second SSRI or a different class of antidepressant suggest a marginal benefit of switching from one class to another on remission rates only (Papakostas *et al*., 2008). In contrast, other groups reported no advantage of switching classes (Bschor & Baethge, 2010; Ruhé *et al*., 2006; Rush *et al*., 2006).

The Thase and Rush staging model is the first attempt to integrate evidence-based data on treatment strategies and level of resistance in a comprehensive model (Thase & Rush, 1997). It represents an easy-to-use tool, providing a logical representation of the levels of resistance for clinicians. Its limitations are that dosing and duration of each sequence are not defined, and that nonresponse to two agents of different classes is assumed to be more difficult to treat than nonresponse to two agents of the same class. It may need revision based on more recent data. In addition, the staging model is limited by the implicit hierarchy of antidepressants (MAOIs > TCAs > SSRIs), for which there is no sufficient evidence in the literature.

European staging model (1999)

The Group for the Study of Resistant Depression (GSRD) developed a quantitative and sequential staging model that does not integrate treatment strategies (Souery *et al*., 1999). Facing the

complexity of definitely specifying the number of failed adequate trials needed to define resistance, the model proposes a simple continuum starting from the first antidepressant failure in the treatment of a depressive episode and continuing with all subsequent unsuccessful trials regardless of the type of treatment. The different stages correspond to the number and duration of antidepressant trials. This model is independent of the treatments used and does not imply a hierarchy of efficacy of antidepressants or treatment strategies. The controversial issue of the number and type of adequate therapeutic trials may be arbitrarily solved using this continuous-quantitative principle. The model is built on naturalistic observation of the outcomes of prescribed treatments. These operational criteria are not to be considered an absolute definition of TRD, but rather a logical instrument that can be used in clinical practice and research projects in order to classify patients based on their level of resistance.

The model proposes distinguishing between nonresponse and five levels of TRD. The starting point is the depressive episode for which lack of response is recognized and the type of drug for which resistance is observed. A single adequately treated episode of nonresponse to an antidepressant is in itself sufficient to raise the issue of resistance. Patients who do not respond to one type of adequately prescribed drug (e.g. an SSRI-resistant depressive episode) are classified as nonresponders to any antidepressant therapy. It is assumed that the dose and duration of the antidepressant trial are adequate. Following this, five levels of TRD, defined according to the number of treatments (TRD1 to TRD5), are proposed. The usual treatment duration is between 4 and 8 weeks. TRD5 corresponds to nearly 1 year of treatment containing at least five different consecutive unsuccessful antidepressants trials, while TRD1 corresponds to 1 year of treatment with one unsuccessful trial. These stages apply to acute treatments and do not consider prolonged durations of treatment resistance. An additional concept is *chronic refractory depression* (CRD), which is when a patient is treated with several antidepressants for more than 12 months with unsatisfactory response.

The advantage of the European Staging Model (ESM) is its simplicity, transposing into a continuous approach the

observed outcome of adequate antidepressant trials. It can easily be used in clinical research to define the level of resistance of patients included in clinical trials, for example. It keeps open the question of any threshold in defining TRD based on the number of failed trials. However, it may be considered incomplete since it does not consider the weight of treatment strategies such as augmentation, combination or ECT. It may be misleading in distinguishing between nonresponse and resistance, with resistance being viewed as a lack of response after two failures. Nonresponse should be considered the first level of TRD.

Massachusetts general hospital staging model (2003)

The Massachusetts General Hospital staging method (MGH-S) is also primarily a quantitative approach, generating a continuous score that represents the degree of resistance (Fava, 2003). Three categories of score are proposed, integrating the number of trials and types of treatment strategy.

In category 1, nonresponse to each in a sequence of adequate (at least 6 weeks of an adequate dosage of an antidepressant) antidepressant trials increases the score by 1 point. While the labelling of each stage uses scores instead of TRD categories (TRD1 to TRD5), this approach is similar to that of the ESM. There is no limit to the number of failed trials, which are not considered from a longitudinal perspective. The MGH-S differs in considering augmentation and optimization strategies in the degree of resistance. ECT is also included in the model.

In category 2, the global score of resistance is increased by 0.5 points per trial when an optimization or augmentation strategy is used: optimization of dose and duration, and augmentation or combination of each trial. The MHG-S was developed together with the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire, a useful tool for collecting reliable data on previous treatments.

In category 3, the score is further increased by 3 points if ECT is applied.

The MHG-S makes no distinction and builds no hierarchy based on antidepressant mechanism of action. In category 1, any adequate trial with any antidepressant will increase the score. In category 2, augmentation, combination, dosage and duration optimization are equally weighted. A qualitative component is incorporated in the apparent quantitative approach in category 2 and 3 scores, where scores of 0.5 and 3 are artificially attributed to optimization and ECT, respectively. The MHG-S was examined for reliability in predicting nonremission in a retrospective analysis, and demonstrated greater ability than the Thase and Rush method (Petersen *et al*., 2005).

Maudsley staging model (2009)

Most of the existing staging models rely on treatment response and number of medications as key criteria by which to define TRD. While the lack of efficacy of a prescribed antidepressant represents a core element of treatment resistance, many other factors related to the depressive episode need to be considered. This multidimensional approach has clearly been neglected in previously proposed definitions of TRD.

Parker *et al*. (2005) have identified a set of key elements related to mood states unresponsive to treatments that are not considered in most TRD definitions. These proposed 'paradigm failures' include failure to diagnose and manage bipolar disorder, failure to diagnose and manage psychotic depression, failure to diagnose and manage melancholic depression, diagnosis and/or management of a nonmelancholic condition as if it were melancholic depression, misdiagnosis of secondary depression and failure to identify organic determinants. Failure to adequately assess the severity or type of depression and failure to identify organic determinants are the main causes of misclassification of depressive episodes not responding to treatment.

Beyond the treatment-outcome parameter, the multidimensional nature of TRD has been considered in developing the Maudsley staging model (MSM) (Fekadu *et al*., 2009). Treatment resistance is viewed as a continuum produced and maintained by various dimensional factors. The severity and duration of a depressive illness are incorporated in this staging model of TRD, while the number of treatments sequentially failing to produce improvement remains a key parameter in the level of resistance. Between- and within-class switching and type of treatment are not considered in the MSM.

Three sets of parameters/dimensions are integrated in the model: *duration*, *symptoms severity* and *treatment failures*:

- The *duration* of the presenting episode is classified into three categories: acute (1 year or less), subacute (between 1 and 2 years) and chronic (longer than 2 years). The duration of the episode is specified irrespective of treatment experience and scored from 1 to 3.
- The *severity dimension* is based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) classification of syndromal depression (mild, moderate, severe without psychosis and severe with psychosis). Subsyndromal depression is also included in the symptom-severity variable. Severity is scored from 1 to 5.
- In the *treatment failures* parameter, five levels are proposed (from level 1: 1–2 medications to level 5: >10 medications). Treatment failures also includes augmentation used or not (score 0 or 1) and ECT used or not (score 0 or 1). The maximal score for treatment failures is 7.

The global TRD score should be between 3 and 15. Staging of resistance can be expressed in three categories: mild (scores 3–6), moderate (scores 7–10) and severe (scores 11–15). The principal added value of the model consists in the possibility of emphasizing in each case the most important factors of the presenting episode contributing to resistance to treatment. As

stated by the authors, the model does not include psychosocial stressors or functional impairment.

The MSM was validated through prospective fellow-up study and showed significant association with persistence of depressive disorder (Fekadu *et al*., 2009).

Definition of TRD in clinical trials

A growing number of studies looking at the efficacy of therapeutic interventions in TRD have been published in the last decade. A systematic review of randomized clinical trials of antidepressant use in TRD highlights the variability in the ascertainment of TRD (Berlim & Turecki, 2007). Among the 47 randomized clinical trials analysed, the majority did not use systematic methods to collect data on previous treatments at baseline. The number of failed trials required to define TRD varied considerably across studies, ranging from nonresponse to one treatment to nonresponse to two or more antidepressants. In eight studies, this information was not available. The other randomized studies used at least six different definitions of TRD based on the number of previous antidepressant failures and the need to have antidepressants with different mechanisms of action. The available studies also differed in diagnostic evaluation of the depressive episode, treatment outcome, treatment duration, treatment dosage and compliance.

Lack of consensus on these issues clearly limits the interpretation of findings and their translation to clinical practice in terms of treatment efficacy in the management of TRD (Berlim & Turecki, 2007).

In Europe, no specific treatments have been approved for TRD, and the available staging models have been considered of limited value in the regulatory setting. The European Medicines Agency (EMA) guideline on the clinical investigation of medicinal products in the treatment of depression (European Agency for the Evaluation of Medicinal Products, 2002) considers monotherapy in patients with TRD a separate claim and proposes a clinical trial design and definition for TRD. TRD is considered *when treatment*

with at least two different antidepressant agents prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence showed lack of clinically meaningful improvement. This pragmatic definition differs from the complex available staging models but is mainly intended to be used within clinical trials as a reference by which to characterize patients based on the number and type of previous treatments.

This EMA definition differs from that of previous versions, where two products of different pharmacological classes were requested. This important revision is in line with the most recent data, showing no advantage in favour of switching to a different class of antidepressant (Bschor & Baethge, 2010; Papakostas *et al*., 2008; Ruhé *et al*., 2006; Rush *et al*., 2006; Souery *et al*., 2011a, 2011b).

A compound with substantiated general major depression indication needs at least one additional trial using this definition in order to support extension of the indication to TRD. The proposed study design requires that at least one treatment failure should be prospectively shown. Patients are included in clinical trials based on retrospective assessment of treatment failure to at least one adequate antidepressant. Following this, prospective confirmation of treatment failure to the next antidepressant is needed. Patients are then randomized to receive the investigated medication or the active comparator.

The EMA guidelines exclude the use of augmentation strategy in TRD. Augmentation is considered a separate indication for partial responders. Patients with TRD (who show no clinically meaningful change from baseline as result of treatment) are not suitable candidates for augmentation as there is no response to augment.

Clinical characteristics and predictors of TRD

Beyond the definition, the identification of factors associated with TRD remains unclear. Numerous studies have been performed with the aim of identifying predictive factors of treatment response to antidepressants, but the heterogeneity in the

definitions or criteria used for treatment response and the small sample sizes limit replication and prevent definitive conclusions (Nierenberg, 2003). Misdiagnosis, suboptimal treatment and duration of illness remain among the more frequently encountered problems. Despite these difficulties in defining TRD, there is evidence that both poor response and persistent depression can be predicted by specific variables.

Genetic determinants of treatment response to antidepressants have been investigated but currently their role remains limited in clinical practice. The most significant and replicated findings concern the gene encoding for the serotonin transporter (SERT), particularly its functional polymorphism located in the SERT promoter region (SERTPR) (Serretti *et al*., 2009).

Outcome studies of nonresponse to antidepressants have been able to recognize a number of demographic and clinical characteristics. It should be noted that these variables are based on the results of uncontrolled, retrospective or long-term prospective studies of chronic depression and may include a significant proportion of pseudoresistant cases.

At the clinical level, frequent issues associated with nonresponse remain severity, chronicity and comorbid symptoms. Comorbid psychiatric disorders include substance abuse or dependence, personality disorders, eating disorders, obsessive–compulsive disorders and panic or generalized anxiety disorders (Hirschfeld *et al*., 1988; Maser & Cloninger, 1990). In treatment failure, a thorough evaluation of these conditions should always be considered. It has been observed that in depression, concomitant personality disorders reduce the efficacy of antidepressant treatments and may contribute towards treatment resistance (Black *et al*., 1988; Pfohl *et al*., 1984; Shea *et al*., 1990, 1992). It is not clear, therefore, whether the observed 'treatment resistance' relates to the depressive state or the comorbid personality disorder (Thase, 1996). Older age and female sex appear to be associated with a higher risk of nonresponse to antidepressant treatment (Keller *et al*., 1986; Paykel *et al*., 1973). The illness characteristics that have been frequently associated with poor response are unipolar illness, psychotic depression, neurotic premorbid personality, familial predisposition to affective

disorders, multiple loss events and a low socioeconomic level (Burrows *et al*., 1994; Scott, 1995; Scott & Eccleston, 1991). A range of concurrent medical conditions may also contribute to TRD; results from several studies have shown that thyroid dysfunction may be associated with it (Gold *et al*., 1981; Hatterrer & Gorman, 1990; Howland, 1993). Other medical conditions have been implicated as organic causes of depression and require documentation and exclusion in TRD (Gruber *et al*., 1996). They should be labelled as mood disorder due to a general medical condition. Examples of such conditions are Cushing's syndrome, Parkinson's disease, neurological neoplasms, pancreatic carcinoma, connective-tissue disorders, vitamin deficiencies and certain viral infections. Several types of medication, such as beta-blockers, immunosuppressants, steroids and sedatives, may also precipitate or contribute to chronic depression and adversely affect remission and response.

These factors seem to influence treatment response to antidepressant therapy, but more research is needed to clarify their weight in the variability of treatment response (Serretti *et al*., 2009).

The investigation of clinical factors associated with TRD has mostly been conducted through studies looking at nonresponse to a single antidepressant treatment, without taking into account multiple treatment failures. Very few studies have been conducted on clinical features associated with failure to at least two consecutive antidepressant trials. The GSRD conducted the largest study on specific clinical and demographic factors associated with major depressive disorder (MDD) in patients who failed to reach response or remission after at least two consecutive adequate antidepressants (Souery *et al*., 2007). Demographic, diagnostic and treatment outcome data were available for a total of 955 patients who met criteria for a major depressive episode and had received at least 4 weeks' adequate antidepressant treatment at optimal dose. Among these patients, 702 received at least two consecutive antidepressant trials for their current or last episode and were thus considered for the analysis. A total of 229 reached a HAM-D-17 score < 17 after the initial antidepressant and 117 had a score < 17 after a second

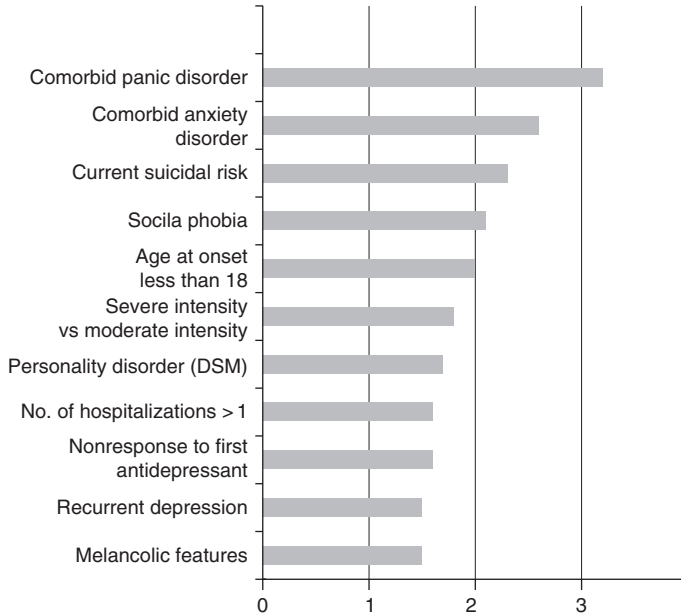

Figure 1.1 Odds ratios for clinical factors associated with treatment-resistant depression (TRD) in the European multicentre study performed by the Group for the Study of Resistant Depression (GSRD) (Souery *et al.*, 2007). Variables with p values < 0.05

consecutive antidepressant trial following failure of the initial trial. These 346 patients were considered 'nonresistant'. The remaining 356 patients were considered 'resistant' as their HAM-D-17 score remained greater than or equal to 17 after two consecutive adequate antidepressant trials.

A Cox logistic regression model was applied in the search for factors associated with resistance. The clinical factors significantly associated (p values < 0.05) with TRD are shown in Figure 1.1, ranked by odds ratios. Given the likelihood that several clinical variables are correlated, a stepwise Cox regression model was used to independently test the factors associated with TRD in the first step. Four variables emerged as being independently correlated to TRD: comorbid anxiety disorder,

current suicidal risk, melancholic features and nonresponse to first antidepressant lifetime.

Although the retrospective assessment represents a limitation of the study, the findings provide a set of relevant clinical variables associated with treatment resistance, defined as nonresponse to two consecutive antidepressant trials, regardless of mechanism of action.

Conclusions

The definition of TRD has acquired a certain maturity thanks to the staging models published over the last 15 years. These models include most of the key parameters needed to conceptualize TRD and allow for a better characterization of patients. We have to admit that these efforts towards a better definition of TRD exist with insufficient dialogue and with very few exchanges between the various research centres involved. It will be necessary to create an international network of reflection on the subject in order to allow us to reach a consensus. This is important not only for the clinical approach but also and especially for research on treatment strategies and the biology of TRD. It is also essential to move the interests and views of clinicians closer to those of regulatory authorities.

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