# The Clinical Definitions of Treatment-Resistant Depression

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Treatment-resistant depression is a pleomorphic phenomenon occurring in 30% of patients with depression. The chance to achieve remission decreases with every subsequent episode. It constitutes a significant part of the global disease burden, causes increased morbidity and mortality, and is associated with poor quality of life. It involves multiple difficult-to-treat episodes, with increasing resistance over time. The official consensus on the definition of TRD (treatment-resistant depression) is still lacking, but based on systematic analysis, the most used definition is a lack of response after two to three adequate antidepressant treatment trials, irrespective of the drug class, plus an adequate trial of psychotherapy.

Keywords: treatment-resistant depression ; difficult-to-treat depression ; staging ; ketamine ; downstaging

## 1. Treatment-Resistant Depression

The official consensus on the definition of TRD (treatment-resistant depression) is still lacking, but based on systematic analysis, the most used definition is a lack of response after two to three adequate antidepressant treatment trials, irrespective of the drug class, plus an adequate trial of psychotherapy [1]. Depression that did not respond to three or more antidepressants and ECT (electroconvulsive therapy) is called treatment-refractory [2]. The concept of TRD came from the clinical observation of patients who do not respond to treatment, and it is unquestionably clinically relevant, although very difficult to define the phenomenon. The main obstacles in the way of a clear definition are the heterogeneity of the group, different levels of resistance, psychiatric and somatic comorbidities, age of onset, and the number of episodes. There is also no clear distinction between response, partial response, and non-response, and no consensus on what is an ‘adequate’ antidepressant trial, including outcome measures, AD class, and psychotherapy status [3]. Other factors such as spontaneous evolution, the placebo effect, and patients’ personal beliefs also need to be considered when treatment outcome is analyzed [4]. A recent systematic review and meta-analysis of studies on concomitant treatment used the term ‘early-stage’ TRD, which describes non-response to one adequate pharmacological or psychological therapy [5]. This perspective allowed the authors to include more studies for analysis. Concurrently, the authors state that it is not known if ‘early-stage’ TRD progresses into the next stages of the disease. Inconsistencies involved in TRD definition concern not only clinical practice but also research [1][6]. Aspects like pseudo-resistance, non-compliance, and poor tolerability further complicate defining resistant depression [7].

## 2. Difficult-to-Treat Depression

A more practical, real-life approach is presented by the concept of Difficult-to-Treat Depression (DTD) proposed by Rush [8] and developed later in the form of an international consensus guideline [9]. The purpose of this approach was to define a practical basis for allowing decisions on when to re-evaluate patients’ treatment. It postulates that sometimes remission is not possible, but there is still a place for optimal symptom control when psychosocial stressors and coping strategies are defined [8][9]. DTD nomenclature has a smaller stigma potential than TRD, gives more hope, and describes depression as difficult but not impossible to treat. It emphasizes clinicians’, but also patients’ responsibility for the treatment outcome and involves the patient in the decision-making process. Unlike TRD, it considers patients’ perspectives and quality of life apart from clinicians’ evaluation. It also underlines the need to engage the family and caregivers in the healing process. Such an approach resembles the management of chronic diseases, such as heart failure, where the main goal is optimal symptom control, and where strategies such as psychotherapy, diet, self-help, and physical exercise are considered very useful [8][10]. Rush et al., in their recent paper, further develop the concept of DTD and recognize three issues to be addressed in clinical research involving this group of patients. One is defining and distinguishing subtypes of this heterogeneous group. The second problem is the assessment of outcomes. The authors point out that the traditional perspective used in trials with treatment-responsive patients is not optimal for the DTD group. This approach is based on short-term effects and does not focus on the durability of DTD, its side effect burden, and daily function. Another challenge

is developing a clinical trial design that would allow generalizability and making a causal inference. The authors underline the need to further develop a taxonomy of DTD considering specific clinical features such as oversensitivity to medications. They also suggest a multidimensional approach to DTD clinical factors such as the course of the disease, family history, previous therapies, comorbid conditions, early life trauma, and treatment adherence. This way of describing patients would allow people to distinguish subgroups of patients which could later be investigated in clinical trials. The authors suggest that outcome assessment should also include evaluation of such aspects as symptom dynamics, functioning, general health, quality of life, costs, and other ones [11].

## 3. Staging

Chronic diseases of a progressive nature are often described with the use of staging. The first attempt at describing resistant depression derived from oncology and laid the ground for developing staging TRD models [12]. The above-mentioned definition of early-stage TRD corresponds with Stage I TRD according to Thase and Rush's model [5]. It has been suggested that, unlike in oncology, where the absence of the disease is defined by the lack of neoplastic cells, depression has no categorical indicator of disease activity. Nevertheless, inventing staging models is still a breakthrough in the understanding of TRD, helping to find the best strategy at a certain point of the disease continuum [8]. Staging models describe the level of resistance in TRD and reflect a dimensional approach. They consider the number and duration of treatments, different modalities, and the severity of symptoms. According to the recent systematic review, five staging models of TRD have been described. The authors point out the strengths and weaknesses of all models and analyze the definitions of TRD used in each of them. They conclude with crucial suggestions for future development such as measuring the strength of treatment, including the strength of augmentation strategies, which could give a clear indication of when to switch to an antidepressant or add an adjunctive agent. They also propose giving higher scores to treatments such as ketamine and ECT. Another suggestion is to develop guidelines for patients who do not respond to ECT or ketamine [13].

The models with the most evidence are the Maudsley Staging Model (MSM) and the more recent Dutch measure for the quantification of treatment resistance in depression (DM-TRD). MSM is the first model to include disease characteristics, such as the duration and severity of the current episode, although it does not allow for assessing the level of resistance in the current episode [13]. The Dutch model is more detailed and includes the response to psychotherapy, uses ratings for functional impairment and psychosocial stressors, and considers the presence of comorbidities [14][15]. An example of implementing the idea of staging in treatment guidelines can be found in the National Institute for Clinical Excellence (NICE) 2009 TRD guideline which is based on the stepped care approach [16]. Day et al. conducted a study to retrospectively assess the practical use of this guideline in 178 patients with TRD. They found treatment gaps between guidelines and the reality of care in this group of patients. The first one was the long delay in starting treatment, the second was poor access to psychotherapy, and the third was the delay in antidepressant medication change after 4–8 weeks. Another one is not starting adjunctive therapies such as lithium and atypical antipsychotics after two unsuccessful antidepressant trials, which again confirms the great need for improvement in the treatment of TRD. The authors also point out the lack of guideline standardization concerning the sequence, the number of steps, and the assessment of the best moment to go to another step [17].

Inventing new, more effective strategies acquires an understanding of processes taking place in the brain in the course of TRD. It would not be possible without taking a closer look at neuroplasticity, specifically the neuroplastic processes which occur in the adult brain.

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