Successful management of patients with treatment-resistant depression requires a thorough understanding of the biological basis for both the depression and its failure to respond to standard treatments. This book clearly and succinctly summarizes the latest scientific research and its applications in clinical practice.

A first step is a clear definition of what constitutes treatment-resistant depression so that clinical trials and other studies are using common criteria, enabling comparison and meta-analysis of their outcomes. The opening chapter reviews definitions and predictors of treatment-resistant depression originating from different fields and discusses their usefulness in clinical practice and clinical research. The next chapter proposes a new definition, adapting terminology from medicine.

Biological classification requires identification of genetic risk factors and gene variants have been identified as accounting for 50% of the variance in the clinical outcomes of antidepressant treatments. Chapter 3 describes several genes already associated with treatment-resistant depression and, while further work is needed to translate findings into clinical recommendations, suggests that genetic prediction of treatment resistance could become a widespread clinical reality within a few years.

Most patients with treatment-resistant depression will be treated pharmaco-logically, so three chapters review the latest evidence for pharmacological best practice in switching strategies for antidepressants, the role of antipsychotics and augmentation strategies to complement lithium.

There are two major alternatives to pharmacotherapy: neuromodulation and psychotherapy. The brain intervention chapter summarizes clinical research and experience with electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation and magnetic seizure therapy. The final chapter reviews the literature pertaining to the effectiveness of various forms of psychotherapy in patients who have not responded to antidepressant pharmacotherapy, explaining that patients who have not responded to one or two trials of antidepressant medication have a 30%-50% chance of responding to a focused psychotherapy. It proposes indications for psychotherapy in treatment-resistant depression and summarizes general therapeutic principles.

Essential reading for all psychiatrists managing patients with this distressing disorder.
Treatment-resistant Depression
Treatment-resistant Depression

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Clinical depression is both a symptom and a debilitating disorder. The World Bank estimates that, by 2020, depression will become the most common noncommunicable disease in the world, with the heaviest burden of disease. Depression carries with it stigma, and the disease is misunderstood as a lack of will power. The proven strategies for treating depression include both pharmacotherapy and psychotherapy, as well as a mixture of the two.

Treatment-resistant depression remains relatively common and the reasons for this vary from missing diagnoses to inadequate therapeutic interventions. Definitions of treatment-resistant depression also vary. Treatment-resistant depression can be a staging process, which can enable clinicians to intervene appropriately and adequately, so that the burden of the disease is reduced and quality of life for the patient and their carers can be improved. Investigations for staging models must include both biological and nonbiological factors. In addition, cultural variations must be taken into account. Psychotherapy alone or in combination with pharmacotherapy is part of the therapeutic armamentarium.

The editors, both eminent psychiatrists in the field, with international reputations, have brought together a star-studded cast to explain not only the staging process but interventions too, making this volume of great interest and much use for clinicians in their clinical practice. For this alone, the editors deserve our congratulations and thanks.

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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.
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