



The clinical inadequacy of the concept of treatment-resistant depression: Innovative strategies in assessment and psychotherapeutic management

Jenny Guidi^{a,*}, Giovanni A. Fava^b

^a Department of Psychology 'Renzo Canestrari', University of Bologna, Bologna, Italy

^b Department of Psychiatry, State University of New York at Buffalo, Buffalo, New York, USA

ARTICLE INFO

Keywords:

Treatment-resistant depression
Psychosocial factors
Assessment
Clinimetrics
Psychotherapy
Withdrawal
Antidepressants

ABSTRACT

Pharmacological strategies have been developed for patients with major depressive disorder who fail to respond to standard drug treatment. The current clinical approach primarily relies on counting episodes that fulfill specific criteria and regards non-pharmacological strategies as of marginal value, despite their recognized importance in treating depression. Most attention is devoted to treatment-resistant patients' characteristics rather than to the process related to therapeutic management. However, how the patient experiences the treatment process, his/her interaction with the physician/therapist and significant others, and the patient's role in treatment plan (self-management) are all essential therapeutic components. A broader evaluation of factors related to the patient (e.g., illness denial, psychological reactance, demoralization), the therapy (e.g., clinician's attitude, behavioral toxicity of antidepressants), the environment (e.g., allostatic load/overload and health-damaging behaviors), and morbidity (e.g., medical and psychiatric comorbidity) is warranted. Assessment based on clinimetric methods (i.e., staging, macro-analysis) and clinical judgment allow a differential diagnosis of phenomena such as non-response, pseudo-resistance, treatment resistance, loss of clinical effect during maintenance antidepressant treatment, failure to achieve remission after a psychotherapy trial, partially remitted depression (i.e., presence of residual symptoms). Choice of the psychotherapeutic approach for treatment-resistant depression (TRD), particularly cognitive-behavioral therapy, mindfulness-based cognitive therapy and interpersonal psychotherapy, should follow the indications derived from clinical assessment. Treatment of TRD can thus be conceptualized as an integrated therapeutic approach to different components encompassing symptoms, psychosocial factors, lifestyle and psychological well-being.

1. Introduction

There is increasing awareness that the majority of patients with major depressive disorder either fails to respond to an appropriate antidepressant drug trial or presents a partial response, with substantial residual symptomatology and, as a consequence, an increased risk of relapse (Fava, 2003; McIntyre et al., 2023). Several pharmacological strategies have been developed for patients with depression who fail to respond to standard drug treatment, even though the lack of a consensus definition of treatment-resistant depression (TRD) (e.g., even only one failed therapeutic trial) has often led to heterogeneous populations enrolled in clinical trials (McIntyre et al., 2023). Such strategies characterize the current clinical approach, that regards non-pharmacological approaches as of marginal value (McIntyre et al., 2023), despite their recognized importance in treating depression (Guidi & Fava, 2015;

Rogan & Wilkinson, 2023). Indeed, psychotherapy is excluded from the definition of TRD, that consists of failure to respond to antidepressant medications trials (McIntyre et al., 2023). However, if the role of psychosocial factors is not sufficiently acknowledged in the clinical assessment of TRD (Dodd et al., 2021; McIntyre et al., 2023; Rikhani, Vas, & Jha, 2023), it is unlikely that such factors may be adequately considered in the therapeutic management. The aim of this review is to outline the clinical flaws and deficiencies of current conceptualizations of TRD and new perspectives in the psychosocial approach to its assessment and treatment.

2. Definitions and staging models of treatment-resistant depression

In 1995 Thase and Rush proposed a staging model of treatment

* Corresponding author at: Department of Psychology 'Renzo Canestrari', University of Bologna, Viale Berti Pichat 5, 40127 Bologna, Italy.

E-mail address: jenny.guidi2@unibo.it (J. Guidi).

resistance in depression based on previous response to treatment, ranging from the situation where an individual did not have a single adequate trial of medication (stage 0) to various forms of non-response along a continuum of failed antidepressant trials, from one adequate trial (stage 1) to multiple trials also involving augmentation strategies and electroconvulsive therapy (stages 2 to 5). Non-response was defined as insufficient drop in a depression rating scale score (Thase & Rush, 1995). This framework yielded a subsequent, widely used definition of TRD as failure to respond to two or more antidepressant medications trials, despite adequate modalities and adherence (Fava, 2003; McIntyre et al., 2023). The application of this definition by the *Food and Drug Administration* and the *European Medicines Agency* stimulated the development of investigational interventions specifically geared to TRD, such as ketamine and esketamine, in addition to switching, combining and augmenting treatment strategies (McIntyre et al., 2023).

The classification of treatment-resistant depression retained its basic structure in subsequent proposals, despite some differences in their formulations (Cosci & Fava, 2022; McIntyre et al., 2023). Distinct staging systems with various levels of resistance for drug-resistant depression have been suggested. However, most of them do not take into account non-response to evidence-based psychotherapeutic interventions and the role of iatrogenic factors, with a few notable, recent exceptions (Cosci & Fava, 2022), and are simply based on the number of failed adequate therapeutic trials (McIntyre et al., 2023). Further, psychosocial factors in non-response and resistance generally found little room in TRD frameworks (Dodd et al., 2021; McIntyre et al., 2023; Rikhani et al., 2023), even though they may provide important sources of clinical interpretation.

The European Staging Method (ESM) (Souery et al., 1999) classified patients using three distinctive categories: non-responders (i.e., those who failed to respond to one treatment regimen of appropriate duration), with treatment-resistant depression (TRD) (i.e., failure to two treatments of different classes of antidepressants), or with chronic resistant depression (i.e., a depressive episode lasting at least 1 year despite multiple adequate interventions, including augmentation strategies). The Massachusetts General Hospital staging model (MGH-S) (Fava, 2003) was mainly based on the number of failed trials and the intensity or optimization of each trial, without assumptions on the hierarchy of antidepressant classes. It introduced an explicit point-based system yielding a composite score for treatment resistance. One point per each failed antidepressant trial contributed to the total score. Optimization of dose/duration, augmentation/combination of each trial increased the overall score of 0.5 point per trial. A special weight was given for failure of treatment with ECT, which received a score equivalent to three antidepressant failures. The Maudsley Staging Method (MSM) (Fekadu et al., 2009) incorporated, in addition to the number of failed treatment trials, factors considered to be closely related to the depressive illness itself: duration, severity, treatment failure to antidepressants, use of augmentation, and use of electroconvulsive therapy. At the end, the stage of treatment resistance was represented as a single score ranging from 3 and 15. However, all these configurations refer to episodes that are resistant to drug treatment and ECT, and not to psychotherapy. The Dutch Measure for quantification of Treatment-Resistant Depression (DM-TRD) (Peeters et al., 2016) represents an extension of the Maudsley Staging Method including factors that are associated with unfavorable treatment response such as functional impairment, comorbid anxiety symptoms, personality disorders and current psychosocial stressors, as well as failed psychotherapy augmenting strategies and intensified treatment, in addition to duration, severity and previous failed pharmacological/ECT treatments of the present major depressive episode. Nonetheless, there is no definition of TRD that is universally accepted.

2.1. Psychosocial factors contributing to treatment resistance in depression

The prevailing reliance on diagnostic criteria for identification of TRD contributed to the fact that most attention was devoted to treatment-resistant patients' characteristics rather than to the process related to its therapeutic management (Fava, Cosci, Guidi, & Rafanelli, 2020; Rogan & Wilkinson, 2023). How a patient experiences the treatment process, his/her interaction with the physician/therapist and significant others, the patient's role in treatment plan (self-management) are all essential therapeutic components. Indeed, treatment outcome represents the cumulative result of the interaction of different types of variables with a selected treatment: living conditions (e.g., nutrition, housing and work environment, social support), patient characteristics (e.g., age, sex, health status, genetics, personality, psychological well-being), illness characteristics and previous therapeutic experience, self-management, and treatment setting (e.g., patient's health attitudes, physician's attitude) (Fava, Guidi, Rafanelli, & Rickels, 2017). Such variables may be therapeutic or counter-therapeutic. In certain patients their interactive combination may lead to improvement, whereas in other cases it may yield no effect or even worsening of the condition.

A number of potential counter-therapeutic factors contributing to treatment resistance in depression have been acknowledged (Fava et al., 2020): behavioral toxicity (i.e., loss of clinical effect during maintenance treatment, paradoxical effects, switching to hypomania/mania while on antidepressants, lack of response to a previously effective treatment after a drug-free period, new withdrawal or rebound syndromes, persistent postwithdrawal disorder after tapering and discontinuation); comorbidity not limited to disease entities (e.g., family problems, impairment, medical illnesses and concurrent use of medical drugs); illness behavior (including poor self-management and psychological reactance) and dysfunctional cognitive schemas. These counter-therapeutic factors are generally neglected in clinical practice, yet they may all be associated with unfavorable clinical course and greater symptom severity (Fig. 1).

2.2. Patient factors

It is of considerable interest that, in clinical psychology and particularly in the area related to cognitive-behavioral therapy, a more comprehensive account of the variables that may affect outcome is presented when treatment fails to meet expectations (Freeman & McCloskey, 2003). For instance, in the model outlined by Freeman and McCloskey (2003), the term "resistance", also for its psychoanalytic implications, is substituted by terms such as "impediment" or "road-block", that encompass factors related to the patient, the therapist, the environment and morbidity. The Authors provide a long list of factors that may hinder the therapeutic process in psychotherapy. Some of these elements may be part of attitudes to treatment in their experiential, cognitive and behavioral aspects (De Las Cuevas & de Leon, 2017; Fava, Cosci, Sonino, & Guidi, 2023). Freeman and McCloskey (2003) cite several examples of patient factors, such as lack of skill to comply with therapeutic regimen, negative cognitions regarding previous treatment failure, lack of motivation to change, fear of changing one's actions, thoughts, or feelings, a negative set, frustration with lack of treatment progress over time, and lack of personal resources. Two additional major patient impediments are represented by psychological reactance and illness denial. Psychological reactance, a motivational state that may ensue when the individual fears loss of control, may contribute to care-resistant or oppositional attitudes and behavior, including non-adherence to treatment (De Las Cuevas & de Leon, 2017). Illness denial is a maladaptive reaction to the symptoms, signs, diagnosis and treatment of a disease (Fava et al., 2023; Horwitz & Cullen, 2023; Patierno, Fava, & Carrozzino, 2023; Wise, 2023). It may be associated with delayed seeking or refusal of medical attention and lack of adherence. Such clinical phenomena do not invariably occur in every patient

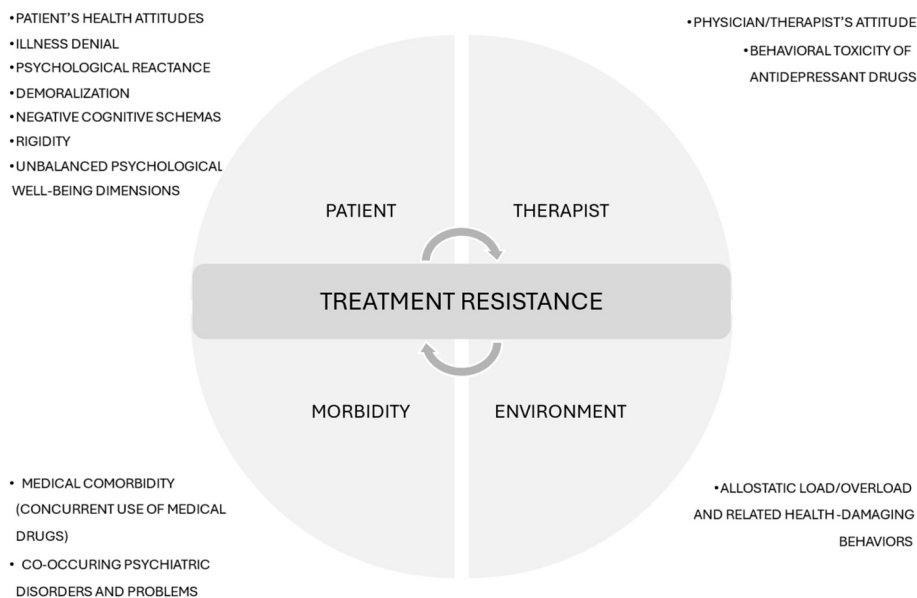


Fig. 1. Psychosocial factors contributing to treatment resistance in depression.

with certain characteristics, since they are affected by the patient-doctor interaction (De Las Cuevas & de Leon, 2017; Fava et al., 2023).

Furthermore, cognitive and emotional rigidity may prevent the patient from therapeutic learning, alternative thinking and healthier functioning. Similarly, patient's negative self-attributions and self-devaluation (possibly leading to fear of disclosure, self-defeating behaviors and hopelessness), as well as patient's need for autonomy and unwillingness to accept professional help (or, conversely, patient's dependence), may yield difficulties in engaging in a therapeutic relationship, trusting the therapist and cooperating with the suggested treatment plan (Freeman & McCloskey, 2003). Patient's personality characteristics, including cognitive rigidity, may also negatively affect the duration of the adaptation process to major environmental challenges (e.g., losses or changes in life).

Indeed, these clinical aspects can be properly conceived according to the conceptual framework of euthymia (Guidi & Fava, 2020, 2022) as unbalanced psychological well-being dimensions (e.g., flexibility, self-acceptance, autonomy, environmental mastery), possibly intertwined with concurrent patient's distress.

2.3. Therapist factors

Other impediments from effective treatment may derive from the physician/therapist's attitude (Fava et al., 2023). For instance, if a new treatment is presented as breakthrough cure, its failure sets the stage for the onset of demoralization, a feeling state characterized by subjective incompetence, discouragement, helplessness and hopelessness (Fava & Guidi, 2023a). Patients may interpret unfulfilled expectations about therapy as a proof that their condition is untreatable, and such conviction may be reinforced if they perceive disillusionment and frustration in the clinician as well. Among factors attributable to the therapist, Freeman and McCloskey (2003) point to lack of skill or experience, impaired working alliance, inadequate data collection, poor timing of interventions, lack of flexibility and creativity in treatment planning. In double-blind placebo-controlled trials in psychopharmacology, physician attitudes were found to affect the differentiation between active drug and placebo (Uhlenhuth et al., 1966). A re-analysis of data from the National Institutes of Mental Health's (NIMH) 1985 Treatment of Depression Collaborative Research Program (TDCRP) (McKay, Imel, & Wampold, 2006) found that psychiatrist effects on patient outcomes were greater than the treatment effects, thus indicating that the effective

psychiatrists may augment the effects of the active ingredients of antidepressant medication as well as placebo. Finally, a major problem that a physician may introduce is represented by iatrogenic effects of treatment that may lead to resistance to antidepressant drugs (Fava, 2021; Fava, 2024b; Fava et al., 2020). Indeed, phenomena such as loss of clinical effect during long-term treatment, paradoxical reactions, switching to hypomania, resistance to re-challenge, withdrawal and postwithdrawal syndromes, tend to impair responsiveness and may share a common mechanism that has been defined as oppositional model of tolerance (Fava, 2021; Fava, 2024b; Fava et al., 2020).

2.4. Environmental factors

The family and social environment of an individual may also play a major role in determining the likelihood of response to pharmacological and/or psychotherapeutic treatments (Freeman & McCloskey, 2003). McEwen (1998) suggested a formulation of the relationship between stress and the processes leading to disease based on the concept of allostasis, the ability of the organism to achieve stability through change. The definition of allostatic load provided a synthesis of the cumulative effects of experiences in daily life that involve both ordinary events as well as major challenges (McEwen, 1998). When the cost of chronic exposure to fluctuating and heightened neural or neuroendocrine responses exceeds the individual's resources, allostatic overload ensues (Fava et al., 2019; Sonino, Fava, Lucente, & Guidi, 2023). The conceptual framework of allostatic load extends to work, unemployment, adverse living conditions, social and educational experiences and income inequality throughout life span (Fava et al., 2019; McEwen, 1998). This comprehensive model also includes the physiological consequences of the resulting health-damaging behaviors, such as physical inactivity, unhealthy eating, poor sleep, smoking, alcohol, and drug consumption (Fava et al., 2019; McEwen, 1998). The findings of a systematic review (Guidi, Lucente, Sonino, & Fava, 2021) indicate that higher allostatic load is associated with negative health outcomes and impaired responsiveness.

2.5. Morbidity factors

Factors related to morbidity may represent an additional source of impediment to effective treatment (Freeman & McCloskey, 2003), with particular regard to comorbid medical illness and concurrent use of

medical drugs, co-occurring psychiatric disorders or other serious problems. According to [Feinstein's \(1970\)](#) original definition, however, the concept of comorbidity refers to any 'additional coexisting ailment' separate from the primary disease, even though not qualifying as a disease per se.

3. Assessment and differential diagnosis

The clinical evaluation of treatment non-response is far more complex than it is currently assumed ([McIntyre et al., 2023](#); [Rikhani et al., 2023](#)). It requires clinical reasoning and careful consideration of the potential reasons for failure to respond in an individual case of depression ([Table 1](#)). A helpful start is considering "non-response" to the most recent treatment a patient has received, deferring the use of the term "resistance" to a later stage in more selected cases. A global evaluation scale (more than an observer-rated scale with several items) offers a good way to begin with, in line with the high sensitivity of global judgments in randomized controlled trials ([Fava, Rafanelli, & Tomba, 2012](#); [Fava, Sonino, & Guidi, 2025](#)). Kellner's global rating scale for measuring treatment changes ([Kellner, 1972](#)) is a simple clinimetric index with a score ranging from 1 ('a lot better') to 3 ('better') to 5 ('no change') to 7 ('worse') to 9 ('a lot worse'), and the possibility of intermediate scores. It includes both improvement and deterioration induced by a specific therapy, whereas deterioration should be differentiated from non-response and may be associated with iatrogenic causes ([Fava, 2021](#); [Fava, 2024b](#); [Fava et al., 2020](#)).

[Fig. 2](#) displays the continuum of responses that may ensue with treatment of a single episode of major depressive disorder. On the left side, we may find a full response to either pharmacotherapy or psychotherapy that is substantially devoid of residual symptomatology, an event that appears to be rather infrequent ([Guidi, Tomba, Cosci, Park, & Fava, 2017](#)). A far more common occurrence is concerned with positive response associated with residual symptoms, whether or not included in the core depressive manifestations ([Guidi et al., 2017](#)). Progressing to the right, we may find partial response (improvement in symptomatology, but presence of major symptoms that affect quality of life and level of functioning) and non-response (a clinical picture that is substantially unaffected by treatment). We reserve the term "resistance" to a major depressive episode that appears to be unchanged, or even deteriorated, after treatment, possibly due to behavioral toxicity (e.g., loss of clinical effect or lack of response to a previously effective antidepressant treatment when it was started again after a drug-free period) and/or counter-therapeutic factors (e.g., psychological reactance) ([Fava et al., 2020](#)). It is conceivable that resistance may be addressed by appropriate therapeutic strategies ([Fava et al., 2020](#)). At the right end of the spectrum we indicate refractoriness to multiple previous therapeutic attempts, including psychotherapy. It may also ensue after one or more episodes of resistance ([Fava et al., 2020](#)).

The appropriateness of the intervention, including the correct indications and use of a therapeutic strategy according to the stage of the depressive illness, should then be considered ([Fava, 2024a](#); [Hanlon & Schmader, 2022](#)). The expected outcome of the intervention, that was selected according to staging of the patient's clinical condition, should be evaluated ([Cosci & Fava, 2022](#); [Fava, 2024a](#); [Fava et al., 2020](#); [Fava & Kellner, 1993](#)). Indeed, in complex clinical situations, a particular treatment (e.g., antidepressant medication) is likely to yield only partial

remission. For instance, when depression ensues after a long-standing anxiety disorder, it is wishful thinking to hope that a course of antidepressant therapy is going to entail solution to the pre-existing disturbances ([Cosci & Fava, 2021](#); [Fava, 2024a](#)). The likelihood of clinical phenomena related to the natural course of the disorder or regression to the mean should also be entertained.

Another important related issue is that of "pseudo-resistance" ([Nierenberg & Amsterdam, 1990](#)), defined as non-response to inadequate treatment, with specific regard to duration or dose of the antidepressant that was administered. Pharmacokinetic factors, such as concomitant use of metabolic inducers, may also contribute to the phenomenon of pseudo-resistance. Pseudo-resistance may also apply to patients who are misdiagnosed as having unipolar depression when they present with diseases such as bipolar illness, vascular dementia, or anxiety disorders ([Nierenberg & Amsterdam, 1990](#)).

The following step is to compare the outcome of the current episode with previous ones ([Table 1](#)). Were there differences between episodes? Were there similar instances? Did non-response/deterioration occur in all instances or only in part of them? Indeed, further evaluation extending over several lines of inquiry is required. First, the potential contribution of iatrogenic factors that may encompass medical ([Fava et al., 2020](#); [Fava & Guidi, 2023b](#)) and psychotropic drugs ([Fava, 2021](#); [Fava, 2024b](#); [Fava et al., 2020](#)), as well as psychotherapy should be assessed. A staging system for evaluating behavioral toxicity and manifestations of oppositional tolerance has been suggested ([Fava, 2021](#); [Fava et al., 2020](#)) and may assist the physician in identifying iatrogenic manifestations. The term "resistance" may find its applicability here. A highly prevalent form of resistance occurs when a drug which yielded clinical response in past episodes is no longer effective when started again after a drug-free period ([Fava, 2021](#); [Fava, 2024b](#); [Fava et al., 2020](#)). Resistance may also present as loss of clinical effect in a patient who previously responded to an antidepressant medication. Other clinical manifestations related to behavioral toxicity are withdrawal syndromes and persistent postwithdrawal disorders ([Fava, 2021](#); [Fava, 2024b](#); [Fava et al., 2020](#)). In all these cases, either switching or augmentation pharmacological strategies, triggered by a rushed and superficial definition of resistance, may propel depressive illness into a refractory phase, characterized by low remission, high relapse, and high intolerance ([Fava, 2024b](#); [Fava et al., 2020](#); [Rush et al., 2006](#)).

Evaluating non-response to treatment requires assessment strategies that are broader than those used for reaching a categorical diagnostic formulation according to DSM-5-TR/ICD-11 criteria ([American Psychiatric Association, 2022](#); [World Health Organization, 2022](#)) (see [Table 2](#)). Case formulation should include careful exploration, based on adequate clinical interviewing, of problem areas such as stressful life situations and allostatic load, lifestyle, illness behavior, psychological well-being, family and interpersonal relationships in addition to psychiatric assessment ([Fava et al., 2012](#); [Fava et al., 2024](#)). An additional aspect deserving clinical attention is medical comorbidity, that may hinder satisfactory response to antidepressant drugs ([Fava et al., 2020](#); [Fava & Guidi, 2023b](#)).

A clinimetric approach ([Fava et al., 2025](#)) may help expanding the narrow range of information encompassed by diagnostic criteria, supplementing them with a broad global evaluation of clinical phenomena (e.g., behavioral toxicity, comorbidity, allostatic load/overload); assessment of subclinical symptoms, psychological well-being, illness

Table 1

Key steps for implementing clinimetric strategies in the evaluation of non-response to treatment in depression.

1. Evaluation of the patient's response to the latest treatment using Kellner's global rating scale for change.
2. Check of the suitability of the intervention according to the characteristics and staging of the clinical condition and its appropriateness.
3. Comparison of current condition with previous treatment trials. Determination of resistance.
4. Likelihood of behavioral toxicity after pharmacological treatment according to a staging method.
5. Evaluation of allostatic load and illness behavior.
6. Looking for counter-therapeutic factors across different treatment episodes.
7. Planning a suitable, individualized treatment plan.

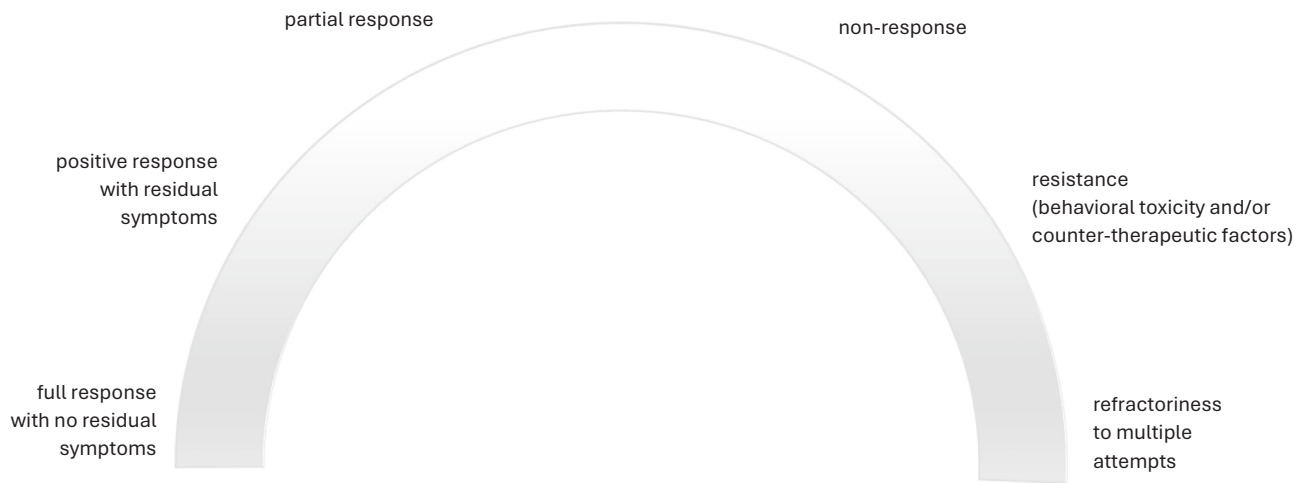


Fig. 2. The spectrum of responses to treatment (pharmacotherapy and/or psychotherapy) of a single episode of major depressive disorder.

Table 2

Areas to be explored in addition to traditional psychiatric assessment.

1. Stressful life situations and allostatic load
2. Lifestyle
3. Illness behavior
4. Psychological well-being
5. Family and interpersonal relationships

behavior and lifestyle; staging methods to describe the longitudinal development of disorders and to identify individual trajectories; discrimination of symptoms according to a number of variables (e.g., intensity, duration, longitudinal course, impact on patient's life); repeated assessments over time (e.g., re-assessment after the initial evaluation, post-treatment and follow-up assessments). Diagnostic criteria may thus be integrated with clinimetrics to capture the unique personal attributes and the environment of each individual patient, as well as the progression of his/her depressive disorder over time (Fava et al., 2025).

The clinimetric method of macro-analysis (Emmelkamp, Bouman, & Scholing, 1993; Fava, 2022; Fava et al., 2012) allows to establish a relationship between co-occurring syndromes and problems. Macro-analysis postulates that, in most cases, there are functional relationships with different problem areas, and that the targets of treatment may vary during the longitudinal course of a disorder. Their hierarchical organization may depend on a variety of factors (e.g., urgency, availability of treatment tools), including the patient's preferences and priorities. Macro-analysis can also be used to inform the patient about the relationship between different problem areas and motivate the patient for change. It may reflect clinical judgment on the predominance of one disorder compared to the other (i.e., primary/secondary distinction), on the basis of severity, burden to the patient, and impairment.

Such an assessment allows to perform a differential diagnosis of the clinical situations that are generally subsumed under the undifferentiated definition of TRD. In particular:

- a) an antidepressant medication that previously resulted in clinical response is no longer effective when it is administered again after a drug-free period. The prevalence of this type of resistance varies, but may occur in up to one third of patients with major depressive disorder (Fava, 2021; Fava, 2024b; Fava et al., 2020);
- b) loss of clinical effect in a patient who previously responded to antidepressant drug treatment. The return of depressive symptoms during maintenance antidepressant treatment is a frequent occurrence (Fava, 2021; Fava, 2024b; Fava et al., 2020);
- c) failure to achieve response after an evidence-based psychotherapy trial of appropriate characteristics and duration (Fava, 2021; Fava et al.,

2020);

d) presence of residual symptomatology that interferes with quality of life and functioning despite improvement of depressed mood (Guidi et al., 2017).

4. Psychotherapeutic management

Selection of treatment according to evidence-based medicine relies primarily on randomized controlled trials and meta-analyses. However, this evidence applies to the “average” patient and ignores the fact that psychiatric taxonomy does not include patterns of symptoms, severity and rate of progression of illness, comorbid conditions, timing of clinical manifestations, previous treatment responses, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise may be considered deceptively similar since they have been diagnosed with the same psychiatric disorder (Fava et al., 2012). Clinical features that are unlikely to emerge as significant variables in controlled trials may play a substantial role in the individual case.

Indeed, the *American Psychiatric Association* practice guideline for the treatment of patients with Major Depressive Disorder states that “the ultimate recommendation regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data, the psychiatric evaluation, and the diagnostic and treatment options available. Such recommendations should incorporate the patient's personal and socio-cultural preferences and values to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes” (Work Group on Major Depressive Disorder, 2010, p.11). Indeed, patients receiving their preferred treatment (whether pharmacotherapy or psychotherapy) respond significantly better than those who do not receive their preferred therapy (Mergl et al., 2011). More recently, the *National Institute for Health and Care Excellence* guidelines (National Institute for Health and Care Excellence (NICE), 2022) encompassing further-line treatments for depression suggested that some types of psychotherapy may have an important place in overcoming treatment resistance. Several approaches to overcoming TRD have been evaluated, including pharmacology, physical interventions and psychological

therapy. There is a need for expanding practice guidelines for the treatment of TRD with patient-specific recommendations that take into account the role of the abovementioned psychosocial factors, patient's characteristics and history, as well as previous treatment responses.

The major limitation of current therapeutic approaches to TRD is concerned with the implicit assumption that resistance after administration of a selected treatment is a unitary phenomenon yielding a homogeneous group of treatment-resistant patients, and with the neglected role of iatrogenic and psychosocial factors in resistance to antidepressant drugs leading to clinical deterioration and refractoriness.

The clinical definition of refractoriness should reflect a number of requirements (Table 3). First therapeutic trials should have involved both medications and psychotherapy, whether alone or in combination. Second, therapeutic choices should not only reflect the indications that derive from evidence-based medicine, but should also include consideration of the clinical complexity of the particular case. It is wishful thinking, for instance, to postulate that a single course of an antidepressant may entail solution to the complexity of clinical situations with extensive comorbidities or characteristics of chronicity, such as in double depression. Third, exploration of counter-therapeutic factors, as indicated in Table 2, is warranted. Further, major depressive episodes related to behavioral toxicity of antidepressant drugs (e.g., loss of clinical effects, resistance to re-challenge) should be differentiated. Finally, the outdated attitude of the physician deciding what is best with the patient in an alleged case of TRD, without any attempt of sharing decisions, is in striking contrast with what occurs in other areas of medicine (Sonino, Fava, Aron, & Guidi, 2025) and should come to an end (Table 3).

There is extensive evidence (McIntyre et al., 2023; O'Connor, Hewitt, Kuc, & Orsini, 2023; Rikhani et al., 2023; Rogan & Wilkinson, 2023) that patients with TRD are at substantial risk of self-harm (suicidal thoughts and behavior) and suicide. An issue that needs to be considered is that the diagnosis of TRD may be perceived by the patient as an indication that the condition is untreatable, increasing feelings of helplessness and hopelessness, particularly if previous medications had been presented as magic bullets, as it is frequently the case in current practice (Fava & Guidi, 2023a). In our clinical experience, we found that a realistic appraisal of the therapeutic history (e.g., "the treatments you received had very partial targets") and the emphasis on the potential role of the patient as health producer (Fava, 2023) may effectively counteract demoralization and hopelessness (Fava & Guidi, 2023a).

When a psychotherapeutic intervention is planned in the setting of current drug treatment, the choice of switching or augmenting strategies should be guided by clinical judgment (Otto et al., 2022). When switching is endorsed, it is generally wise to postpone it to a later phase of psychotherapy, also because discontinuation symptoms, that do not necessarily abate in a couple of weeks (Fava, 2021, 2024a), may have an unfavorable impact on the initial phase of psychotherapy.

In clinical practice there may be barriers to the administration of psychotherapy, such as low access to quality evidence-based treatment and its insufficient integration in mental health services. The emerging field of digital mental health therapy (DMHT) and prescription digital therapeutics may afford new opportunities for access and scaling of psychosocial interventions (Rajeshkumar et al., 2024).

4.1. Psychotherapeutic approaches to drug-resistant depressive disorder

Available evidence derived from reviews and meta-analyses largely supports the effectiveness of psychotherapies for TRD, particularly cognitive-behavioral therapy, mindfulness-based cognitive therapy and short-term dynamic/interpersonal psychotherapy, most often combined with pharmacotherapy and/or other approaches (i.e., ECT, ketamine/esketamine, TMS) (Gloster et al., 2020; Havlik et al., 2024; Ijaz et al., 2018; Li et al., 2018; McIntyre et al., 2023; Otto et al., 2022; Rogan & Wilkinson, 2023; Trivedi, Nieuwsma, & Williams Jr, 2011; van Bronswijk, Moopen, Beijers, Ruhe, & Peeters, 2019). Despite methodological limitations (e.g., substantial heterogeneity in the definition of TRD for study inclusion criteria, as well as in the measures used to determine depressive symptoms and outcomes), the findings support the utility of psychotherapy as an adjunctive treatment to antidepressant pharmacotherapy. Nonetheless, a large European cross-sectional, observational study provided negative data for the addition of psychological treatment to medication for TRD (Bartova et al., 2021).

Psychotherapeutic approach to TRD generally required modifications from standard cognitive therapy (Beck, Rush, Shaw, & Emery, 1979; Moore & Garland, 2003), with emphasis given to the cognitive treatment components. Brief but frequent initial sessions have been recommended to enhance patient's learning and retention of homework assignments and in-session rehearsal, as well as techniques derived from cognitive therapy of personality disorders (Cole, Brittlebank, & Scott, 1994; Thase & Howland, 1994). Involvement of the spouse or significant others to provide psychoeducation has also been suggested (Keitner & Mansfield, 2012). The maladaptive cognitions and behaviors that sustain chronic depressive symptoms can be modified by cognitive restructuring, whereas activity scheduling, social skills training and other behavioral interventions can help overcome anhedonia, interpersonal or social problems, and coexisting anxiety (Casey, Perera, & Clarke, 2013; Fava, Savron, Grandi, & Rafanelli, 1997). Specific core therapeutic elements are teaching patients new skills to improve with a chronic illness; establishing short-term goals (specifically addressing symptoms and/or problems), and then intermediate and long-term goals (once symptom improvement and short-term goals are accomplished); setting realistic expectations; addressing hopelessness and improving tolerance of negative emotions (Keitner & Mansfield, 2012; Thase & Howland, 1994).

Research findings support beneficial effects of mindfulness-based cognitive therapy (MBCT) in patients with more persistent forms of major depressive disorder, particularly in those who have not responded to prior interventions (Gloster et al., 2020; Li et al., 2018; van Bronswijk et al., 2019). In a large RCT among adult outpatients with major depressive disorder who failed to respond to at least two adequate trials, Eisendrath et al. (2016) found significantly higher benefits of MBCT compared to an active psychological control condition on depression severity. Subsequent, yet smaller, RCTs (Chiesa, Mandelli, & Serretti, 2012; Cladder-Micus et al., 2018) provided further evidence supporting the role of MBCT in chronic, drug-resistant depression. MBCT is specifically aimed at helping patients disengage from maladaptive patterns of thinking (i.e., decentering), providing them with sustainable skills to effectively reduce depressive symptoms and keep patients well for the

Table 3

Diagnostic criteria for refractoriness in case of failure to respond to treatment in depression (A through E are necessary).

- | | |
|----|--|
| A. | Failure of at least two adequate therapeutic trials. One of these trials should have involved psychotherapy (alone or in combination with drug treatment). The duration of each trial should range from 4 to 8 weeks for medications, from 20 to 52 weeks for psychotherapy. Drugs should have been used at appropriate dosages. |
| B. | Therapeutic trials should have been appropriate in terms of evidence-based indications and should have addressed the clinical complexity of the case (e.g., extensive comorbidities, double depression). |
| C. | Clinimetric assessment of allostatic load, lifestyle, illness behavior, psychological well-being, family and interpersonal relationships should supplement the customary psychiatric examination. |
| D. | Depressive episodes should not have resulted from loss of clinical effect of antidepressants during maintenance treatment or lack of response to a previously effective antidepressant treatment when it was started again after a drug-free period. |
| E. | The patient has been provided with an adequate appraisal of the psychiatric situation, with opportunity for discussion, clarification and shared decision. |

longer term.

Interpersonal psychotherapy (IPT) has also been suggested as a valid alternative strategy for the treatment of TRD (Casey et al., 2013; Ijaz et al., 2018; Markowitz, 2003; Trivedi et al., 2011; van Bronswijk et al., 2019). The theoretical foundation of IPT is that interpersonal stressors (i.e., grief and loss, interpersonal disputes, role transitions, and interpersonal sensitivity/deficits) are central to depression onset and persistence. However, clinical evidence supporting the efficacy of IPT is scarce (Souza et al., 2016) and modified research paradigms are needed to define its preferential utility in the treatment of TRD (Casey et al., 2013; Ijaz et al., 2018; Parker, Parker, Brotchie, & Stuart, 2006; van Bronswijk et al., 2019).

The cognitive behavioral analysis system of psychotherapy (CBASP) is a psychotherapeutic strategy specifically developed for patients with chronic depression to promote more adaptive responses to the environment, including interpersonal interactions (McCullough, 2000). CBASP has been found to be helpful in both outpatients and inpatients with treatment-resistant and chronic depression (Brakemeier et al., 2015; Negt et al., 2016; Schramm et al., 2015).

An emerging area of application of psychotherapy in TRD is concerned with psychedelic-assisted psychotherapy, particularly psilocybin (Haikazian et al., 2023). A major difficulty in interpreting this literature, however, is to discern the precise role of psychotherapy in the treatment process (Aday et al., 2024).

We suggest that psychotherapeutic management of TRD should be individualized according to psychosocial factors characterizing the patient's clinical situation, including psychological reactance, illness denial and demoralization (often affecting the likelihood of medication non-adherence), patient's health attitudes and behavior, allostatic load and detrimental lifestyle (Dodd et al., 2021; Fava, 2024b; Fava et al., 2020). It should be geared to actively engaging patients in self-management, modifying illness behavior, and dealing effectively with environmental factors and allostatic load, which in turn may lead to health-damaging behaviors (Fava, 2023). Indeed, illness behavior may be responsive to psychotherapeutic management (i.e., application of psychological understanding to the management and rehabilitation of the individual patient, including establishing a therapeutic relationship, identifying concurrent problems, and encouraging self-management), without providing any formal psychotherapy (Fava et al., 2023). Further, in patients with allostatic overload, promoting personal changes and/or modifications of the environment (e.g., work settings, family interactions) may yield more significant improvements than formal psychotherapy or pharmacotherapy (Fava, 2023; Guidi & Fava, 2024).

It would be of great interest to compare in a randomized controlled trial a standard undifferentiated approach to TRD, as is currently practiced, with an individualized therapeutic plan geared to treatment process, with particular reference to long-term outcomes to be tested through extensive follow-ups. It would also be important to test whether continuation of drug treatment may yield better results than its discontinuation. By performing such studies, additional sources of variation (e.g., regression to the mean, natural course) can be controlled for. In the meanwhile, the clinician should always keep the possibility of such non-specific effects open.

Explanatory therapy (ET) was developed by Robert Kellner (1979, 1986) for improving illness behavior and treating hypochondriacal fears and beliefs. It encompasses different therapeutic components, such as providing accurate information, clarification, explaining the principles of selective perception (i.e., a strong tendency to pay attention to some parts of the body and to perceive threatening stimuli accordingly), reassurance and repetition. This psychotherapeutic strategy, that has been recently manualized (Fava, 2021), can be effectively used also in patients with depression, particularly in those dealing with manifestations of behavioral toxicity, including withdrawal symptoms after discontinuation of AD.

4.2. Loss of clinical effect

In two pilot investigations (Fabbri, Fava, Rafanelli, & Tomba, 2007; Fava, Ruini, Rafanelli, & Grandi, 2002), patients with recurrent major depressive disorder who had previously responded to antidepressant drugs, and then relapsed during maintenance treatment were randomly assigned to dose increase and clinical management or psychotherapy (cognitive-behavioral therapy or family intervention, respectively). Results provided support to the clinical utility of a psychotherapeutic approach to loss of clinical effect during long-term antidepressant treatment.

The former study (Fava et al., 2002) involved the sequential combination of cognitive-behavioral therapy (CBT) and Well-Being Therapy (WBT). WBT is a short-term, psychotherapeutic strategy aimed at modulating psychological well-being and pursuing euthymia (Fava, 2016; Guidi & Fava, 2020, 2021a, 2022). WBT emphasizes self-observation of psychological well-being with the use of a structured diary, cognitive restructuring of interfering thoughts and behavior leading to premature interruption of well-being, and homework assignments. The goal of intervention is the achievement of balanced levels in psychological well-being dimensions and the pursuit of euthymia (Guidi & Fava, 2022), and emphasis is given to patient monitoring of episodes of well-being rather than distress (Guidi & Fava, 2020, 2021a).

The latter study (Fabbri et al., 2007) used a family intervention based on the McMaster Model (Ryan, Epstein, Keitner, Miller, & Bishop, 2005), namely Problem Centered Systems Therapy of the Family, in patients with recurrent major depressive disorder who relapsed while taking AD and their significant others. The intervention protocol was based on emphasis on macro-stages of treatment (i.e., assessment, contracting, treatment, closure); collaborative set; open and direct communication with the family; focus on current problems, behavioral changes, and family strengths; and limited time frame (6 to 12 sessions). According to this approach, the treatment goal is to actively involve family members and allow them to develop problem-solving abilities through concrete, behavioral tasks that can be easily evaluated and are geared to increasing adaptive behaviors rather than decreasing dysfunctional ones. The application of this family approach was found to provide a viable strategy for improving illness management, functioning and quality of life in patients with TRD (Casey et al., 2013; Keitner & Mansfield, 2012).

4.3. Failure to achieve remission after a psychotherapy trial

The concept of pseudo-resistance may be particularly helpful also in case of failure to achieve remission after a psychotherapy trial. One should explore whether a psychotherapeutic approach whose effectiveness is supported by controlled studies in depression has been used. Further, it is also helpful to investigate non-specific ingredients such as patient's expectations, therapeutic alliance and readiness to change (Casey et al., 2013; Freeman & McCloskey, 2003; Mintz & Flynn, 2012).

The utility of adding antidepressant medication after non-remission with initial psychotherapy has been scarcely investigated. In a study by Stewart, Mercier, Agosti, Guardino, and Quitkin (1993), 36 outpatients with depression received 16 weekly sessions of cognitive therapy. Non-responders (53 %) were then randomly assigned to 6-week treatment with imipramine or placebo. Of 12 patients completing the double-blind medication trial, all 5 treated with imipramine showed a clear-cut response, whereas none of those randomized to placebo displayed significant benefits. Despite the small sample size, findings from this study suggested that psychotherapy and pharmacotherapy are effective for different subgroups of depressed patients.

Among women with recurrent depressive disorder, Frank et al. (2000) administered an SSRI in addition to interpersonal psychotherapy (IPT) after non-remission with psychotherapy alone ($n = 159$). The remission rate (79 %) was significantly greater compared to that (66 %)

of another cohort in which IPT and imipramine were simultaneously combined from the outset of treatment ($n = 180$). Despite several methodological limitations, findings from this study suggest that providing IPT and, when remission is not achieved, sequentially adding antidepressant medications can be an effective treatment strategy without prolonged exposure to pharmacotherapy.

In another investigation (Schatzberg et al., 2005), outpatients with chronic major depressive disorder ($n = 140$) who did not respond to 12-week treatment with either nefazodone or CBASP were crossed over to the alternate treatment. Both treatment switching options resulted in clinically and statistically significant symptom improvements. Further, intent-to-treat response rates were significantly higher for patients who crossed over to CBASP from nefazodone than viceversa (57 % vs 42 %). These findings supported the utility of switching to CBASP when a medication does not yield response, and, conversely, of switching to a medication for non-responders to an adequate trial of psychotherapy.

Dekker et al. (2013) reported that among outpatients with moderately severe depression ($n = 103$), initially randomized to either short-term supportive psychodynamic therapy (PDT) or antidepressants (AD) for 8 weeks, non-responsive patients (i.e., less than a 30 % decrease in symptoms) receiving PDT were offered additional AD for 16 weeks and improved more than those initially receiving AD and then complementary PDT. Notably, about 40 % of the patients refused the additional therapy, despite unsuccessful monotherapy. Nonetheless, offering combined treatment after initial non-response to monotherapy appeared to be a beneficial intervention strategy.

In another study (Dunlop et al., 2019), previously untreated adults with major depressive disorder who did not achieve remission after 12-week CBT were treated with escitalopram for 12 weeks in addition to psychotherapy ($n = 37$). They were compared to those who did not achieve remission with an antidepressant (i.e., escitalopram or duloxetine) and were assigned to additional CBT ($n = 75$). Both treatment options were found to be equally effective in achieving remission and helpful in preventing relapse or recurrence of depression at 18-month follow-up. Particularly, adding an antidepressant medication was found to be effective for patients who did not achieve remission with initial CBT, suggesting that pharmacotherapy may be indicated in those who have not achieved remission with first-line psychotherapy.

4.4. Partially remitted depression

The presence of residual symptoms after completion of acute-phase pharmacotherapy or psychotherapy for depression has been associated with poor long-term outcomes (Buckman et al., 2018; Fava & Kellner, 1991). These findings supported the hypothesis that residual symptoms may progress to become prodromal symptoms of depressive relapse, and that treatment directed toward residual symptoms may yield enduring benefits (Fava & Kellner, 1991).

Given the prognostic value of residual symptoms and the role of comorbidity in treatment outcomes and functional recovery in mood disorders, it is conceivable that one course of treatment (whether pharmacotherapy or psychotherapy) is unlikely to address the clinical complexity of affective disturbances, in both research and clinical practice settings (Guidi, Tomba, & Fava, 2016).

The sequential administration of pharmacotherapy and psychotherapy according to the stages of the disorder (i.e., use of pharmacotherapy in the acute phase and psychotherapy in the residual phase) has been found to be a viable strategy for preventing relapse and recurrence in major depressive disorder (Guidi et al., 2017; Guidi & Fava, 2021b). The sequential model is particularly indicated whenever substantial residual symptoms are present despite acute-phase pharmacological treatment and only partial recovery has been achieved. The preventive effects of the sequential administration of psychotherapy appear to be related to the amelioration of residual symptoms and/or the pursuit of a state of euthymia. Indeed, a full recovery from depression can be achieved only through interventions that promote balanced levels of psychological

well-being and resilience (i.e., WBT).

According to the sequential approach, psychotherapeutic strategies can be integrated when they are most likely to make a unique and separate contribution to patient's well-being and to provide a more pervasive recovery. Further, the target of psychotherapeutic work may vary according to the characteristics and intensity of residual symptoms (Table 4).

Findings from a systematic review and meta-analysis based on 17 high-quality RCTs (Guidi & Fava, 2021b) indicated that the sequential administration of psychotherapy (i.e., CBT and its modifications, such as preventive cognitive therapy, CBT of residual symptoms, MBCT, WBT) after response to acute-phase pharmacotherapy, either alone or in combination with antidepressant medications, was associated with significantly reduced risk of relapse and recurrence at follow-up (RR, 0.84; 95 % CI, 0.74–0.94) in major depressive disorder compared to control conditions (i.e., antidepressant medications, treatment as usual, clinical management, psychoeducation).

According to these results, it can be argued that psychotherapy promotes skills that patients are able to practice even after treatment termination, reducing both internal and external triggers for relapse or recurrence. Further, psychotherapeutic strategies specifically geared to euthymia, such as WBT, may help the patient effectively manage chronic and subtle sources of stress (i.e., allostatic overload) (Fava et al., 2019), and modify lifestyle habits.

5. Conclusion

The clinical approach to non-response to treatment in depression ultimately depends on the quality of the data that are collected (Balon, 2005; Fava et al., 2024). If assessment primarily relies on counting episodes that fulfill specific criteria (Berk et al., 2017; Fava, 2003; McIntyre et al., 2023), only pharmacological strategies are likely to emerge. If assessment is filtered by clinical judgment and expanded to consideration a number of psychosocial factors, such as characteristics and severity of depressive illness, co-occurring symptomatology and problems (not necessarily syndromes), medical comorbidities, iatrogenic factors, patient's perception of previous treatment(s), as outlined in this review, a wider range of options and a primary role for psychotherapeutic approaches may ensue. Such information should be placed within what is actually available in the specific treatment setting and should be integrated with patient's preferences. When medications only are administered, treatment should be associated with psychotherapeutic management (Fava et al., 2023).

Treatment of TRD should thus be conceptualized as an integrated therapeutic approach to different components encompassing symptoms, psychosocial factors, lifestyle and psychological well-being. Such an approach is more likely to deal effectively with the complexity of clinical situations and the challenges of TRD treatment.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 4
Steps for implementing the sequential approach in partially remitted depression.

1. Careful assessment of patient 3 months after starting antidepressant drug treatment, with special reference to residual symptoms.
2. Cognitive-behavioral treatment for residual symptoms, including cognitive restructuring and/or homework exposure.
3. Tapering of antidepressant drug treatment at the slowest possible pace.
4. Addition of well-being-enhancing therapy and lifestyle modification.
5. Discontinuation of antidepressant drugs.
6. Careful assessment of patient 1 month after drug discontinuation.

Declaration of competing interest

Both Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Aday, J. S., Horton, D., Fernandes-Osterhold, G., O'Donovan, A., Bradley, E. R., Rosen, R. C., & Woolley, J. D. (2024). Psychedelic-assisted psychotherapy: Where is the psychotherapy research? *Psychopharmacology*, 241(8), 1517–1526. <https://doi.org/10.1007/s00213-024-06620-x>
- American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders (5th ed., text rev.)*. Washington, DC: American Psychiatric Association. <https://doi.org/10.1176/appi.books.9780890425787>
- Balon, R. (2005). By whom and how is the quality of research data collection assured and checked? *Psychotherapy and Psychosomatics*, 74(6), 331–335. <https://doi.org/10.1159/000087779>
- Bartova, L., Fugger, G., Dold, M., Swoboda, M. M. M., Zohar, J., Mendlewicz, J., & Kasper, S. (2021). Combining psychopharmacotherapy and psychotherapy is not associated with better treatment outcome in major depressive disorder - evidence from the European Group for the Study of Resistant Depression. *Journal of Psychiatric Research*, 141, 167–175. <https://doi.org/10.1016/j.jpsychires.2021.06.028>
- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. New York, NY: Guilford Press.
- Berk, M., Post, R., Raheesch, A., Gliddon, E., Singh, A., Vieta, E., & Dood, S. (2017). Staging in bipolar disorder. *World Psychiatry*, 16(3), 236–244. <https://doi.org/10.1002/wps.20441>
- Brakemeier, E. L., Radtke, M., Engel, V., Zimmermann, J., Tuschen-Caffier, B., Hautzinger, M., ... Normann, C. (2015). Overcoming treatment resistance in chronic depression: A pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychotherapy and Psychosomatics*, 84(1), 51–56. <https://doi.org/10.1159/000369586>
- van Bronswijk, S., Moopen, N., Beijers, L., Ruhe, H. G., & Peeters, F. (2019). Effectiveness of psychotherapy for treatment-resistant depression: A meta-analysis and meta-regression. *Psychological Medicine*, 49(3), 366–379. <https://doi.org/10.1017/S003329171800199X>
- Buckman, J. E. J., Underwood, A., Clarke, K., Saunders, R., Hollon, S. D., & Pilling, S. (2018). Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. *Clinical Psychology Review*, 64, 13–38. <https://doi.org/10.1016/j.cpr.2018.07.005>
- Casey, M. F., Perera, D. N., & Clarke, D. M. (2013). Psychosocial treatment approaches to difficult-to-treat depression. *Medical Journal of Australia*, 199(S6), S52–S55. <https://doi.org/10.5694/mja12.10629>
- Chiesa, A., Mandelli, L., & Serretti, A. (2012). Mindfulness-based cognitive therapy versus psycho-education for patients with major depression who did not achieve remission following antidepressant treatment: A preliminary analysis. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 18(8), 756–760. <https://doi.org/10.1089/acm.2011.0407>
- Cladder-Micus, M. B., Speckens, A. E. M., Vrijzen, J. N., Donders, T., A. R., Becker, E. S., & Spijker, J. (2018). Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: A pragmatic randomized controlled trial. *Depression and Anxiety*, 35(10), 914–924. <https://doi.org/10.1002/da.22788>
- Cole, A. J., Brittlebank, A. D., & Scott, J. (1994). The role of cognitive therapy in refractory depression. In W. A. Nolen, J. Zohar, S. P. Roose, & J. D. Amsterdam (Eds.), *Refractory depression* (pp. 117–120). Chichester, UK: Wiley.
- Cosci, F., & Fava, G. A. (2021). When anxiety and depression coexist: The role of differential diagnosis using clinimetric criteria. *Psychotherapy and Psychosomatics*, 90(5), 308–317. <https://doi.org/10.1159/000517518>
- Cosci, F., & Fava, G. A. (2022). Staging of unipolar depression: Systematic review and discussion of clinical implications. *Psychological Medicine*, 52, 1621–1628. <https://doi.org/10.1017/S0033291722001507>
- De Las Cuevas, C., & de Leon, J. (2017). Reviving research on medication attitudes for improving pharmacotherapy: Focusing on adherence. *Psychotherapy and Psychosomatics*, 86(2), 73–79. <https://doi.org/10.1159/000450830>
- Dekker, J., Van, H. L., Hendriksen, M., Koelen, J., Schoevers, R. A., Kool, S., & Peen, J. (2013). What is the best sequential treatment strategy in the treatment of depression? Adding pharmacotherapy to psychotherapy or vice versa? *Psychotherapy and Psychosomatics*, 82(2), 89–98. <https://doi.org/10.1159/000341177>
- Dodd, S., Bauer, M., Carvalho, A. F., Eyre, H., Fava, M., Kasper, S., ... Berk, M. (2021). A clinical approach to treatment resistance in depressed patients: What to do when the usual treatments don't work well enough? *World Journal of Biological Psychiatry*, 22(7), 483–494. <https://doi.org/10.1080/15622975.2020.1851052>
- Dunlop, B. W., LoParo, D., Kinkead, B., Mletzko-Crowe, T., Cole, S. P., Nemeroff, C. B., & Craighead, W. E. (2019). Benefits of sequentially adding cognitive-behavioral therapy or antidepressant medication for adults with nonremitting depression. *American Journal of Psychiatry*, 176(4), 275–286. <https://doi.org/10.1176/appi.ajp.2018.18091075>
- Eisendrath, S. J., Gillung, E., Delucchi, K. L., Segal, Z. V., Nelson, J. C., McInnes, L. A., & Feldman, M. D. (2016). A randomized controlled trial of mindfulness-based cognitive therapy for treatment-resistant depression. *Psychotherapy and Psychosomatics*, 85(2), 99–110. <https://doi.org/10.1159/000442260>
- Emmelkamp, P. M. G., Bouman, T. K., & Scholing, A. (1993). *Anxiety Disorders* (pp. 55–67). Chichester, UK: Wiley.
- Fabbri, S., Fava, G. A., Rafanelli, C., & Tomba, E. (2007). Family intervention approach to loss of clinical effect during long-term antidepressant treatment: A pilot study. *Journal of Clinical Psychiatry*, 68(9), 1348–1351. <https://doi.org/10.4088/jcp.v68n0904>
- Fava, G. A. (2016). *Well-Being Therapy. Treatment manual and clinical applications*. Basel: Karger.
- Fava, G. A. (2021). *Discontinuing antidepressant medications* (pp. 65–81). Oxford, UK: Oxford University Press.
- Fava, G. A. (2022). Clinimetric integration of diagnostic criteria for a personalized psychiatry. *Psychotherapy and Psychosomatics*, 91(6), 373–381. <https://doi.org/10.1159/000527493>
- Fava, G. A. (2023). Patients as health producers: The psychosomatic foundation of lifestyle medicine. *Psychotherapy and Psychosomatics*, 92(2), 81–86. <https://doi.org/10.1159/000529953>
- Fava, G. A. (2024a). Clinical use of staging in psychiatry. *Psychotherapy and Psychosomatics*, 93(3), 143–150. <https://doi.org/10.1159/000538526>
- Fava, G. A. (2024b). The clinical meaning of withdrawal with antidepressant drugs. *Psychotherapy and Psychosomatics*, 93(4), 224–229. <https://doi.org/10.1159/000540033>
- Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The deceptive manifestations of treatment resistance in depression: A new look at the problem. *Psychotherapy and Psychosomatics*, 89(5), 265–273. <https://doi.org/10.1159/000507227>
- Fava, G. A., Cosci, F., Sonino, N., & Guidi, J. (2023). Understanding health attitudes and behavior. *American Journal of Medicine*, 136(3), 252–259. <https://doi.org/10.1016/j.amjmed.2022.10.019>
- Fava, G. A., & Guidi, J. (2023a). Clinical characterization of demoralization. *Psychotherapy and Psychosomatics*, 92(3), 139–147. <https://doi.org/10.1159/000530760>
- Fava, G. A., & Guidi, J. (2023b). Management of depression in medical patients: The role of clinical evaluation. *Psychotherapy and Psychosomatics*, 92(5), 287–291. <https://doi.org/10.1159/000533954>
- Fava, G. A., Guidi, J., Rafanelli, C., & Rickels, K. (2017). The clinical inadequacy of the placebo model and the development of an alternative conceptual framework. *Psychotherapy and Psychosomatics*, 86(6), 332–340. <https://doi.org/10.1159/000480038>
- Fava, G. A., & Kellner, R. (1991). Prodromal symptoms in affective disorders. *American Journal of Psychiatry*, 148, 223–230. <https://doi.org/10.1176/ajp.148.7.823>
- Fava, G. A., & Kellner, R. (1993). Staging: A neglected dimension in psychiatric classification. *Acta Psychiatrica Scandinavica*, 87(4), 225–230. <https://doi.org/10.1111/j.1600-0447.1993.tb03362.x>
- Fava, G. A., McEwen, B. S., Guidi, J., Gostoli, S., Offidani, E., & Sonino, N. (2019). Clinical characterization of allostatic overload. *Psychoneuroendocrinology*, 108, 94–101. <https://doi.org/10.1016/j.psyneuen.2019.05.028>
- Fava, G. A., Rafanelli, C., & Tomba, E. (2012). The clinical process in psychiatry: A clinimetric approach. *Journal of Clinical Psychiatry*, 73(2), 177–184. <https://doi.org/10.4088/JCP.10r06444>
- Fava, G. A., Ruini, C., Rafanelli, C., & Grandi, S. (2002). Cognitive behavior approach to loss of clinical effect during long-term antidepressant treatment: A pilot study. *American Journal of Psychiatry*, 159(12), 2094–2095. <https://doi.org/10.1176/appi.ajp.159.12.2094>
- Fava, G. A., Savron, G., Grandi, S., & Rafanelli, C. (1997). Cognitive-behavioral management of drug-resistant major depressive disorder. *Journal of Clinical Psychiatry*, 58(6), 278–284. <https://doi.org/10.4088/jcp.v58n0608b>
- Fava, G. A., Sonino, N., Aron, D. C., Balon, R., Berrocal Montiel, C., Cao, J., & Patierno, C. (2024). Clinical interviewing: An essential but neglected method of medicine. *Psychotherapy and Psychosomatics*, 93(2), 94–99. <https://doi.org/10.1159/000536490>
- Fava, G. A., Sonino, N., & Guidi, J. (2025). Measuring clinical findings: The value of clinimetrics. *Postgraduate Medical Journal*. <https://doi.org/10.1093/postmj/qgaf082> (in press).
- Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*, 53, 649–659. [https://doi.org/10.1016/s0006-3223\(03\)00231-2](https://doi.org/10.1016/s0006-3223(03)00231-2)
- Feinstein, A. R. (1970). The pre-therapeutic classification of comorbidity in chronic disease. *Journal of Chronic Diseases*, 23(7), 455–468. [https://doi.org/10.1016/0021-9681\(70\)90054-8](https://doi.org/10.1016/0021-9681(70)90054-8)
- Fekadu, A., Wooderson, S., Donaldson, C., Markopoulou, K., Masterson, B., & Cleare, A. J. (2009). A multidimensional tool to quantify treatment resistance in depression: The Maudsley staging method. *The Journal of Clinical Psychiatry*, 70(2), 177–184. <https://doi.org/10.4088/jcp.08m04309>
- Frank, E., Grochocinski, V. J., Spanier, C. A., Buysse, D. J., Cherry, C. R., Houck, P. R., & Kupfer, D. J. (2000). Interpersonal psychotherapy and antidepressant medication: Evaluation of a sequential treatment strategy in women with recurrent major depression. *Journal of Clinical Psychiatry*, 61(1), 51–57.
- Freeman, A., & McCloskey, R. D. (2003). Impediments to effective psychotherapy. In R. L. Leahy (Ed.), *Roadblocks in cognitive-behavioral therapy* (pp. 24–48). New York, NY: The Guilford Press.
- Gloster, A. T., Rinner, M. T. B., Ioannou, M., Villanueva, J., Block, V. J., Ferrari, G., & Karelka, M. (2020). Treating treatment non-responders: A meta-analysis of randomized controlled psychotherapy trials. *Clinical Psychology Review*, 75, Article 101810. <https://doi.org/10.1016/j.cpr.2019.101810>
- Guidi, J., & Fava, G. A. (2015). Psychosocial management of treatment-resistant mood disorders: Current evidence. In A. F. Carvalho, & R. S. McIntyre (Eds.), *Treatment-resistant mood disorders* (pp. 95–105). Oxford, UK: Oxford University Press.
- Guidi, J., & Fava, G. A. (2020). The emerging role of euthymia in psychotherapy research and practice. *Clinical Psychology Review*, 82, Article 101941. <https://doi.org/10.1016/j.cpr.2020.101941>

- Guidi, J., & Fava, G. A. (2021a). Conceptual and clinical innovations of Well-Being Therapy. *International Journal of Cognitive Therapy*, 14, 196–208. <https://doi.org/10.1007/s41811-021-00101-1>
- Guidi, J., & Fava, G. A. (2021b). Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: A systematic review and meta-analysis. *JAMA Psychiatry*, 78(3), 261–269. <https://doi.org/10.1001/jamapsychiatry.2020.3650>
- Guidi, J., & Fava, G. A. (2022). The clinical science of euthymia: A conceptual map. *Psychotherapy and Psychosomatics*, 91(3), 156–167. <https://doi.org/10.1159/000524279>
- Guidi, J., & Fava, G. A. (2024). Innovative strategies in evaluation and treatment of burnout in medical workers. *Psychotherapy and Psychosomatics*, 93(6), 361–366. <https://doi.org/10.1159/000541309>
- Guidi, J., Lucente, M., Sonino, N., & Fava, G. A. (2021). Allostatic load and its impact on health: A systematic review. *Psychotherapy and Psychosomatics*, 90(1), 11–27. <https://doi.org/10.1159/000510696>
- Guidi, J., Tomba, E., Cosci, F., Park, S. K., & Fava, G. A. (2017). The role of staging in planning psychotherapeutic interventions in depression. *Journal of Clinical Psychiatry*, 78(4), 456–463. <https://doi.org/10.4088/JCP.16r10736>
- Guidi, J., Tomba, E., & Fava, G. A. (2016). The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: A meta-analysis of the sequential model and a critical review of the literature. *American Journal of Psychiatry*, 173(2), 128–137. <https://doi.org/10.1176/appi.ajp.2015.15040476>
- Haikazian, S., Chen-Li, D. C. J., Johnson, D. E., Fancy, F., Levinta, A., Husain, M. I., & Rosenblatt, J. D. (2023). Psilocybin-assisted therapy for depression: A systematic review and meta-analysis. *Psychiatry Research*, 329, Article 115531. <https://doi.org/10.1016/j.psychres.2023.115531>
- Hanlon, J. T., & Schmadler, K. E. (2022). The Medication Appropriateness index: A clinimetric measure. *Psychotherapy and Psychosomatics*, 91(2), 78–83. <https://doi.org/10.1159/000521699>
- Havlik, J. L., Wahid, S., Teopiz, K. M., McIntyre, R. S., Krystal, J. H., & Rhee, T. G. (2024). Recent advances in the treatment of treatment-resistant depression: A narrative review of literature published from 2018 to 2023. *Current Psychiatry Reports*, 26(4), 176–213. <https://doi.org/10.1007/s11920-024-01494-4>
- Horwitz, R. I., & Cullen, M. R. (2023). Biology is not destiny. *Psychotherapy and Psychosomatics*, 92(4), 205–207. <https://doi.org/10.1159/000533449>
- Ijaz, S., Davies, P., Williams, C. J., Kessler, D., Lewis, G., & Wiles, N. (2018). Psychological therapies for treatment-resistant depression in adults. *The Cochrane Database of Systematic Reviews*, 5(5), CD010558. <https://doi.org/10.1002/14651858.CD010558.pub2>
- Keitner, G. I., & Mansfield, A. K. (2012). Management of treatment-resistant depression. *Psychiatric Clinics of North America*, 35(1), 249–265. <https://doi.org/10.1016/j.psc.2011.11.004>
- Kellner, R. (1972). 2. Improvement criteria in drug trials with neurotic patients. *Psychological Medicine*, 2(1), 73–80. <https://doi.org/10.1017/s0033291700045645>
- Kellner, R. (1979). Psychotherapeutic strategies in the treatment of psychophysiological disorders. *Psychotherapy and Psychosomatics*, 32(1–4), 91–100. <https://doi.org/10.1159/000287376>
- Kellner, R. (1986). *Somatization and hypochondriasis*. New York, NY: Praeger.
- Li, J. M., Zhang, Y., Su, W. J., Liu, L. L., Gong, H., Peng, W., & Jiang, C. L. (2018). Cognitive behavioral therapy for treatment-resistant depression: A systematic review and meta-analysis. *Psychiatry Research*, 268, 243–250. <https://doi.org/10.1016/j.psychres.2018.07.020>
- Markowitz, J. C. (2003). Interpersonal psychotherapy for chronic depression. *Journal of Clinical Psychology*, 59(8), 847–858. <https://doi.org/10.1002/clp.10177>
- McCullough, J. P. (2000). *Treatment for chronic depression. Cognitive behavioral analysis system of psychotherapy*. New York, NY: Guilford Press.
- McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *The New England Journal of Medicine*, 338(3), 171–179. <https://doi.org/10.1056/NEJM199801153380307>
- McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., & Maj, M. (2023). Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*, 22(3), 394–412. <https://doi.org/10.1002/wps.21120>
- McKay, K. M., Imel, Z. E., & Wampold, B. E. (2006). Psychiatrist effects in the psychopharmacological treatment of depression. *Journal of Affective Disorders*, 92(2–3), 287–290. <https://doi.org/10.1016/j.jad.2006.01.020>
- Mergl, R., Henkel, V., Allgaier, A. K., Kramer, D., Hautzinger, M., Kohnen, R., & Hegerl, U. (2011). Are treatment preferences relevant in response to serotonergic antidepressants and cognitive-behavioral therapy in depressed primary care patients? Results from a randomized controlled trial including a patients' choice arm. *Psychotherapy and Psychosomatics*, 80(1), 39–47. <https://doi.org/10.1159/000318772>
- Mintz, D. L., & Flynn, D. F. (2012). How (not what) to prescribe: Nonpharmacologic aspects of psychopharmacology. *Psychiatric Clinics of North America*, 35(1), 143–163. <https://doi.org/10.1016/j.psc.2011.11.009>
- Moore, R. G., & Garland, A. (2003). *Cognitive therapy for chronic and persistent depression*. Chichester, UK: John Wiley & Sons.
- National Institute for Health and Care Excellence (NICE). (2022). *Depression in adults: treatment and management*.
- Negt, P., Brakemeier, E. L., Michalak, J., Winter, L., Bleich, S., & Kahl, K. G. (2016). The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: A systematic review and meta-analysis of randomized-controlled clinical trials. *Brain and Behavior: A Cognitive Neuroscience Perspective*, 6(8), Article e00486. <https://doi.org/10.1002/brb3.486>
- Nierenberg, A. A., & Amsterdam, J. D. (1990). Treatment-resistant depression: Definition and treatment approaches. *Journal of Clinical Psychiatry*, 51(Suppl), 39–50.
- O'Connor, S. J., Hewitt, N., Kuc, J., & Orsini, L. S. (2023). Predictors and risk factors of treatment-resistant depression: A systematic review. *Journal of Clinical Psychiatry*, 85(1), 23r14885. <https://doi.org/10.4088/JCP.23r14885>
- Otto, M. W., Birk, J. L., Fitzgerald, H. E., Chauvin, G. V., Gold, A. K., & Carl, J. R. (2022). Stage models for major depression: Cognitive behavior therapy, mechanistic treatment targets, and the prevention of stage transition. *Clinical Psychology Review*, 95, Article 102172. <https://doi.org/10.1016/j.cpr.2022.102172>
- Parker, G., Parker, I., Brotchie, H., & Stuart, S. (2006). Interpersonal psychotherapy for depression? The need to define its ecological niche. *Journal of Affective Disorders*, 95(1–3), 1–11. <https://doi.org/10.1016/j.jad.2006.03.019>
- Patierno, C., Fava, G. A., & Carrozzino, D. (2023). Illness denial in medical disorders: A systematic review. *Psychotherapy and Psychosomatics*, 92(4), 211–226. <https://doi.org/10.1159/000531260>
- Peeters, F. P., Ruhe, H. G., Wichers, M., Abidi, L., Kaub, K., & van der Lande, ... 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>
- Rajeshkumar, L., Mishkind, M., Coleman, J. J., Pahwa, M., LaPreze, D., Solenske, S., & Wright, J. H. (2024). Computer-assisted cognitive behavior therapy and mobile apps for depression and anxiety: Evidence-based digital tools for clinical practice. *Journal of Psychiatric Practice*, 30(6), 389–399. <https://doi.org/10.1097/PRA.0000000000000815>
- Rikhani, K., Vas, C., & Jha, M. K. (2023). Approach to diagnosis and management of treatment-resistant depression. *Psychiatric Clinics of North America*, 46(2), 247–259. <https://doi.org/10.1016/j.psc.2023.02.011>
- Rogan, T., & Wilkinson, S. T. (2023). The role of psychotherapy in the management of treatment-resistant depression. *Psychiatric Clinics of North America*, 46(2), 349–358. <https://doi.org/10.1016/j.psc.2023.02.006>
- Rush, A. J., Trivedi, M. H., 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/ajp.2006.163.11.1905>
- Ryan, C. E., Epstein, N. B., Keitner, G. I., Miller, I. W., & Bishop, D. S. (2005). *Evaluating and treating families: The McMaster approach*. New York, NY: Routledge Taylor & Francis Group.
- Schatzberg, A. F., Rush, A. J., Arnow, B. A., Banks, P. L., Blalock, J. A., & Borian, ... Keller, M. B. (2005). Chronic depression: Medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Archives of General Psychiatry*, 62(5), 513–520. <https://doi.org/10.1001/archpsyc.62.5.513>
- Schramm, E., Zobel, I., Schoepf, D., Fangmeier, T., Schnell, K., Walter, H., & Normann, C. (2015). Cognitive behavioral analysis system of psychotherapy versus escitalopram in chronic major depression. *Psychotherapy and Psychosomatics*, 84(4), 227–240. <https://doi.org/10.1159/000381957>
- Sonino, N., Fava, G. A., Aron, D. C., & Guidi, J. (2025). The role of interviewing in endocrine practice. *Journal of Endocrinological Investigation*. <https://doi.org/10.1007/s40618-025-02565-w>
- Sonino, N., Fava, G. A., Lucente, M., & Guidi, J. (2023). Allostatic load and endocrine disorders. *Psychotherapy and Psychosomatics*, 92(3), 162–169. <https://doi.org/10.1159/000530691>
- Souery, D., Amsterdam, J., de Montigny, C., Lecrubier, Y., Montgomery, S., Lipp, O., & Mendlewicz, J. (1999). Treatment resistant depression: Methodological overview and operational criteria. *European Neuropsychopharmacology*, 9(1–2), 83–91. [https://doi.org/10.1016/s0924-977x\(98\)00004-2](https://doi.org/10.1016/s0924-977x(98)00004-2)
- Souza, L. H., Salum, G. A., Mosquero, B. P., Caldieraro, M. A., Guerra, T. A., & Fleck, M. P. (2016). Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. *Journal of Affective Disorders*, 193, 373–380. <https://doi.org/10.1016/j.jad.2016.01.004>
- Stewart, J. W., Mercier, M. A., Agosti, V., Guardino, M., & Quitkin, F. M. (1993). Imipramine is effective after unsuccessful cognitive therapy: Sequential use of cognitive therapy and imipramine in depressed outpatients. *Journal of Clinical Psychopharmacology*, 13(2), 114–119.
- Thase, M. E., & Howland, R. H. (1994). Refractory depression: Relevance of psychosocial factors and therapies. *Psychiatric Annals*, 24(5), 232–240. <https://doi.org/10.3928/0048-5713-19940501-09>
- Thase, M. E., & Rush, A. J. (1995). Treatment-resistant depression. In F. E. Bloom, & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (pp. 1081–1097). New York, NY: Raven Press.
- Trivedi, R. B., Nieuwsmma, J. A., & Williams, J. W., Jr. (2011). Examination of the utility of psychotherapy for patients with treatment resistant depression: A systematic review. *Journal of General Internal Medicine*, 26(6), 643–650. <https://doi.org/10.1007/s11606-010-1608-2>
- Uhlenhuth, E. H., Rickels, K., Fisher, S., Park, L. C., Lipman, R. S., & Mock, J. (1966). Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia*, 9(5), 392–418. <https://doi.org/10.1007/BF00406450>
- Wise, T. N. (2023). Illness denial in medical conditions: The time has come to include it in DSM iterations. *Psychotherapy and Psychosomatics*, 92(5), 292–294. <https://doi.org/10.1159/000533287>
- Work Group on Major Depressive Disorder. (2010). Practice guideline for the treatment of patients with major depressive disorder (Third Edition). *American Journal of Psychiatry*, 167(Suppl), 1–118.
- World Health Organization. (2022). *ICD-11: International classification of diseases (11th rev.)*. <https://icd.who.int/>.