The Role of Staging in Planning Psychotherapeutic Interventions in Depression

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ABSTRACT

Context: The purpose of this critical review is to examine the role of staging in planning a psychotherapeutic intervention in depressive disorders.

Evidence Acquisition: English-language studies concerned with staging in depressive disorders were identified in MEDLINE, PsycINFO, and Web of Science and by manual search of the literature. Selection of articles was based on their methodological quality and implications for clinical practice.

Results: Staging may allow clinicians to apply a psychotherapeutic intervention to specific phases of the development of depressive disorders: certain psychotherapeutic approaches, such as well-being therapy and mindfulness-based cognitive therapy, appear to be uniquely suited for addressing the residual phase of depression, whereas interpersonal psychotherapy has been mainly tested in the acute phase. Cognitive-behavioral treatment appears to be suitable for all phases, but with chronic or double depression, its modifications (eg, cognitive-behavioral analysis system of psychotherapy) appear to be indicated. Staging may also allow clinicians to assess past and potential resistance to treatment.

Conclusions: Treatment options, including psychotherapy, need to be filtered by clinical judgment and patient-specific problems that take into account individual staging classifications of the depressive illness.

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Clinical psychology and psychiatry had, for a long time, neglected staging as a model to classify the development of mental disorders. In 1993, Fava and Kellner[1] introduced the clinimetric concept of staging in psychiatric classification. Staging differs from the conventional diagnostic practice in that it not only defines the extent of the progression of a disorder at a particular point in time, but also defines where a person currently is along the continuum of the course of the illness.[2] In addition, staging encourages clinicians to select treatments relevant to the stages of the disorder. For instance, interventions at the early stages may be more effective and less harmful than treatments delivered later in the illness course and might help to prevent progression to more advanced stages or promote regression to an earlier stage, including full and sustained remission.[2] Staging, therefore, has the potential to improve the logic and timing of interventions in clinical psychology and psychiatry, just as it does in many complex and serious medical disorders.

In the past decade, there have been further developments in the literature on staging in psychiatry,[2–6] and a staging model has been suggested in schizophrenia, unipolar depression, bipolar disorder, panic disorder, substance use disorders, and anorexia and bulimia nervosa.[2]

Several efforts have also been made to develop methods to stage the degree of treatment resistance. The information that is required may encompass the number of trials completed, the intensity/optimization of each trial, issues of pseudoresistance (nonresponse to inadequate treatment in terms of duration, doses, or indications),[7] and the loss of therapeutic effects after clinical response.[8]

The first application of the staging of level of treatment resistance occurred in unipolar depression[8–11]; later, this model was applied to panic disorder and alcohol use disorders.[2] The various levels of treatment resistance have been shown to be of great importance. From a clinical point of view, it is quite different to treat a patient with a psychiatric disorder who displayed positive responses to previous therapeutic trials and a patient who failed to respond to various therapeutic trials, including one concerned with augmentation/combination.[8]

In this critical review, we will illustrate the importance of staging for planning psychotherapeutic interventions in depression and examine how staging supported by clinical judgment may be crucial in selecting evidence-based treatments for depression. In view of the broad areas that are covered, a comprehensive and systematic review is not feasible. English-language articles concerned with staging in depressive disorders and published in peer-reviewed journals were included. Articles were selected to illustrate the conceptual points and research opportunities.

STAGING OF LONGITUDINAL DEVELOPMENT OF DEPRESSIVE DISORDERS

Fava and Kellner[1] described a staging model of unipolar depression that was updated in 2013.[2] The prodromal phase (stage 1) is characterized by no depressive symptoms (with mild functional change or decline) or by

Table 1. Stages of Primary Unipolar Depression

Stage	
1	Prodromal phase a. No depressive symptoms (generalized anxiety, irritability, anhedonia, sleep disorders) with mild functional change or decline b. Mood symptoms (sad mood, subsyndromal depression)
2	Major depressive episode
3	Residual phase a. No depressive symptoms (sleep disturbance, generalized anxiety, irritability, anorexia, impaired libido) b. Mood symptoms (depressed mood, guilt, hopelessness) c. Dysthymia
4	a. Recurrent depression b. Double depression
5	Chronic major depressive episode (lasting at least 2 years without interruptions)

mood symptoms. At stage 2, subjects present with major depressive episode; then a residual phase (stage 3) may occur with no depressive symptoms, mood symptoms, or dysthymia. Stage 4 is characterized by recurrent depression or double depression; while at stage 5, subjects have chronic major depressive episode (Table 1).

Interestingly, stage 3 (residual symptoms) may constitute a psychobiological risk for relapse, despite apparent recovery.[12,13] High relapse rates have been observed in depressed patients with residual symptoms: about 76% compared with 25% in subjects without residual symptoms.[13] In addition, relapse is less common after full remission: patients with residual symptoms relapse 3 times faster than those without and mainly in the 4 months after remission.[13]

In this framework, the staging method, which ranges from the prodromes to the residual and chronic phases of the illness and considers the longitudinal history of the patient's disease, can be applied to clinical cases at risk for depressive relapse and may pave the way for more effective modalities of treatment selection and relapse prevention.

Stage 1

In medicine, prodromes can be identified with early signs and symptoms that differ from the acute clinical phase. The evaluation of prodromal symptoms has been of importance for many progressive, dangerous, and treatable diseases in which early detection and timely treatment (particularly of recurrences) are crucial.[14] The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness.

Several studies have addressed the issue of symptom development in unipolar depression, suggesting that a substantial prodromal symptomatology exists before the onset of depressed mood.[2,12,15] In particular, it has been emphasized that (*a*) anxiety and irritability appear to dominate the clinical picture of the prodromal phase; (*b*) the characteristics of these prodromal symptoms affect the longitudinal course of the illness; and (*c*) prodromes are quite similar to residual symptoms.[12,16,17]

Clinical Points

- Since the introduction of the concept of staging in psychiatric classification in the early 1990s, there have been important developments in the literature. Staging models may guide the choice of psychotherapy in depression.
- Staging has the potential to improve the logic and timing of interventions in clinical psychology and psychiatry. When supported by clinical judgment, staging may be crucial in selecting evidence-based treatments for depression according to an individualized treatment plan.

Prodromal symptoms may encompass tension and vague feelings of anxiety, irritability, impaired work and initiative, trouble concentrating, fatigue, sleep and eating disturbances, diminished sexual drive, somatic complaints, and feelings of worthlessness.[12]

In assessing subclinical symptoms that are—by definition—milder than those of the full clinical syndrome, the capacity of the assessment instrument to measure small increments or small changes near the normal end of the spectrum (ie, sensitivity) becomes important, together with the traditional aspects of validity and reliability.[18]

Kupfer et al[19] outlined the clinical advantages of early treatment intervention in recurrent depression. A group of 45 patients with recurrent major depression was treated with combined pharmacotherapy and interpersonal psychotherapy in a similar fashion for 2 consecutive episodes. In the second episode, an early, aggressive treatment was performed. This latter strategy was found to significantly shorten the episode by approximately 4 to 5 months.[19]

Stage 2

When the clinician is confronted with the presence of a major depressive disorder, pharmacotherapy and/or psychotherapy may be pursued. Even though the 2 types of treatment are roughly equivalent for the average case,[20] there are important distinctions when clinical judgment is applied to the specific patient.[21]

There is solid evidence for the efficacy of 2 psychotherapeutic approaches for the treatment of an acute episode of depression: cognitive-behavioral therapy (CBT) and interpersonal psychotherapy.[20] The joint use of psychotherapy and pharmacotherapy in treating the acute phase of depression was found to yield limited benefits as to relapse prevention compared to antidepressant drug treatment alone.[22]

The management of depression, however, is complicated by comorbidity: depression usually occurs alongside symptoms of anxiety, substance misuse, and personality disorders.[23] In particular, the relationship of major depression to anxiety has been substantiated by several investigations. Smits and colleagues[24] found that anxious depressed patients needed more cognitive therapy sessions than nonanxious patients with depression to reach full symptomatic recovery. The comorbidity with anxiety

disorders was the only significant predictor of late remission in the study by Roca et al.[25]

In this context, an important assessment issue is concerned with the primary/secondary distinction of depressive versus anxiety disorders that is based on chronology.[26] For instance, after years of social phobia, an individual may become depressed; thus, depression is secondary. Conversely, if a patient develops a depressive disorder that, after a few months, becomes characterized by overwhelming anxiety, depression is defined as primary. Such a distinction has important clinical implications. In a study of 255 depressed outpatients,[27] comorbid anxiety disorders were present in about half of the patients. While both social phobia and generalized anxiety disorder preceded the first episode of major depressive disorder in most of the cases, panic disorder and agoraphobia most often appeared subsequently.[27]

A staging system may allow clinicians to monitor whether the patient's response to treatment of the acute phase of the illness has placed him/her into an asymptomatic stage or shifted him/her into stage 3.

Stage 3

Stage 3 is more complex and subsumes multiple scenarios, including failure to achieve remission and the occurrence of relapse that may lead to recurrent episodes. Residual symptoms may occur at stage 3 (Table 1).[2]

Residual symptoms—defined as the persistence of symptoms and signs despite apparent remission or recovery—are the rule after completion of drug or psychotherapeutic treatment of depression. Cosci and Fava[2] defined this stage as 3a (Table 1). If depressive mood occurs, the patient may be defined as in stage 3b or 3c (dysthymia), based on whether he/she satisfies the requirements for dysthymic disorder. Similarly, Kurian et al[28] described 2 types of residual symptoms: (*a*) symptoms depicted as continued manifestations of core depressive symptoms (ie, impairments in sleep, interest, guilt, energy, cognition, appetite, psychomotor activity, suicidal ideation, and depressed mood) and (*b*) residual symptoms as nonclassic symptoms of major depressive disorder (ie, pain, anxiety, or irritability). Other common residual symptoms after completion of drug continuation treatment are impairment of libido and hopelessness.[2] Social and interpersonal maladjustments also appear to be common in the residual phase of the depressive illness.[12,29] The majority of residual symptoms were also present in the prodromal phase of illness.[30] In addition, their presence has been correlated with poor outcome and may progress to become prodromal symptoms of relapse.[12] As a result, treatment directed toward residual symptoms may yield long-term benefits.[31]

There appears to be a relationship between residual and prodromal symptomatology. Certain prodromal symptoms may be overshadowed by the acute manifestation of the disorder, but persist as residual symptoms and progress to become prodromes of relapse. In fact, prodromal symptoms of relapse tend to mirror those of the initial episode.[12] The prodromal phase of depression has a large interindividual variability and lacks diagnostic specificity. As a result, it is impossible to outline a stage 0 for major depression, characterized by specific symptoms that connote an impending risk of occurrence of a major depressive disorder.[2] However, within each patient, there is striking consistency in the prodromal symptoms that precede each episode, even though the same initial symptoms of the acute disorder may occur and not be followed by another episode. As a result, it is important to record the prodromal symptoms of the last episode of depression and, if in the longitudinal monitoring of a patient who received psychotherapy for depression such symptoms recur, booster sessions or a new course of psychotherapy may be applied.

Roca et al[25] compared the residual symptoms in early and late remitters from depression after antidepressant treatment. The major differences between early and late remission are in items related to the core depressive criteria (ie, mood, energy, guilt, concentration, and decision-making), while all of the considered noncore depressive items (ie, pain, somatic symptoms, and irritability) did not differ between the 2 groups. Decreased somatic anxiety and increased psychological anxiety, loss of appetite, loss of libido, and hypochondriasis were also found to be predictors of relapse/recurrence in patients who responded to acute-phase continuation-phase cognitive therapy.[32]

There are major difficulties in separating the residual phase of depressive illness from incomplete remission. In 2 randomized controlled psychotherapy trials concerned with depression,[30,33] psychotherapeutic intervention was applied according to a staging method in the residual phase (stage 3) and was found to yield long-term benefits.[34,35] In these trials, only the patients who were rated as "better" or "much better" according to Kellner's global rating of improvement,[36] who met the criteria of Frank et al[37] for full remission, and who had no evidence of depressed mood after treatment according to Paykel's Clinical Interview for Depression[38] were considered fully remitted.

Clinical evidence suggests that the sequential administration of pharmacotherapy and psychotherapy according to the stages of the disorder (ie, use of pharmacotherapy in the treatment of the acute episode and psychotherapy in the residual phase) is a viable strategy for preventing relapse and recurrence in major depressive disorder both in adults[31] and in children and adolescents.[39] The sequential approach may include discontinuation of antidepressant drug treatment or its maintenance, thereby offering the advantage of yielding enduring effects while limiting exposure to drug therapy. Modifications of cognitive-behavioral techniques, such as mindfulness-based cognitive therapy (MBCT),[40] CBT of residual symptoms,[30] and well-being therapy (WBT),[41] were used in most of the available studies.

The preventive effects of the sequential strategy appear to be related to abatement of residual symptoms and/or increase in psychological well-being and coping skills.[31] A state of euthymia[42] can be promoted by WBT with enduring benefits, as was found to be the case in 3 randomized

Table 2. Steps for Implementing the Sequential Approach in Recurrent Depression

1. Careful assessment of patient 3 months after starting antidepressant drug treatment, with special reference to residual symptoms
2. Cognitive-behavioral treatment of residual symptoms (ie, cognitive restructuring and/or homework exposure) followed by well-being therapy when appropriate or mindfulness-based cognitive therapy
3. Tapering of antidepressant drug treatment at the slowest possible pace
4. Antidepressant drug discontinuation
5. Completion of psychotherapy
6. Careful assessment of patient 1 month after drug discontinuation

controlled trials[35,39,43] aimed to reduce recurrence in depression. Further, substantial evidence confirmed relapse prevention effects of MBCT in the treatment of recurrent major depression.[44–52]

A sequential strategy is particularly indicated whenever substantial residual symptoms are present despite response to pharmacotherapy, which appears to be a common finding in clinical practice.[12,53,54] A second indication is provided by recurrent depression. Some individual studies on the sequential integration of pharmacotherapy and psychotherapy were concerned specifically with recurrent depression,[35,43,45–49,55] or benefits were more pronounced in case of recurrent depression.[50,51] A third important indication occurs when the physician or the patient or both intend to interrupt drug treatment. Research findings support the feasibility and favorable long-term outcome of the sequential option of drug tapering and discontinuation when these take place under the close monitoring of the second phase of the sequential treatment,[31] also with close consideration of discontinuation problems that may arise.[56–58]

In Table 2, we illustrate the steps for implementing the sequential approach in recurrent depression. A careful assessment of patients 3 months after starting antidepressant drug treatment, with special reference to residual symptoms, should be the first step. The literature offers interesting tools to be used in this phase. For instance, Kellner's global rating scale for change after treatment (GSC) is a global evaluation of the change due to a treatment with excellent clinimetric properties; change is rated on a 1–9 scale with the following anchor points: 1 = a lot better, 3 = better, 5 = same, 7 = worse, 9 = a lot worse.[36] A second step is the administration of a cognitive-behavioral treatment of residual symptoms, which might include cognitive restructuring and/or homework exposure, and may be followed by another psychotherapeutic strategy such as WBT[41] or MBCT.[40] Thereafter, tapering and discontinuation of antidepressant drug treatment should be scheduled. Finally, psychotherapy should be completed and the patients should be carefully assessed 1 month after drug discontinuation. Once again, an instrument such as the GSC could be used.

The sequential use of psychotherapy after discontinuation of antidepressant medication was found to be significantly more effective in reducing relapse/recurrence compared to control conditions (ie, clinical management or antidepressant drugs).[31] The evidence also suggests that discontinuation of antidepressant drugs is feasible when psychotherapy is provided and may yield enduring results. Indeed, research findings show a greater advantage of the sequential option with drug tapering and discontinuation in preventing relapse or recurrence compared to continuation of antidepressants.[31]

The rationale of the sequential approach is to use psychotherapeutic strategies when they are most likely to make a unique and separate contribution to patient well-being and achieve a more pervasive recovery. The target of psychotherapeutic work is thus no longer predetermined, but varies according to the nature, characteristics, and intensity of the patient's residual symptomatology. Tapering should be performed during psychotherapeutic treatment at the slowest possible pace, to minimize the risk of antidepressant medication discontinuation syndromes.[56–58] Slow tapering may allow the detection of emerging symptoms in their prodromal phases, which may become the target of psychotherapeutic strategy.[21] The advantages of maintaining the patient on antidepressant drugs are not clear, unless one aims to keep pharmacotherapy indefinitely and use the addition of psychotherapy only as a boosting strategy.

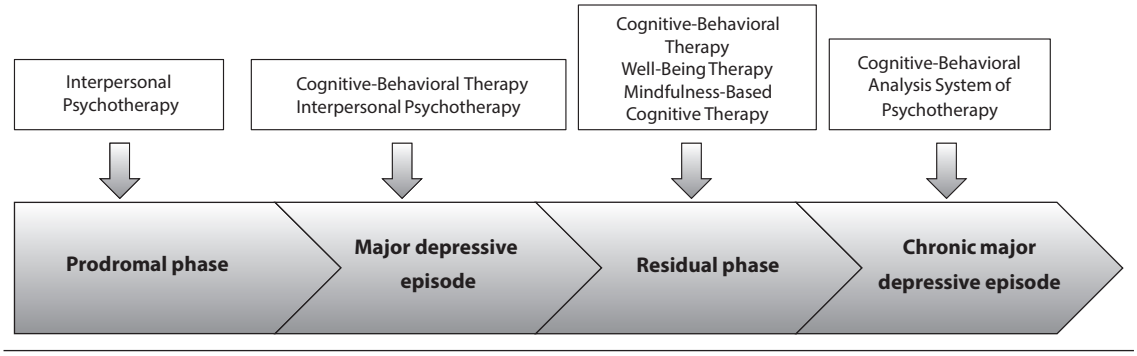
A final aspect of the sequential approach lies in a careful assessment of the patient once both pharmacotherapy and psychotherapy have been terminated. If improvement appears to have occurred, the patient can be seen at regular follow-up visits to help identify early depressive relapses and assess any subclinical symptomatology in case it occurs. If substantial residual symptomatology persists despite clinical response, or minimal/no benefits have been achieved by psychotherapeutic approach, then continuation of drug treatment can be discussed with the patient.

Stages 4 and 5

Recurrence—defined as a new major depressive episode after recovery, that is after at least 6 months without meeting full diagnostic criteria for a major depressive episode—is a common and vexing problem.[59] Approximately 8 of 10 people experiencing a major depressive disorder have 1 or more further lifetime episodes (ie, a recurrent major depressive disorder). In some patients, the episodes are separated by symptom-free years of normal functioning; for others, the episodes become increasingly frequent. This latter course appears to be the more prevalent, in both psychiatric and primary care settings.[60] Incomplete recovery from first lifetime major depressive episode heralds a chronic course of illness, and partial remission between episodes appears to be extremely common[60] and associated with residual disability.[59]

When major depressive episodes are superimposed on preexisting dysthymia (ie, double depression), the prognosis is even worse.[61] Klein and colleagues[62] observed that about 74% of patients with dysthymic disorder who recovered from a major depressive episode for the second time experienced another relapse into depression, for an estimated relapse rate of 93.2%. In addition, about 24% of patients with dysthymic disorder who had recovered had a relapse into chronic depression.[63]

Figure 1. Psychotherapeutic Intervention to Specific Phases of Development of Depressive Disorders



Finally, chronic major depression seems to be frequent. One of 4 patients with nonchronic major depressive disorder progresses to a chronic disorder, while half of the patients with chronic major depressive disorder remain chronic during a 4-year follow-up.[64] As a result, for most people, depression is a lifelong episodic disorder with multiple recurrences (averaging 1 episode in every 5-year period).[64] The adverse economic, interpersonal, and medical consequences (eg, work impairment, family dysfunction) of the course of unipolar depression are considerable.[65]

The cognitive-behavioral analysis system of psychotherapy (CBASP) is a stage-specific psychotherapy developed to treat chronic depression.[66] It has been tested in a large clinical trial[67] and was found to be as effective as pharmacotherapy (33% remission) and most effective in combination with pharmacotherapy (48% remission) in chronically depressed patients. These findings were further confirmed by a recent study comparing CBASP and escitalopram in chronically depressed outpatients.[68] It has also been applied in a clinical trial of CBASP versus regular care in outpatient clinics[69] and appeared to be as effective as standard evidence-based treatments for chronic depression and to yield greater reduction of depressive symptoms in the long term. According to the sequential model, CBASP has been successfully administered after electroconvulsive therapy for the treatment of severe persistent depressive disorder.[70,71]

In conclusion, WBT[41] and MBCT[40] appear to be uniquely suited for addressing a residual phase of depression, while interpersonal psychotherapy has been mainly tested in acute phases. Cognitive-behavioral therapy is the only approach that appears to be suitable for all stages, although, when chronic or double depression occurs, its modification (CBASP) appears to be suitable (Figure 1).

STAGING OF TREATMENT RESISTANCE

Another application of the staging model is the assessment of treatment resistance, which is a frequent problem in depression[10,72] and a challenge for clinicians. There have been various staging methods of classifying treatment resistance,[2] however, such methods have substantial conceptual and clinical weaknesses. First, they do not discriminate clinical deterioration (ie, the condition of the patient is worse than when treatment was started) from nonresponse (ie, the condition is substantially unchanged). Second, they do not take into account clinical phenomena related to tolerance of pharmacologic treatment (ie, loss of clinical effects, paradoxical reactions, resistance after the drug was initially found to be efficacious).[10] Third, they are usually not specifically geared to psychotherapy interventions.

Table 3. Staging of Levels of Psychotherapy Resistance in Depression

Stage	
0	No history of failure to respond to a psychotherapy trial with a technique that is appropriate for the condition
1	No response or insufficient response to 1 appropriate psychotherapy trial
2	No response or insufficient response to 1 appropriate psychotherapy trial associated with pharmacotherapy
3	Worsening after an appropriate psychotherapy trial
4	Failure of 2 or more psychotherapy trials, whether associated with pharmacotherapy or not

An issue that is frequently overlooked at this stage is the fact that the current patient's chronic symptomatology may have developed over the years and be an "iatrogenic comorbidity," that is, the lasting effects that previous treatments may entail, well beyond their time of administration.[73] Examples may be provided by switching into a bipolar course, by persisting affective lability a long time after discontinuation of paroxetine, or by generalized unresponsiveness after switching and augmentation with antidepressant drugs. Iatrogenic comorbidity may, thus, affect the outcome of a trial by contributing to the treatment resistance of a patient.

Negative effects may also occur as a result of psychotherapeutic treatment, whether due to techniques, patient or therapist variables, or inappropriate use.[74] Such experiences may affect new treatments that are offered and represent iatrogenic comorbidity as well.[73] Table 3 suggests

a staging method for assessing treatment resistance and clinical deterioration during psychotherapy of depression.

Motivation to treatment and changing behavior has also been submitted to a staging system and may yield valuable insights into psychological resistance of the patient. Di Clemente and Prochaska[75] developed a helpful staging method: "precontemplation" (ie, people do not recognize that a problem exists and have no intention to change), "contemplation" (ie, individuals accept that a problem exists but are ambivalent about it), "preparation/determination" (ie, a perceived discrepancy between current and desired study), "action," and "maintenance" of the new patterns. It is difficult to suggest a psychotherapeutic treatment, despite pertinent indications, to a patient who is in the "precontemplation" stage. However, staging is seldom considered, particularly in randomized controlled trials of psychotherapy.

TIMING AND SELECTING TREATMENT

In psychiatry, as in other fields of medicine, there is increasing awareness of the need for augmenting practice guidelines with patient-specific recommendations that take into account individual variables and history, as well as previous treatment responses.[21] The American Psychiatric Association's 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 sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes."[20(p9)] However, this is what occurs in clinical practice, although it is often dismissed as an expression of highly subjective clinical evaluation. In addition, clinical guidelines seem to ignore that the selection of a treatment according to evidence-based medicine relies primarily on randomized controlled trials/meta-analyses and can be properly applied only to the "average" patient.

Clinical guidelines also tend to underestimate that customary clinical taxonomy does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same diagnosis.[2] Further, clinical guidelines tend to ignore that depressed patients appear to express stronger preferences for psychotherapy than for antidepressant medications, a finding that is of considerable clinical importance given that treatment preference is a potent moderator of response to therapy.[21]

Forand et al[76] have reviewed the complex literature that is concerned with combining medication and psychotherapy in the treatment of major mental disorders. What emerges from their analysis is the fact that a combined treatment does not necessarily mean a better treatment and that there is the need for proper assessment tools to evaluate the pros and cons of each approach.

The clinical selection of treatments (including psychotherapy) has been impoverished by an exclusive reliance on diagnostic criteria that may not reflect the complex thinking underlying therapeutic decisions in clinical psychological and psychiatric practice.[8] A considerable improvement in the accuracy of clinical judgment has been addressed,[8] particularly to the extent that it is guided by clinimetrics, the science of clinical measurement.[77–80] Psychotherapy trials are often concerned with a flat, cross-sectional view of disorders (*DSM* diagnoses) that ignores longitudinal development of disturbances and previous treatment history. There is pressing need of randomized controlled trials using staging methods in the selection of patients.

This critical review thus suggests the importance of applying psychotherapy to depression according to an individualized treatment plan encompassing clinimetric characterization and not as an undifferentiated solution regardless of treatment history, staging, comorbidity, and patient's preferences.

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