Treatment-Resistant Depression

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Treatment-resistant depression (TRD) is a common clinical occurrence among patients treated for major depressive disorder. However, a clear consensus regarding the criteria defining TRD is lacking in the psychiatric community. Many patients who are considered treatment resistant are actually misdiagnosed or inadequately treated. Clinicians need to accurately diagnose TRD by examining primary and secondary (organic) causes of depression and acknowledging paradigm failures that contribute to a misdiagnosis of TRD. A correct determination of what constitutes TRD requires consensus on criteria of treatment response (i.e., dose, duration, and compliance) and on the number of adequate trials required before a patient is determined to be nonresponsive. Additionally, clinical validation of available staging models needs to be completed. While several studies have identified predictors of nonresponse, clinical studies investigating the predictors of resistance following the failure of 2 or more antidepressant trials should be pursued. In managing TRD, 3 pharmacotherapy strategies are in clinical use: optimization of antidepressant dose, augmentation/combination therapies, and switching therapies. However, the optimal strategy for treating TRD has yet to be identified. Therefore, further controlled clinical trials are essential to identify the most effective treatment strategies.

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In major depressive disorder (MDD), complete remission of symptoms is the optimal therapeutic goal.[1] Remission occurs when the patient fully recovers psychosocial functioning with a minimal burden of residual effects. However, despite the rapid evolution of pharmacologic therapies over the past 50 years, research shows that only 60% to 70% of patients who are tolerant to antidepressants will respond to first-line monotherapy,[2] and more than one third of patients treated for depression will become treatment resistant.[3] In the past several years, the focus on treatment-resistant depression (TRD) has increased sharply.[4]

Several studies have demonstrated that a significant proportion of patients treated for depression do not achieve full remission. In a meta-analysis of placebo-controlled, double-blind studies conducted by Fava and Davidson,[3] data suggested that 29% to 46% of depressed patients treated with standard-dose antidepressants for at least 6 weeks failed to respond fully. Specifically, 12% to 15% of patients studied attained only a partial response, whereas 19% to 34% of this population was nonresponsive. In another meta-analysis, Golden et al.[5] reviewed 25 double-blind trials involving 4016 patients and found that more than 50% of patients treated with a single antidepressant failed to reach full remission. Even among patients considered to be full responders to a clinical trial of a single antidepressant, Nierenberg et al.[6] noted patients still experienced a significant burden of residual symptoms such as insomnia and fatigue. Paykel et al.[7] found residual symptoms to be associated with an increased risk of relapse in 76% of patients studied.

These studies focused on single antidepressant trials, but results of sequential treatments show no significant improvement in responsiveness either. A chart review by Petersen et al.[8] assessing treatment outcome in MDD patients at an academic psychiatric specialty clinic found that only 50% of patients achieved full remission. The remaining patients experienced either a partial response or no response.

PSEUDORESISTANCE VERSUS TREATMENT RESISTANCE

When assessing TRD, the phenomenon of *pseudoresistance* must be carefully considered.[9] Major causes of pseudoresistance include inadequate dosing and/or early discontinuation of treatment prior to completion of an

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adequate trial, atypical pharmacokinetics that reduce agent effectiveness, patient noncompliance due to adverse effects, and misdiagnosis of the primary disorder, i.e., other mood disorders or depressive subsets mistreated as unipolar depression. For example, evidence shows that a substantial proportion of patients with major depression referred to specialty settings are typically undertreated and receive inadequate doses of antidepressants.[10] Therefore, many patients believed to be treatment resistant are actually pseudoresistant.[11]

The lack of a clear consensus in the psychiatric community regarding the criteria for TRD also contributes to the misidentification of patients as treatment resistant.[11] Generally the term has been used to identify patients with MDD who are nonresponsive to conventional therapeutic approaches.[12] However, standardization regarding what constitutes treatment adequacy during antidepressant trials—dose, duration, and compliance—is essential. Nonresponse to a single trial of an antidepressant should not be considered resistance, but patients who experience a second failure of a second antidepressant trial of adequate dose and duration embody the truly resistant cases.

KEY PARAMETERS OF TREATMENT-RESISTANT DEPRESSION

Several factors are important when treating nonresponsive depression, including the need for an accurate diagnosis, the criteria of treatment response, the number of adequate trials required, and adequate treatment guidelines.

Making the correct primary diagnosis is of the utmost importance in treating patients with depression.[11] Additionally, secondary causes of depression need to be identified during diagnosis.[9] Organic causes of depression include medications, substance abuse, metabolic disorders, and other medical conditions. Evidence demonstrates that treatment strategies vary significantly in effectiveness depending upon diagnosis, i.e., psychotic depression, bipolar depression, atypical depression, unipolar depression, and other subtypes of depression.[9,11] Misdiagnosis of patients may present major consequences and contribute to treatment failure and the mislabeling of the patient as treatment resistant.

Patients with TRD should be thoroughly evaluated for the presence of comorbid psychiatric or general medical disorders.[9] Anxiety disorders, substance abuse, and Axis II personality disorders are frequently cited as comorbid conditions predicting nonresponse to antidepressant therapy. Additionally, the effects of psychosocial stressors should be taken into account when assessing treatment outcome in depressed patients.

Defining satisfactory clinical response as it pertains to resistance in depression is a complicated issue.[13] Responses are typically determined through various rating scales such as the Hamilton Rating Scale for Depression (HAM-D) by gauging the percentage of symptomatic response against baseline symptom severity.[14] On the basis of clinical research consensus, response is usually defined as a 50% or greater decrease in scores at trial endpoint compared with baseline assessment scale scores.[13,15] The concept of remission is also used to assess treatment response to antidepressants. Remission refers to full response or a score below or equal to 7 on the 17-item HAM-D. However, determining what comprises a satisfactory clinical response can be difficult to interpret given the variety of findings in the available literature.

The number of adequate failed trials required to declare a patient treatment resistant has also been a subject of controversy. Several definitions of TRD exist, depending on the number of trials completed, the type of antidepressant received (agents from the same class or agents/therapies from different classes), or both. TRD has been variously defined as failure to respond to one trial of antidepressant monotherapy, as failure to respond to 2 or more trials of different antidepressant monotherapies, or as failure to respond to 4 or more various antidepressant trials, including augmentation, combination, and electroconvulsive therapy (ECT).[13]

Finally, the criteria comprising adequate treatment must be resolved before a definition of treatment resistance can truly be developed. While several antidepressant clinical trials have demonstrated minimum dosages necessary in order to achieve a therapeutic response, the administration of inadequate dosage remains an issue.[11] In addition, little consensus exists regarding the adequate duration of an antidepressant trial before a patient is pronounced treatment resistant. Patient compliance also is a key factor; a patient should not be classified as nonresponsive if he or she has not adhered to the prescribed treatment regimen.

PARADIGM FAILURES CONTRIBUTING TO TREATMENT-RESISTANT DEPRESSION

TRD may emerge from a variety of factors. In a recent 2-year study, Parker et al.[16] studied 164 outpatients with a severe and/or treatment-resistant mood disorder. Six paradigm errors (Table 1) were identified as contributing to the mislabeling of patients as treatment resistant when in reality they were inadequately diagnosed and treated. In fact, 82% of the sample were diagnosed with some level of treatment resistance.

By identifying and applying these paradigm failures and other additional factors in clinical decision making, clinicians can more accurately assess patients during the diagnosis and management phases.[16] Patients who are considered to be treatment resistant may in actuality be pseudoresistant when these paradigm errors are taken into account, and their illness could be more adequately managed.

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Table 1. Paradigm Errors Identifying Potential Antidepressant Treatment Failure[a]

Paradigm Error	Description	Quantifying Data
Paradigm error 1	Failure to diagnose and manage bipolar disorder	> 30% of patients never diagnosed with or treated for bipolar disorder
Paradigm error 2	Failure to diagnose and manage psychotic depression	5 patients (3%) incorrectly diagnosed with psychotic depression by referring physician
Paradigm error 3	Failure to diagnose and manage melancholic depression	> 70% of patients misdiagnosed with non-melancholic depression by referring physician (46% satisfied criteria for DSM-IV melancholia; 28% for clinical melancholia). ≤ 77% of patients treated with an SSRI rather than a TCA, MAOI, or SNRI
Paradigm error 4	Diagnosing and/or managing a non-melancholic condition as if it were melancholic depression	54 patients misdiagnosed with melancholic depression. 93% experienced ≥ 1 contributing psychosocial factor. Adequate psychotherapy (91%) and/or social support/interventions (59%) were not administered to address these factors
Paradigm error 5	Misdiagnosing secondary depression	Comorbid psychiatric conditions (ie, anxiety, panic, social phobia, obsessive-compulsive behavior, and other personality functioning disorders) found to be inadequately diagnosed in patients
Paradigm error 6	Failing to identify organic determinants	≤ 10% of patients assessed to have other medical conditions, such as dementia or stroke, which had not been considered as contributing to patient's depression

[a]Data from Parker et al.[16]
Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 2. Thase and Rush Model for Staging the Levels of Treatment-Resistant Depression[a]

Stage I:	Failure of at least 1 adequate trial of 1 major class of antidepressant
Stage II:	Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in Stage I
Stage III:	Stage II resistance plus failure of an adequate trial of a TCA
Stage IV:	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V:	Stage IV resistance plus failure of a course of bilateral ECT

[a]Adapted from Thase and Rush,[18] with permission.
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

DEFINITION AND STAGING OF TREATMENT-RESISTANT DEPRESSION

Several guidelines or staging methods outline specific requirements (e.g., the number of adequate trials, dosage, duration, and types of agents) that must be obtained prior to the patient's diagnosis as treatment resistant. These methods vary in the degrees of resistance described. Some of the more commonly accepted staging definitions that are in use today include the Committee for Proprietary Medicinal Products (CPMP) guidance,[17] the Thase and Rush staging method,[18] the Massachusetts General Hospital staging method,[8,19] and the Souery et al.[20] operational criteria for TRD.

CPMP Guidance

CPMP is the section of the European Medicines Agency that defines the basic principles for agents being considered for particular medical indications. The CPMP guidance[17] for the evaluation of antidepressants states that "a patient is considered therapy resistant when consecutive treatment with 2 products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect."[17(p4)] However, "a sufficient length of time" and "adequate dose" are not defined. The concept of class corresponds to the mechanism of action of the product but does not indicate if agents with similar mechanisms of action belong to the same class or different classes.

Thase and Rush Staging Model

Thase and Rush[18] proposed a model for staging the 5 levels of TRD (Table 2). Although the Thase and Rush staging system is a useful tool in clarifying treatment resistance in depression, several methodological issues exist[8,19]; for example, the dosing and duration of each trial are not thoroughly explained. Stage I fails to address whether nonresponse to only 1 trial is actually resistance and does not account for 2 consecutive selective serotonin reuptake inhibitor (SSRI) trials. One common explanation for nonresponse may be that the patient has resistance to a particular compound but not to the class of agents as a whole. Another explanation may be that the patient was misdiagnosed and mistreated.

Additionally, a hierarchy of treatment is implied with this staging system—monoamine oxidase inhibitors (MAOIs) are considered to be more effective than tricyclic antidepressants (TCAs), while TCAs are considered to be more effective than SSRIs.[8,19] In Stage II, by switching to an antidepressant in a different class, the assumption is made that switching to an agent in the same class would be less effective.[19] This system also implies that it is more difficult to treat nonresponse after 2 trials of agents from different classes than it is to treat nonresponse after 2 trials of agents in the same class.[8,19] Therefore, for example, pa-

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tients in Stage IV are assumed to have a more severe resistance profile compared with patients in Stage I who have had only 1 failed trial. Additionally, this system does not consider augmentation or combination strategies.[19]

Massachusetts General Hospital Staging Method

Compared with the Thase and Rush staging model, the Massachusetts General Hospital (MGH) staging method[8] is a more quantitative model producing a continuous variable that represents the degree of treatment resistance by scoring the number of trial failures as well as the intensity and optimization of various therapies (Table 3). It is important to note that antidepressant nonresponse is scored regardless of class or mechanism of action, and a trial duration of at least 6 weeks is required. Therefore, this method makes no assumptions regarding an antidepressant class hierarchy. Augmentation/combination treatments are also included with this method. A recent study[8] reported that the MGH staging method was more closely predictive of ultimate remission than the Thase and Rush staging model.

Table 3. Massachusetts General Hospital (MGH) Staging Method for Quantifying Treatment-Resistant Depression[a]

Stage	Description	Points Toward Score of Resistance
1	Nonresponse to each adequate (at least 6 weeks of an adequate dose of antidepressant) trial of a marketed antidepressant	1 point per trial (overall score of resistance)
2	Optimization of dose, optimization of duration, and augmentation/combination of each trial (based on the MGH or Antidepressant Treatment Response Questionnaire)	0.5 point per trial per optimization/strategy
3	Electroconvulsive therapy	3 points

[a]Based on Petersen et al.[8]

Souery et al. Operational Criteria for TRD

An alternative staging system has been proposed by Souery and coworkers,[20] comprising a team of North American and European researchers. While this method is similar to the MGH method, it differs in that treatment resistance is considered to begin following at least 2 consecutive failed trails and instead of after nonresponse to 1 adequate antidepressant therapy of any class (including ECT) for 6 to 8 weeks (Table 4). This method also acknowledges that patients may have chronic resistant depression after 1 year of nonresponse to multiple therapies.

IDENTIFICATION OF PREDICTIVE FACTORS OF RESISTANCE TO ANTIDEPRESSANTS

Predictors of resistance to a single antidepressant treatment and predictors of resistance to multiple antidepressant treatments differ. Predictors of nonresponse may include Axis II personality disorders, anxiety comorbidities, and delay in initiating treatment. Many of these predictors are considered to additionally predict resistance. However, there is a lack of clinical studies investigating predictors of resistance following at least 2 failed trials of antidepressant therapy.

A European multicenter study from the Group for the Study of Resistant Depression (GSRD) is currently examining the predictive factors associated with resistance, defined as nonresponse to multiple (at least 2 trials), adequate, and consecutive antidepressant treatments received during the most recent depressive episode (D.S., P. Oswald, S. Kasper, et al.; unpublished data, 2006). This 7-center study will be a true treatment-resistance study—not just a nonresponse study—with multiple clinical demographic data available for analysis and will be available in a future publication.

Data to be collected include current and previous antidepressant treatments received during the last episode, treatment name and class, treatment duration, dose, and patient compliance. An antidepressant trial lasting at least 4 weeks at optimal dose as indicated in the product information is considered adequate treatment for this study. The data will be used to define treatment resistance within the sample and to assign patients to 2 different categories: resistance and nonresistance. Patients assigned to the nonresistance category include those patients who achieve a response at the completion of the first trial as well as those patients who failed to respond to the first antidepressant treatment but responded at the end of the second trial. Because the resistance status requires at least 2 consecutive antidepressant treatments, patients with nonresponse to a single antidepressant trial will not be included in the logistic regression analyses for predictive factors.

Although this study has not been completed, preliminary results suggest that qualitative measures, such as comorbid disorders and intensity and features of the current episode, should be added to the quantitative staging of resistant depression so that not only the number and type of antidepressants received are examined, but the phenomenological profile of the depressive episode is considered as well.

SELECTED TREATMENT STRATEGIES IN TREATMENT-RESISTANT DEPRESSION

Three basic strategies exist for treating TRD: (1) optimizing antidepressant dose, (2) augmenting or combining therapies, and (3) switching therapies.[2,13,14] No conclusive data identify the optimal strategy,[21] and these strategies should be further evaluated using validated definition(s) of TRD.

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Table 4. Souery et al. Model for Staging Treatment-Resistant Depression (TRD) and Chronic Resistant Depression (CRD)[a]

Stage	Definition	Duration of Trial
A: Nonresponder	Nonresponse to 1 adequate trial of TCA, SSRI, MAOI, SNRI, ECT, or other	6–8 wk
B: TRD	Resistance to 1 or more adequate antidepressant trials	TRD 1: 12–16 wk TRD 2: 18–24 wk TRD 3: 24–32 wk TRD 4: 30–40 wk TRD 5: 36 wk to 1 y
C: CRD	Resistance to several antidepressant trials, including augmentation strategy	At least 12 mo

[a]Based on Souery et al.[20]
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Dose Optimization/Augmentation and Combination Treatment Strategies

In maximizing initial treatment, strategies include extending the initial antidepressant trial or adjusting the dose.[2] As for augmentation and combination strategies, some common add-on agents include lithium,[2,22] thyroid hormones such as liothyronine (triiodothyronine),[2,22] reserpine,[2] antiepileptic agents[2,22] (valproic acid, carbamazepine, lamotrigine), atypical antipsychotics[2,22] (olanzapine, clozapine, risperidone), or psychostimulants[2,22] (methylphenidate). Another option is augmenting an SSRI with another agent[2] such as pindolol[21,22] or adding another antidepressant (reboxetine[22] or mirtazapine[21–23]).

Switching Treatment Strategies

In determining switching strategies for TRD, a review of the literature shows a lack of adequate, placebo-controlled studies with large sample sizes.[2] The majority of studies are open-label trials with a small patient population. Common switching strategies with some supporting evidence include switching from one TCA to another[2,24,25]; switching from one TCA to a second-generation heterocyclic[2]; switching from a TCA or heterocyclic to an SSRI[2,26–32]; switching from an SSRI to a TCA,[2,21] a serotonin-norepinephrine reuptake inhibitor (SNRI),[21,33–37] bupropion,[21,38,39] or another norepinephrine reuptake inhibitor; switching from one SSRI to another[2,21,40–42]; or switching to an MAOI.[2,43–46]

Studies show that when patients are switched from an SSRI, the most commonly prescribed type of antidepressant, to an SNRI, there is a 30% to 60% chance of response.[33–37] However, if the patient is switched to an agent in the same class (i.e., from one SSRI to another SSRI), a 40% to 50% response rate may occur.[40–42] Switching from one type of TCA to another TCA shows a poorer response rate.[24,25]

Optimizing Initial Treatment

Given the evidence, the strategy of preventing TRD by selecting the optimal initial treatment (either agents or therapies) with the highest chance of success in preventing treatment resistance may be the most effective option.[47] In selecting the treatment with the highest rate of success, evidence shows that treatment with certain agents and strategies may be associated with greater remission rates, such as venlafaxine rather than SSRIs[33] or augmenting SSRI treatment with mirtazapine.[48] Treatment with agents such as SNRIs[33] and mirtazapine[21] may result in a rapid response rate. Other agents or strategies may result in a greater resolution of specific depressive symptoms, such as mirtazapine for insomnia,[49] benzodiazepines plus SSRIs for anxiety[50] and insomnia,[51] duloxetine for painful symptoms of depression,[52] or venlafaxine for psychiatric and somatic anxious symptoms of depression.[53] While most double-blind comparator studies on TRD published to date employ TCAs[54] or SSRIs[1,13] as a treatment starting point, perhaps a change in the standard of treatment care for depression is necessitated, using other first-line treatments and phasing out the TCAs.[25,47]

Sequenced Treatment Alternatives to Relieve Depression

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[1,13,55,56] sponsored by the U.S. National Institute of Mental Health will determine the best subsequent treatment strategies (i.e., identifying which combinations and which sequences of treatment are effective with minimal side effects) following nonresponse of an initial monotherapy with citalopram. This multisite, prospective, sequentially randomized controlled trial targeted 4000 adults with nonpsychotic major depressive disorder. Following treatment failure at each of the 4 sequential levels, patients progressed to the next level, where they were randomly assigned to the various treatment options (Figure 1). Independent evaluators, blinded to level and treatment, conducted periodic clinical outcome assessments. These additional results will provide information on symptom severity, level of functioning, adverse effect burden, patient satisfaction/quality of life, and health care utilization and cost.[1] Once patients have obtained a satis-

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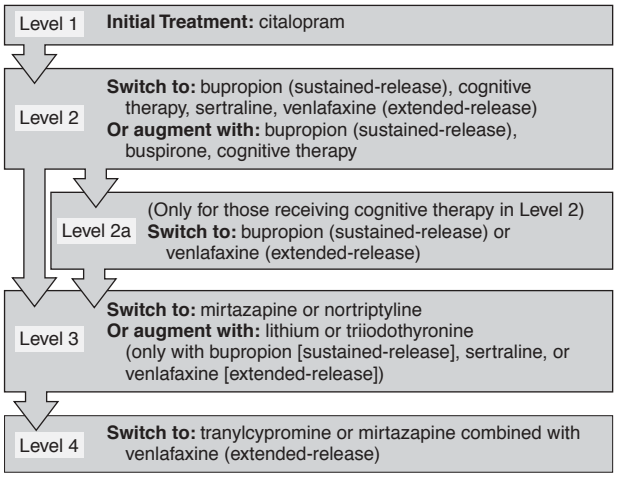
Figure 1. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Algorithm[a]



[a]Adapted from Rush et al.,[56] with permission.

factory response, follow-up assessment will determine the degree and timing of possible relapse. Results are expected to provide clinicians with possible solutions on the optimal sequence of treatment for the various degrees of TRD.[56]

CONCLUSIONS

Although TRD is a common clinical occurrence,[19] a greater consensus is required regarding the definition and operational criteria for staging response and resistance to antidepressant treatments. In order to revamp our understanding of TRD, more clinical trials examining treatment resistance rather than response are needed, as are trials validating the available staging models and identifying effective treatment strategies. Predictive factors must be identified to recognize patients who are more likely to experience resistance following 2 adequate, consecutive antidepressant trials. Pharmacogenomic studies also are needed to assist in identifying biological predictive factors. Once this information is obtained, appropriate controlled therapeutic studies are essential to validate clinical criteria and neurobiological predictive factors.

REVIEW QUESTION

Ms. A, 47-year-old married housewife, is a new patient who reports difficulty sleeping, depressed mood, feelings of worthlessness, anxiety, pessimism, and occasional thoughts of suicide. She states that she does not enjoy things that she used to enjoy. She has told herself to "get over it" but cannot do it.

Her previous clinician has referred her to you. That clinician had prescribed an SSRI, which she took regularly for 6 weeks, with only mild improvement. He then decided to gradually switch her to a different SSRI. Six weeks after completing the switch to the new SSRI, Ms. A still reports only mild improvement in mood, sleeping, feelings of self-worth, and anxiety. She still does not enjoy activities that she used to enjoy and wonders if she will ever really enjoy life again, and she still has occasional thoughts of suicide.

Do you consider Ms. A to be treatment-resistant? What course of treatment would you recommend?

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), duloxetine (Cymbalta), lamotrigine (Lamictal), liothyronine (Cytomel, Triostat, and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Metadate, Ritalin, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), pindolol (Visken and others), reserpine (Serpalan and others), risperidone (Risperdal), sertraline (Zoloft), tranylcypromine (Parnate), valproic acid (Depakene, Myproic Acid, and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, buspirone, carbamazepine, clozapine, lamotrigine, liothyronine, lithium, methylphenidate, olanzapine, pindolol, reserpine, risperidone, valproic acid, and reboxetine have not been approved by the U.S. Food and Drug Administration for the treatment of depression.

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