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STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Psychiatry Board Review Manual* is a study guide for residents and practicing physicians preparing for board examinations in psychiatry. Each manual reviews a topic essential to the current practice of psychiatry.

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Treatment-Resistant Depression

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INTRODUCTION

Refractory depression, also called treatment-resistant depression, is commonly encountered by mental health professionals, even in the context of treatment with appropriate antidepressants. Approximately half of depressed patients have an inadequate response to monotherapy,[1–4] and as many as 20% have chronic depression despite multiple interventions.[5,6]

Treatment-resistant depression can be broadly defined as a failure to respond completely to a treatment known to be effective for major depression. However, in clinical practice, treatment-resistant depression is best defined as occurring along a continuum ranging from partial response to complete refractoriness, in which the degree of treatment resistance is ascertained by taking into account such factors as total number of antidepressant trials and their outcome, the number of failed treatments, and the degree of lack of response.[3,7] Proposed operational definitions for treatment-resistant depression terminology are shown in **Table 1**.

Treatment-resistant depression may contribute to the overwhelming morbidity and mortality rates associated with affective illness [8,9] and account for a disproportionate amount of physician treatment time. This manual reviews the approach to evaluation and treatment of the patient with treatment-resistant depression.

CASE STUDY

INITIAL PRESENTATION

A 65-year-old woman with a history of chronic back pain presents to the clinic for treatment of recurrent and severe major depressive disorder.

HISTORY

The patient reports a 2-month history of worsening depression, initial insomnia and early morning awakening, anergia, seclusion, hopelessness and helplessness, decreased appetite, and a weight loss of 10 lb. She has also stopped engaging in her hobbies of painting and playing music.

The patient was diagnosed with major depressive disorder 25 years earlier and had been treated ever since with adequate courses of various tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) monotherapies, nefazodone, and a combination of citalopram and bupropion. Her previous psychiatrists had also tried augmentation with lithium and triiodothyronine (T_3) but saw only partial improvement. She is currently being treated with a combination of escitalopram 20 mg/day and mirtazapine 30 mg once daily at night. The patient remains chronically depressed with a regular score of 15 or higher on the 21-item Hamilton Depression Rating Scale.

PHYSICAL EXAMINATION

The patient is a thin, frail, elderly woman who looks older than her stated age. Her speech is slow and impoverished, but she is oriented to place and person. She describes her mood as sad, and her affect is restricted and dysphoric. Her thought process is goal-directed and thought content is without any apparent delusions or preoccupations. She denies any suicidal ideations. No evidence of perceptual abnormality is found. No deficits are noted in her attention and concentration, and she has a good insight into her illness.

- **What is the approach to evaluation of the patient with treatment-resistant depression?**

In evaluating a patient with treatment-resistant depression, a careful history of all previous treatments must be elicited. Thase and Rush[10] provide a practical system for staging treatment-resistant depression based on previous courses of treatment (**Table 2**). This system can be used as a guide for applying treatment strategies.

It is important to differentiate between true treatment resistance and pseudoresistance. Failure to provide adequate treatment, ie, prescribing inadequate doses of medication or treating for too short a duration, is a major cause of pseudoresistance. Patient factors that may contribute to pseudoresistance include premature discontinuation of medications due to intolerable side effects or

Table 1. Proposed Terminology for Treatment-Resistant Depression

Treatment nonresponse: a response that is poor enough such that a change in treatment plan is required (eg, < 50% reduction in Hamilton Depression Rating Scale score)

Treatment response: a response that is good enough such that a change in treatment plan is not required (eg, ≥ 50% reduction in Hamilton Depression Rating Scale score)

Remission: attainment of asymptomatic stage (eg, score ≤ 7 on Hamilton Depression Rating Scale) for 2 consecutive months

Recovery: remission for at least 6 consecutive months

Treatment-resistant depression: there has been only a partial response to treatment; patient meets criteria for nonresponse

Treatment-refractory depression: there has been no response to treatment; symptoms unchanged or worse

Adapted with permission from O'Reardon JP, Amsterdam JD. Treatment-resistant depression: progress and limitations. Psychiatr Ann 1998;28:634.

Table 2. Staging Criteria for Treatment-Resistant Depression

Stage	Description
0	No single adequate trial of medication
1	Failure of at least 1 adequate trial of an antidepressant
2	Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants
3	Stage 2 resistance plus failure of an adequate trial of a tricyclic antidepressant
4	Stage 3 resistance plus failure of an adequate trial of a monoamine oxidase inhibitor
5	Stage 4 resistance plus failure of a course of bilateral electroconvulsive therapy

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patient noncompliance as a result of poor understanding of the illness and negative feelings and thoughts about medication.[11] Community-based surveys have revealed that less than 50% of patients receive either an adequate dose or an adequate duration of antidepressant treatment.[12] Regarding dosing, unusual pharmacokinetics (eg, rapid metabolism, malabsorption) in a patient may lead to low serum levels of antidepressant, thereby diminishing effectiveness. For some antidepressants, a plasma level–clinical response relationship has been defined, and drug efficacy may be correlated with adequate plasma levels.[13] While higher doses of antidepressants may be effective in some treatment-resistant patients,[14,15] excessive dosing with SSRIs may not be required, although an extended treatment time may be warranted.[16] As previously noted, the duration of a particular drug treatment is very important. Earlier studies suggest that antidepressants at the therapeutic dose for a minimum of 3 weeks would qualify as an adequate duration of trial for most patients[17]; however, current clinical practice indicates that this is too short. Some experts suggest that the maximum tolerable dose should be given for at least 4 to 6 weeks when treating partial or nonresponders.

PREDICTORS OF NONRESPONSE

Assessment of treatment-resistant depression should include careful attention to various factors that may increase the likelihood of nonresponse to antidepressants. Some specific subtypes of major depression have been found to predict poorer response to antidepressant treatment. For example, psychotic depression responds poorly to antidepressant monotherapy; combination therapy with an antidepressant and an antipsychotic or a course of electroconvulsive therapy (ECT) is usually an effective treatment strategy.[18] Atypical depression, defined by mood reactivity, hypersomnia, hyperphagia, laden paralysis, and rejection sensitivity, was found to be relatively less responsive to TCAs than monoamine oxidase inhibitors (MAOIs).[19,20] Patients with double depression (a major depressive episode superimposed on dysthymia) took much longer to recover completely.[21] In addition, a missed diagnosis of bipolar disorder is common and has major implications with regard to treatment response.[22] Patients with seasonal affective disorder usually show poor response to TCAs.[23]

Studies evaluating predictors of outcome have found that a positive family history of affective illness, extremes of age at onset of depression, and severity and chronicity of illness are linked to treatment resistance.[24–28] Generally, gender has not been found to be a risk factor for treatment-resistant depression, although it may be a factor in predicting response to one type of antidepressant versus another. For example, women have a better treatment response with SSRIs or MAOIs as compared with TCAs.[29]

- **What conditions are commonly cormorbid in depression?**

Table 3. General Medical Conditions that Contribute to Treatment-Resistant Depression

Endocrinopathies
Thyroid disease
Hyperadrenocorticism
Immune-mediated disorders
Infectious diseases (eg, HIV, tuberculosis, syphilis)
Neoplastic processes
Neurologic disorders
Cerebrovascular disease
Parkinson's disease
Sleep disorders
Autoimmune disorders
Systemic lupus erythematosus
Multiple sclerosis

Comorbidity can be defined as any condition other than the illness under treatment or investigation. Keitner and colleagues[30] reported that more than half of patients admitted with major depression have coexisting Axis I, II, or III conditions (termed *compound depression*). Patients with compound depression were found to have lower recovery rates than patients with depression alone.

COMORBID PSYCHIATRIC CONDITIONS

Numerous studies have reported an association between comorbid psychiatric conditions and treatment-resistant depression.[31–33]

Anxiety disorders often coexist with depression and may confer a poorer prognosis.[34] Patients with high anxiety ratings on psychologic scales have slower rates of recovery and incomplete remission of symptoms.[35] Coryell et al[31] noted that depressed patients with panic attacks have a poorer outcome and are most likely to be chronically depressed. Hence, depressed patients with comorbid anxiety tend to be more severely depressed, and as a result, clinical evaluation of refractory depression must include screening for anxiety symptoms and disorders.

Comorbid substance abuse is also very common in depression and adds additional complications for treatment.[36] Because of their acute and chronic effects, substances may worsen depression and can lead to treatment-resistant depression. In clinical studies, ongoing substance abuse was found to be a major contributor to partial or no response to antidepressant treatment, making it a leading cause of treatment-resistant depression.[37]

A significant proportion of patients with depression have comorbid personality disorders. Estimates of prevalence of personality disorders in depressed individuals range from 30% to 70% (mean, 50%).[38–41] Patients with comorbid personality disorders have a poor response to antidepressants and a worse prognosis for long-term outcome.[42] Other common comorbid psychiatric disorders that occur with depression include obsessive compulsive disorder and eating disorders.[43,44] In evaluating patients with treatment-resistant depression, identifying pathologic personality traits or disorders may provide important clues for future treatment plans.

COMORBID MEDICAL CONDITIONS

Depression is prevalent in medically ill patients. Hall and colleagues[45] reported that unrecognized medical illness may either cause or contribute to depression in as many as 50% of patients. Among the general medical conditions associated with depression, endocrinopathies are the most common, with disturbances in thyroid function leading the list.[46,47] There is also close connection between disturbances in the hypothalamic-pituitary-adrenocortical axis and treatment-resistant depression. These disturbances are most commonly manifested by excessive corticosteroid production. It has been estimated that 40% to 90% of patients with Cushing's syndrome have associated depression.[48] In addition to endocrine disorders and some metabolic conditions, some neoplastic, immunologic, hematologic, and neurologic disorders have also been associated with treatment-resistant depression (**Table 3**).

Conditions that can be considered both medical and psychiatric, such as fibromyalgia, chronic fatigue syndrome, premenstrual dysphoric disorder, and irritable bowel syndrome, also are often associated with depressive symptoms. These conditions tend to be underrecognized and undertreated; therefore, it is vital to exclude them before making a diagnosis of treatment-resistant depression.

- **How is refractory depression treated?**

MANAGEMENT OF REFRACTORY DEPRESSION

At present, there are no compelling data that would inform the clinician how to definitively treat refractory depression, and there are very few studies that compare competing strategies. The main strategies include optimizing existing treatment, switching medications, augmentation, combining antidepressants, adding psychotherapy, and finally, ECT.

Optimizing Existing Treatment

The first recommended strategy for managing poor response is to ensure that patients receive an adequate dose of medication for an adequate length of time. Unfortunately, many patients receive multiple inadequate trials, and in those circumstances, it is worth revisiting medications used in the past because higher doses may prove effective.

Some experts suggest that if the patient demonstrates initial refractoriness to conventional doses of medication, the dose should be titrated to the maximum tolerable level within the recommended range and be continued for 4 weeks in complete nonresponders or 6 weeks in partial responders before abandoning therapy.[49,50] However, others have suggested even longer periods of treatment to assure adequacy.[51]

Switching to Another Antidepressant

If there is no or minimal response after an adequate trial of antidepressant, switching to another antidepressant is an effective strategy. Switching medication may also be a better option for patients who have milder illness. Advantages of switching versus augmentation are lower costs of medication, fewer potential side effects, less risk of drug-drug interaction, and better patient compliance.[52,53]

There are insufficient data to guide the switching to another medication within the same class versus a different antidepressant class. Most patients are started on an SSRI. In case of initial SSRI failure, there are few studies that report a reasonable chance that patients will respond to another SSRI.[54,55] Current recommendations support switching to an antidepressant of a different class in the event that 2 antidepressants of the same class are ineffective.[56] Switching from an SSRI to a TCA has shown better success rates. Peselow et al[57] noted a 73% response rate among paroxetine nonresponders when switched to imipramine. If a clinician determines that a switch from a TCA is indicated, there is a variety of additional antidepressants. Switching within the class from secondary amines (ie, nortriptyline, desipramine, protriptyline) to tertiary amines (ie, imipramine, amitriptyline, clomipramine) may be a reasonable consideration. Efficacy of MAOIs over TCAs in patients not responding to a TCA or those with atypical depression has been demonstrated.[58] There are also studies supporting efficacy of using an SSRI in cases of failed TCA treatment.[59] Nierenburg et al[60] reported a response rate of 40% at 12 weeks on 250 mg of venlafaxine in patients who have failed a minimum of 3 adequate antidepressant trials (at least one of which was a TCA).

It is common practice to discontinue the first medication before starting the second one, but in many instances it is possible to start a new medication while tapering the first. There may be a period of heightened side effects, but this usually diminishes within a few days. Particular care must be taken and prolonged washout periods are required when switching patients from an MAOI to another antidepressant and vice versa.

Augmentation Strategies

In treatment-resistant patients, there are advantages to augmentation, including rapid response (sometimes within 48 hours) and minimal or no time lost between regimens (since the second agent is added to the first). Augmentation is often favored by clinicians in partial responders, as it may improve response without losing the initial gain. It also may increase adherence, as patients may be reluctant to discontinue an antidepressant that has produced some benefit.

There have been no studies focusing on the long-term outcome of augmentation strategies; therefore, little is known about the minimum duration of an augmentation trial. A typical approach is to maintain the augmentation agent for 6 to 9 months after obtaining remission before gradually discontinuing it.

The best studied and most established augmentation strategy is the addition of lithium to an antidepressant. In a meta-analysis of 11 double-blind, controlled trials of lithium augmentation, Fava[61] found an average response rate of 52% in 10 studies of 135 lithium-treated patients. In another meta-analysis of 9 studies, Heit and Nemeroff[62] reported that patients with treatment-resistant depression were 3.3 times more likely to respond to lithium if their lithium blood level was greater than 0.5 mEq/L or if their total daily dose of lithium was greater than 800 mg/day. This is in contrast to those with blood levels less than 0.5 mEq/L or receiving smaller doses. Despite the encouraging results, lithium is not widely used because of its bothersome side effects, its narrow therapeutic index, and the need for blood monitoring. Anecdotally, many educators have noted the reluctance of psychiatry residents to use lithium despite its demonstrated usefulness.

The addition of thyroid hormone is another popular augmentation strategy. A controlled study found T_3 to be more effective than thyroxine (T_4).[63] T_3 augmentation in doses of 25 to 50 µg/day has been used successfully among depressed patients refractory to TCAs.[64,65]

Buspirone and pindolol are more recent augmentation medications for use with SSRIs. There are limited small case series and open-label studies reporting a

greater than 50% response rate for buspirone dosed at 20 to 50 mg/day.[66,67] Augmenting antidepressants with pindolol in treatment-refractory depression has shown effectiveness and an accelerated response in some open-label studies.[68–70] However, in placebo-controlled studies, both buspirone and pindolol failed to demonstrate statistically significant treatment response in treatment-resistant patients.[71] A pindolol dose of 2.5 mg 3 times daily was typically used in these studies.[68–71] Based on these findings, the evidence for use of buspirone or pindolol as augmenting agents is inconclusive.

Other augmentation treatments have been reported, including coadministration of dextroamphetamine (5–20 mg/day) and methylphenidate (10–40 mg/day) in divided doses, which have been used to augment TCAs,[72] MAOIs,[73] and SSRIs.[74] There are no double-blind, placebo-controlled studies using stimulants as augmenting agents. However, there are a few open-label studies that suggest that using atypical antipsychotics such as risperidone or aripiprazole for augmentation results in a rapid achievement of remission.[75,76] Atomoxetine,[77] folate, and methylfolate have also shown some efficacy as augmenting agents in small open-label trials, and there are some anecdotal reports of the usefulness of modafanil, carbamazepine, estrogen, omega-3 fatty acids, and dehydroepiandrosterone in patients with treatment-refractory depression.

Combining Antidepressants

Combination strategies are those involving the concomitant use of 2 antidepressant agents with well-established efficacy. Combination strategies enhance the central nervous system effect by combining agents that target different neurotransmitter systems. In addition to the potential for a synergistic effect, there are other advantages of concomitant use of antidepressants. Combining antidepressants of different classes may decrease the overall side effect burden by using lower doses of each medication. It can build on partial response by targeting specific residual symptoms, and patients can also avoiding discontinuation symptoms. Potential disadvantages to combination treatment include adverse drug-drug interactions, reduced compliance, and higher costs of treatment.

There have been no studies focusing on the long-term outcome of combination treatment, and little is known about the minimum duration of treatment in responders. A typical approach is to maintain combination treatment for 6 to 9 months after obtaining remission before gradually discontinuing 1 of the 2 antidepressants. In a meta-analysis of 27 combination treatment studies, the average response rate was 60% and combination treatment was generally well tolerated and beneficial in some nonresponders to monotherapy.[78]

The use of an MAOI and a TCA is the oldest combination treatment, but the risk of lethal hypertensive crises related to drug-drug interactions and the introduction of newer antidepressants have led to the discontinued use of this combination in clinical practice. Moclobemide, a reversible MAOI, does not require the same dietary restrictions as traditional MAOIs and has shown some improvement in response rates when used in combination with SSRIs and TCAs.[79,80]

The combination of an SSRI and a TCA is generally well tolerated and has shown some beneficial results.[81,82] Blood levels in patients on this combination should be monitored, as SSRIs can inhibit cytochrome P450 isoenzymes, which metabolize TCAs. There have been 2 reports showing that patients who do not respond or are intolerant to high doses of SSRIs may benefit from the addition of another SSRI. The sample size in both reports is small and cannot be generalized.[83,84]

Bupropion modulates norepinephrine and inhibits dopamine reuptake, which provides a rationale for combining this agent with an SSRI. There are several small studies that have examined combining bupropion and an SSRI or bupropion and venlafaxine; the response rates were more than 75% in these studies.[85–88] However, bupropion was found to increase blood levels of venlafaxine up to threefold.

Mirtazapine is both a noradrenergic and serotonergic antidepressant. In an open-label study of 20 patients who were nonresponders to standard antidepressants, treatment after 4 weeks showed a response rate of 55% with the addition of mirtazapine.[89]

In a recent 8-week double-blind multicenter study comparing combination of olanzapine/fluoxetine with other monotherapies, there was no statistically significant improvement after 8 weeks, although the improvement in depressive symptoms was faster in the olanzapine/fluoxetine–treated group.[90]

Adding Psychotherapy

Another important strategy for managing treatment-resistant depression is adding psychotherapy. Thase and colleagues[91] concluded that time-limited, procedurally specified forms of therapy for 8 to 16 weeks, such as cognitive behavior therapy or interpersonal psychotherapy, are significantly more effective than waiting list or minimal contact/control conditions. They also reported that response rates in patients receiving these depression-focused therapies are comparable with those found with

antidepressant medications in randomized clinical trials.[91] Studies have demonstrated higher remission rates for partial responders and for patients with chronic, severe recurrent or resistant depression when treated with a combination of cognitive behavior or interpersonal therapy and pharmacotherapy.[92–94] Thase and Howland[95] recommended some psychotherapeutic interventions based on careful assessment and specification of target problems (**Table 4**).

ECT and Other Nonpharmacologic Therapies

ECT should be considered as a treatment option after 3 ineffective treatments for major depressive disorder without psychotic features.[52] Early studies reported a response rate of 50% to 89% in patients who have failed to respond to a single antidepressant.[96] However, more recent studies indicate that the presence of treatment-resistant depression reduces this response rate to 50%.[97] Experts have agreed that up to 12 ECT treatments must be provided in the setting of treatment-resistant depression for a course to be judged adequate.

In addition to ECT, transcranial magnetic stimulation and vagus nerve stimulation both have shown promising preliminary results.[98,99] More studies are needed to determine the future role of these treatment modalities in treatment-resistant depression.

TREATMENT IN THE CASE PATIENT

The patient is gradually tapered off her current medications (escitalopram and mirtazapine) and is started on a serotonin-norepinephrine reuptake inhibitor.

After 6 weeks, the patient shows moderate improvement in her depressive symptom profile. The physician decides to augment the antidepressant with lithium, which is increased and stabilized at 800 mg/day. Her lithium blood levels are in the range of 0.9 to 1.1 mEq/L. The patient tolerates this regimen with minimal side effects, and for the first time in many years she demonstrates marked improvement in mood and affect.

The patient achieves a complete remission of her depressive symptoms after 4 weeks of treatment with lithium and the serotonin-norepinephrine reuptake inhibitor. Currently, her full remission has been maintained for 10 months.

Table 4. Individualized Targets for Psychotherapy in Treatment-Resistant Depression

Problem	Target for Psychotherapy Intervention
Demoralization/ hopelessness	Setting realistic expectations and addressing hopelessness
Inadequate social support	Mobilizing interpersonal resources, family psychoeducation, and structured assignments to expand social network; improving social skills
Dependency and other neurotic traits	Improving self-efficacy, assertiveness, and tolerance of negative effects; learning to tolerate loneliness; learning to test and modify dysfunctional beliefs; enhancing awareness of one's effects on others
Ongoing stressors and adversities	Clarifying nature and duration of difficulties, implementing problem-solving strategies
Inactivity/anergia	Increasing physical exercise and involvement in previously rewarding activities, emphasizing participation as the initial goal rather than enjoyment or satisfaction
Pharmacologic noncompliance	Psychoeducation about illness and its treatment, exploring beliefs about medication and expectations of significant others
Medication-resistant symptoms	Identifying residual symptoms such as anxiety, insomnia, or poor concentration for specific intervention

Adapted with permission from Thase ME, Howland RH. Refractory depression: relevance of psychosocial factors and therapies. Psychiatr Ann 1994;24:238.

SUMMARY

The patient with treatment-resistant depression requires careful assessment. The possibility of pseudoresistance should be considered and the patient should be assessed for predictors of nonresponse, such as comorbid psychiatric and general medical conditions. There are numerous strategies for managing treatment-resistant depression but inadequate empirical information to make formal recommendations. Future studies are needed to evaluate the comparative efficacy and tolerability of these strategies.

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