Clinical Features of Treatment-Resistant Depression

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As many as 30% to 40% of patients with major depressive disorder are unresponsive to a trial of antidepressant medication. Many patients labeled with treatment-resistant depression actually have pseudoresistance, in that they have been inadequately treated or are misdiagnosed. Others may have unrecognized comorbid psychiatric or general medical conditions that contribute to treatment resistance. Variables such as gender, family history, age at onset, severity, and chronicity have also been evaluated as possible risk factors for treatment-resistant depression. This article reviews the current literature regarding the clinical characteristics of treatment-resistant depression, with particular attention to the relevance of these factors for clinical decision making.

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The literature on characteristics of patients with treatment-resistant depression is sparse and difficult to interpret. First, there is variability among studies as to how treatment-resistant depression is defined. Many studies include patients who were labeled treatment-resistant but actually had inadequate treatment trials or were misdiagnosed. Second, the studies vary with regard to the types of patients studied, e.g., different depressive subtypes, different comorbidities, different age groups, inpatients/outpatients. A third concern relates to the study designs themselves; most studies are retrospective and uncontrolled and have small sample sizes. Despite these limitations, several clinical characteristics have emerged that merit discussion as possible risk factors for treatment-resistant depression. This article will review these factors, including comorbidity, gender, family history, age at onset, severity, and chronicity.

TREATMENT RESISTANCE VERSUS PSEUDORESISTANCE

Guscott and Grof[1] note that refractory depression is "first and foremost a sociological fact—a phenomenon of labeling." To accurately label a patient's symptoms, the first task for the clinician is differentiating between true treatment-resistant depression and pseudoresistance. The process of ruling out pseudoresistance falls into 3 areas of focus in the clinical assessment: (1) physician factors, (2) patient factors, and (3) accuracy of diagnosis.

Physician Factors

Prescribing habits vary widely by setting and by specialty.[2] Physicians may prescribe inadequately either by not increasing the antidepressant to high enough dosage levels or by discontinuing the antidepressant before an adequate trial has been completed. Prescribing inadequate doses of medication and treating for too short a duration are 2 major causes of pseudoresistance.[3] Therefore, a careful history of all previous treatments is required in the evaluation of treatment-resistant depression. Thase and Rush[4] provide a practical system for staging treatment-resistant depression based on previous medication trials (Table 1). By using this staging system, various treatment strategies can be appropriately applied in a stepwise fashion.

Patient Factors

Patient factors also may contribute to pseudoresistance. Unusual pharmacokinetics (e.g., rapid metabolism, malabsorption) in a patient may lead to low serum levels of antidepressants, thereby diminishing effectiveness. Often, patients discontinue medications prematurely because of intolerable side effects, preventing the attainment of an adequate dosage or duration of treatment. Patient noncompliance can also occur as a result of poor understanding of the illness or Axis II pathology.[5] Since patients typically are not forthcoming about their noncompliance, a collateral history from past records or the patient's companion and/or measurement of serum drug levels may be useful to verify compliance.

Accuracy of Diagnosis

Another physician-related factor that is a common cause of pseudoresistance is misdiagnosis, i.e., when the patient is given an incorrect primary diagnosis. Diagnoses that may

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Table 1. A System for Staging Treatment-Resistant Depression[a]

Stage 0: no single adequate trial of medication
Stage 1: nonresponse to an adequate trial of 1 medication
Stage 2: failure to respond to 2 different adequate monotherapy trials of medications from different classes
Stage 3: stage 2 plus failure to respond to 1 augmentation strategy
Stage 4: stage 3 plus a failure to respond to a second augmentation strategy
Stage 5: stage 4 plus failure to respond to electroconvulsive therapy

[a]Adapted from Thase and Rush,[4] with permission.

lead to incorrect labeling as treatment-resistant depression include substance-induced mood disorders secondary to alcohol, substances, or medications and depression secondary to general medical conditions, such as hypothyroidism. In a study by Keller et al.,[6] the diagnosis of secondary depression emerged as a major predictor of chronicity of symptoms despite adequate antidepressant treatment.

Patients labeled as treatment-resistant should also be evaluated carefully for the presence of unrecognized depressive subtypes, since they often require a different treatment approach. For example, psychotic depression is usually unresponsive to antidepressant medications alone, the most effective treatment strategy being an antidepressant-antipsychotic combination or a course of electroconvulsive therapy.[7] Psychotic features may be subtle and elusive in some depressed patients, even to an experienced clinician. A missed diagnosis of bipolar disorder also has major implications with regard to the treatment regimen in that it should include the use of a mood stabilizer.[8] Atypical depression, with features of hypersomnia, hyperphagia, mood reactivity, leaden paralysis, and rejection sensitivity, has been shown to respond preferentially to monoamine oxidase inhibitors (MAOIs) over tricyclics.[9] Seasonal affective disorder, characterized by the occurrence of recurrent depressive episodes usually during the winter months and remitting during the spring and summer months, also tends to show a poorer response to tricyclic agents.[10] Finally, a diagnosis of premenstrual dysphoric disorder is often missed in women presenting with depression and appears to respond preferentially to serotonergic antidepressants.[11]

FACTORS ASSOCIATED WITH TREATMENT RESISTANCE

Various factors have been discussed in the literature that may increase the likelihood of nonresponse to antidepressant treatment. Of utmost importance in this regard is the presence of a comorbid psychiatric or general medical disorder. Keitner and colleagues[12] reported that 53% of patients admitted with major depression have coexisting Axis I, II, or III conditions, which they termed *compound depression*. Other factors that warrant consideration in the evaluation of treatment-resistant depression include female gender, family history, early or late onset, severity of illness, and chronicity of course.

Comorbid Psychiatric Disorders

The presence of a comorbid psychiatric disorder increases the likelihood of treatment-resistant depression. Often, these comorbid disorders are missed or are suboptimally treated, and they can confound both the evaluation and treatment of the mood disorder.[12] It is important to systematically evaluate patients with treatment-resistant depression for the presence of comorbid disorders. Psychiatric disorders that are most often comorbid with depression include anxiety disorders, substance abuse, and personality disorders.

Anxiety disorders. Although anxiety disorders and mood disorders are defined as separate entities, the 2 conditions often coexist. Clayton et al.[13] note that of the 10 most common symptoms in primary unipolar depression, 2 are anxiety symptoms (worry and psychic anxiety). Fawcett and Kravitz[14] screened 200 patients with DSM-III major depression and found that 29% had a history of panic attacks; 62% had experienced moderate psychic anxiety; and 72%, moderate worry. To address the overlap of anxiety and depressive symptoms, both the DSM-IV and the ICD-10 have introduced the concept of *mixed anxiety-depressive disorder* to define patients who have subsyndromal states that do not meet criteria for either primary disorder.[15]

Depressed patients with comorbid anxiety tend to be more severely depressed than patients with depression alone. They also have a greater risk for suicide and more functional impairment. In a prospective study of 954 patients with major affective disorder, the severity of anxiety and the presence of panic attacks were correlated with suicide in the first year.[16] Comorbid anxiety also affects the course of depressive illness, with increased rates of chronicity, relapse, and recurrence. Depressed patients with mixed states involving panic attacks have the poorest outcomes and are most likely to be chronically depressed.[17]

The presence of comorbid anxiety also affects treatment response. Such patients respond more poorly to treatment; they tend to have a slower response to medication and an incomplete remission of symptoms. They also tend to be more susceptible to side effects; hence, it is advisable to start them at a lower dose of medication. A lifetime history of anxiety disorder predicts a significantly slower rate of recovery of a major depressive episode. Outpatients with unipolar depression who have higher ratings of anxiety recover more slowly than those with lower levels of anxiety[18] and are more likely to have a positive family history for unipolar depression.[13] Thus, the clinical evaluation of treatment-resistant depression must include screening for anxiety symptoms and disorders.

Substance abuse. Substance abuse further complicates the evaluation of treatment-resistant depression. A detailed

patient history and collateral history for substances of abuse are important in the evaluation process of treatment-resistant depression for 2 reasons. First, acute and chronic effects of substances may cause or worsen depressive symptoms and affect compliance. Even moderate usage of alcohol has been shown to contribute to treatment resistance.[19] Second, the presence of a mood disorder increases the likelihood of a substance use disorder or makes the patient more prone to relapse of the substance abuse.[20] Nunes and colleagues[21] describe treatment resistance in dual-diagnosis patients by conceptualizing that either the substance abuse or the depression or both may be refractory to treatment. Patients may then be divided into 4 types:

Type I: Both conditions in stable remission
Type II: Refractory substance abuse and depression in remission
Type III: Refractory depression and substance abuse in remission
Type IV: Both conditions refractory to treatment

In Types I and II, the mood disorder is in remission. Types III and IV offer unique challenges. In Type III, the substance abuse has remitted, but lapses and relapses are common and complicate the treatment of depression. Although controversy surrounds the concept of *protracted withdrawal*,[22] exactly how long an abstinence is required to eliminate the chronic effects of the substance is still unknown. Type IV represents a common clinical problem in which both depression and substance abuse persist. Unfortunately, there is sparse literature to guide the clinician in this area. Clinical experience shows that aggressive multimodal treatment is most effective for these patients.

Personality disorders. The relationship between depression and personality disorders is complex.[23,24] Personality disturbance has been viewed as a predisposition or vulnerability that precedes the affective disorder, as a complication or attenuated manifestation of the affective disorder, and as a modifier that influences the clinical expression of the affective disorder (the pathoplasty model).[23] Estimates of the prevalence of comorbid personality disorders in patients with major depressive disorder range from 14% to 85%, with a mean of about 50%. Personality disorders most frequently reported as comorbid with depression are in the anxious-fearful cluster (cluster C), followed by the dramatic-unstable cluster (cluster B). Dependent, borderline, and histrionic personality disorders have tended to predominate among studies of major depressive disorder. A recent study of patients with chronic major or double depression also reported that about 50% had a comorbid Axis II disorder.[25] Cluster C disorders were most common in this population as well, with avoidant personality disorder being diagnosed in about 25% and obsessive-compulsive personality disorder in nearly 20%.

Many researchers have opined that depressive symptoms cloud the presentation of personality to such an extent that a valid personality assessment is impossible.[23,24] A patient who appears to have significant Axis II pathology while depressed may look quite different once the depression clears. In support of this argument, Fava and colleagues[26] reported that 44% of depressed patients with borderline personality disorder no longer met criteria for the personality disorder after 8 weeks of fluoxetine treatment. Therefore, one must be careful about prematurely diagnosing personality disorders in depressed patients.

Regarding the effect of personality disorder on treatment response, the conclusions are less than definitive. The weight of evidence indicates that depressed patients with personality disorders are less responsive to antidepressant therapy compared with patients with no Axis II pathology and have a worse prognosis for long-term outcome.[23,24,27] However, it is important to note that the majority of studies on which these conclusions are based used tricyclic antidepressants. In the study by Keller et al.[25] discussed above, the presence of comorbid personality disorder did not affect outcome of treatment with sertraline or imipramine; however, patients with severe borderline, schizotypal, or antisocial personality disorders were excluded from the study.

Other psychiatric disorders. Other psychiatric disorders that may be comorbid with depression and may easily be missed include obsessive-compulsive disorder (OCD), eating disorders, and body dysmorphic disorder (BDD). Often, patients do not reveal such symptoms to the clinician because of shame or embarrassment. Careful direct inquiry is needed because these disorders may also contribute to treatment resistance if they go unrecognized.

There is significant overlap between OCD and depression. Kendell and DiScipio[28] reported a 22% incidence of obsessive-compulsive symptoms in depressed patients. More commonly, patients develop depression during the course of OCD rather than developing OCD secondary to depression.[29] The overlap between these 2 syndromes might help explain their shared responsiveness to SSRIs. Eating disorders co-occur with depression 37% of the time[30] and often are missed by the clinician. Patients with eating disorders may be at risk for noncompliance because of fears of weight gain associated with some antidepressant therapies.

Body dysmorphic disorder is a preoccupation with an imagined or slight defect in appearance. Available data indicate that BDD may respond preferentially to serotonin reuptake inhibitors. In addition, longer treatment trials than those required for depression may be needed to successfully treat depression and comorbid BDD.[31]

Medical Comorbidity

General medical conditions and their treatments may either cause or worsen depression. Hall and colleagues[32]

reported that unrecognized medical illness prompts psychiatric admission and exacerbates psychiatric symptoms in nearly half of psychiatric inpatients. Similarly, depression and other psychiatric illness may affect the management of a comorbid general medical condition. In diabetic patients, for example, the presence of depression is associated with poor glycemic control, which may result both from direct neuroendocrine effects and from indirect effects by influencing patient compliance.[33]

Many patients labeled with treatment-resistant depression have an organic cause that may be uncovered during the evaluation process. Endocrine disorders, such as hypothyroidism, Cushing's disease, and Addison's disease, have received the most attention. However, other medical conditions, medications used to treat general medical conditions, and disorders at the interface of psychiatry and medicine can also complicate the evaluation and management of treatment-resistant depression.[34–36]

Hypothyroidism. A review of studies of depression and thyroid disease found that 52% of refractory depressed patients show evidence of subclinical hypothyroidism (range, 29%–100%).[37] This estimate compares with a prevalence of 8% to 17% in unselected populations of depressed patients. Hypothyroidism can be divided into 4 grades. In grade 1, the patient shows overt signs of hypothyroidism and has abnormal T_3RU or T_4 and TSH levels. Grade 2 is characterized by milder symptoms and only an abnormal TSH level. Grade 3 (subclinical hypothyroidism) is detectable with a thyrotropin-releasing hormone (TRH) stimulation test (response of TSH to a TRH challenge), and grade 4 is marked by abnormal thyroid antibodies.

Gold et al.[38] identified 20 hypothyroid patients from 250 consecutive admissions of depressed inpatients. Eight of these depressed hypothyroid patients had TSH levels greater than 35 μIU/mL. Six of the 8 patients responded to thyroid replacement alone administered in a psychotherapeutic milieu. Interestingly, 2 patients with subclinical hypothyroidism (grade 3) showed a remission of their depressive symptoms with thyroid replacement. Clinical practice mirrors this inconsistent response of depressive symptoms in hypothyroid patients to thyroid supplementation. However, it appears that the more significant the hypothyroidism, the more likely it is that the depression will improve with thyroid replacement.

Medications. Medications used to treat general medical conditions also may significantly confound the evaluation and management of treatment-resistant depression. Extensive lists of possible offending medications are given in other publications.[39] Two classes of medications are especially worthy of mention. Glucocorticosteroids are associated with depression, mania, and delirium.[33] They are often used in the treatment of inflammatory conditions seen in pulmonary medicine and rheumatology. A careful history from the patient usually reveals a pattern of exacerbating depressive symptoms with changes in the steroid dosage separate from other variables. Antihypertensives would be the next agents to consider. Although the risk for depression from these agents is low when 1 patient using 1 agent is considered, their high utilization makes them a significant cause of depressive symptoms.

Other medical conditions. General medical conditions such as diabetes, coronary artery disease, HIV infection, cancer, and chronic pain all may contribute to treatment-resistant depression in that they may not be diagnosed or optimally managed. While depression in association with medical illnesses tends to show a lower response rate to antidepressant treatment,[40] specific psychosocial interventions can decrease morbidity and increase longevity. In addition, unique new drug therapies may be targeted for certain medical conditions (e.g., bupropion and Parkinson's disease), raising our optimism for better treatment outcomes.[35] A complete history, physical, and laboratory evaluation will detect most of these medical disorders. A close working relationship with an internist is helpful in evaluating and managing such patients.

Conditions such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome exist at the interface between medicine and psychiatry and are often associated with depressive symptoms. As they tend to be underrecognized and undertreated, they are important diagnoses to consider in the evaluation of treatment-resistant depression. When the associated depression is treated with a psychotropic drug, there is usually improvement in the somatic symptoms as well. This observation suggests a common etiologic step in these disorders that is addressed by the antidepressant.[36]

Gender

In the older literature, female gender is sometimes mentioned as a risk factor for treatment-resistant depression; however, there is little evidence to support this statement. In any sample of depressed patients, including patients with treatment-resistant depression, there will always tend to be a preponderance of women because of the gender difference in prevalence rates of depression.[41] In studies that have examined predictors of outcome, however, gender has generally not been found to be a predictor.[42] Recent evidence does indicate that gender may be a factor in predicting response to one antidepressant versus another. For example, women may be less responsive than men to tricyclics and may respond preferentially to SSRIs or MAOIs.[43]

Our group recently published an analysis by gender of response to sertraline versus imipramine in patients with chronic major or double depression.[44] Women responded significantly better to sertraline than to imipramine, while men responded significantly better to imipramine. There were also differences in response rates by menopausal status. Premenopausal women responded better to sertraline, but there was no difference in response to the 2 drugs in

postmenopausal women. Thus, both gender and menopausal status are factors that may affect treatment response. The poor responsiveness of women to tricyclics likely accounts for female gender being seen as a risk factor for treatment-resistant depression in the early literature, since tricyclics were the mainstay of antidepressant treatment at that time.

Family History

A positive family history of depression is sometimes mentioned in the literature as a predictive variable for treatment resistance; however, there have been no well-designed studies investigating this association. Nelsen and Dunner[45] studied 26 patients who had been labeled treatment-resistant and matched them by age, gender, and depressive subtype with a group of non–treatment-resistant patients. They did find that the treatment-resistant patients were more likely to have a family history of affective disorder. However, a major problem with this conclusion is that some of the patients labeled as treatment-resistant were found to have had inadequate treatment trials and may not have truly been treatment-resistant. There are studies showing that a positive family history is associated with early onset of depression and with chronicity, both of which have been linked to treatment resistance.[46,47] Scott[48] reported that chronic treatment-resistant depressives showed a significantly greater family history of affective illness in first-degree relatives than nonchronic depressives.

From a clinical perspective, a family history of depression may be helpful in increasing the likelihood of response, if that family member has sought treatment, since a positive response to a medication in a family member may predict a similarly positive response in the patient. A family history of treatment-resistant depression, on the other hand, may suggest a worse prognosis for the patient.

Age at Onset

With age at onset, both ends of the spectrum have been described as risk factors for treatment resistance, although again, the literature is too sparse to draw any real conclusions. There is evidence that early onset of depression is associated with higher rates of comorbid personality disorders and substance abuse, and also a greater family history of mood disorders.[47] Akiskal et al.[49] reported that early onset of depression together with a positive family history are associated with a chronic course of illness, which tends to result in lower response rates and an incomplete remission of symptoms. A recent study by Klein and colleagues[47] examined early onset as a predictor of nonresponse in patients with chronic depression. Early onset was not found to be a predictor, but that finding may not generalize to other subtypes of depression.

Late onset of depression in patients over 60 years is associated with several important features that may lead to treatment resistance. With late-onset depression, one tends to see less family history and fewer personality disorders, but there is a greater likelihood of psychotic depression (which would be less responsive to antidepressant medication alone) and also more comorbid medical conditions that may affect both evaluation and treatment of depression.[50,51] The clinician should pay careful attention to a possible incipient dementia in depressed geriatric patients. A high prevalence of depression co-occurs with dementia and, in addition, depression may represent a prodrome of dementia. There is a high risk of pseudoresistance in geriatric patients, e.g., if the diagnosis of an organic mood disorder is missed or if the patient is unable to reach an adequate dosage of medication due to greater sensitivity to side effects.[52] It is sometimes difficult to sort out whether somatic complaints in depressed elderly are side effects or symptoms of depression; this confusion especially exists with the usage of tricyclics. There is some evidence that geriatric patients may take longer to respond to antidepressant treatment[52]; thus, they are at risk for being declared treatment-resistant prematurely when, in fact, they may need a longer trial of medication.

Illness Severity

Patients who are severely depressed are more apt to be treatment-resistant. Severe depression tends to be associated with greater functional impairment, a longer duration of illness, a lower likelihood of spontaneous remission, and a greater risk of recurrence.[53] Severely depressed patients are also more likely to have psychotic features and more likely to have comorbid psychiatric or general medical disorders. Suicide risk is a concern with severely depressed patients; up to 80% will report suicidal ideation. In 2 studies that compared depressed patients with and without treatment resistance, suicide attempts were more common in the treatment-resistant group.[45,54] Severely depressed patients are also more likely to require hospitalization.

One of the problems with interpreting the literature on severe depression is the lack of consistency in how it is defined. For example, severe depression can be defined by a cutoff of scores on a rating instrument; by subtype, such as psychotic or melancholic depression; or by hospitalization status. In addition, depending on which rating scale is used, the constellation of symptoms may differ considerably; for example, the Hamilton Rating Scale for Depression is weighted more toward neurovegetative symptoms, and the Beck Depression Inventory more toward cognitive symptoms.

There has been some controversy about whether the SSRIs are as effective as the tricyclics in severe depression, although several recent reviews conclude that there is no differential efficacy.[53,55] Severely ill patients do tend to be less responsive to psychotherapy alone. In a recent meta-analysis by Thase and colleagues,[56] patients with severe and recurrent illness responded significantly better to combination treatment with medications and psychotherapy than to psychotherapy alone.

Chronicity

Chronicity of depression increases the likelihood of treatment resistance. Chronicity refers to patients who have either prolonged episodes of illness lasting 2 years or more or an incomplete remission between episodes.[57] Specifically, the chronic subtypes include chronic major depression, which is a major depressive episode of at least 2 years' duration; double depression, which is major depressive disorder superimposed on dysthymia; and recurrent major depressive disorder with incomplete interepisode recovery.

According to data from the National Institute of Mental Health Collaborative Depression Study, about 20% of patients with major depressive disorder will develop a chronic course of illness.[58] For patients with recurrent depression, this same risk of chronicity persists with each new episode of depression.[59] Chronicity tends to worsen the overall prognosis of depression. Patients with double depression are unlikely to achieve a full remission of both major depression and dysthymia; instead, they tend to return to the dysthymic state once the major depressive episode has ended.[60] Patients with double depression also show a higher risk of recurrence compared to those with major depressive disorder alone. The presence of residual depressive symptoms is a risk factor for relapse and recurrence of major depressive disorder even in patients without antecedent dysthymia.[61]

Chronic depressions are associated with substantial comorbidity, particularly anxiety disorders, alcoholism, and personality disorders, all of which tend to worsen treatment outcome. In a study led by Keller et al.[25] of patients with chronic major or double depression, 24% of the patients had at least one lifetime comorbid anxiety disorder; over a third reported a lifetime history of alcohol or substance abuse, and over 50% had at least one Axis II disorder.

Chronic depression is also associated with severe and pervasive functional impairment, to a greater degree than what is seen with acute major depressive disorder, and in fact, more severe than what is seen with many chronic medical disorders, including hypertension, diabetes, and arthritis.[62,63] This lower level of psychosocial functioning is associated with a worse prognosis for recovery.[63,64] Patients with chronic depression also show a greater frequency of suicide attempts and hospitalizations, and an earlier onset of their illness,[65] which also increases the risk for treatment resistance.

It is important to note that many patients with chronic depression do not receive any treatment. Underrecognition and undertreatment are the norm for depression in general, but even more so for chronic depression.[66] Because these patients are ill for so many years without a normal baseline for comparison, the patients, their families, and even physicians may accept this chronically ill state as normal for that patient. In the Keller et al.[25] study of patients with chronic depression, who had an average lifetime illness duration of 16 years, over 40% had never received any antidepressant treatment, and only 20% had received an adequate trial. Thus, in addition to treatment resistance the problem is one of undertreatment.

Until the past decade or so, chronic depression was perceived as a problem of character pathology that was unresponsive to medication.[67] In recent years, the chronic depressions have been reconceptualized as mood disorders and shown to be responsive to antidepressant treatment of adequate dose and duration. However, the response rates are still somewhat lower than those with episodic depression, and these patients are less likely to show a complete remission of symptoms, which increases their risk of relapse and recurrence.[68]

Chronically depressed patients also tend to show a longer time to response. In the study by Keller et al.[25] with sertraline and imipramine, a significant number of patients responded between weeks 8 and 12 of the acute phase, and 46% of patients who were only partial responders after 12 weeks became full responders by the end of the continuation phase after 28 weeks of treatment.[69] Thus, there is a risk that clinicians may give up too soon in these patients and declare them treatment failures, when they might have responded if the treatment were continued longer.

A recently published study[70] suggests that combination treatment with medication and psychotherapy may be particularly beneficial for these chronic disorders. This study compared nefazodone, psychotherapy, and the combination in patients with chronic major depression, double depression, or recurrent major depressive disorder with incomplete interepisode recovery. The type of psychotherapy used in the study was Cognitive-Behavioral Analysis System of Psychotherapy (CBASP), which is a therapy method developed specifically to treat chronic depression.[71] They found that the response rate to combination treatment was markedly better than to either treatment alone. Thus, chronic depression may represent the type of situation in which if one chooses the right treatment, patients will be less likely to be classified as treatment-resistant.

SUMMARY

Assessment of treatment-resistant depression should include careful attention to the possibility of pseudoresistance. Causes of pseudoresistance include prescribing an inadequate dose or duration of treatment, patient noncompliance or unusual pharmacokinetics, and misdiagnosis of the primary disorder by failure to recognize a secondary mood disorder or a depressive subtype. Of the clinical variables reviewed, the presence of a comorbid psychiatric or general medical disorder, older age, greater severity of illness, and chronicity of course show the strongest evidence as risk factors for treatment-resistant depression. Clearly, more research is needed investigating characteristics and predictors of treatment-resistant depression using controlled designs and standardized definitions of treatment resistance.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), nefazodone (Serzone), sertraline (Zoloft).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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