



## Barriers to Diagnosis, Advances in Therapy

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Depression is underdiagnosed in primary care because of several factors, including variances in the clinical presentation of depressive symptoms, as well as comorbid medical, psychiatric, and substance abuse problems. Time constraints imposed by managed care add to the challenge of diagnosis. The current medical system encourages a reliance on somatic symptoms for accurate diagnosis, and tools that measure somatic symptoms, such as the Primary Care Rapid Assessment Scale, may be useful. After diagnosis, the depressed patient may benefit from one of the many new antidepressant modes of therapy and medications in the pipeline. Psychotherapeutic treatment modalities should also be taken into account. These diagnostic and therapeutic options are rapidly becoming available to primary care physicians, who should use them to achieve long-term remission of depressive symptoms.

Primary care physicians recognize mood disorders in only 25% to 50% of affected patients and miss the diagnosis of major depressive disorder in up to 66% of cases.<sup>1,2</sup> Multiple and multifaceted reasons account for why primary care physicians fail to diagnose depression (*Figure 1*).

One significant barrier is that depression itself is fraught with diagnostic nuances. For example, the clinical presentation may vary from a chronic condition to one that cycles. It may be comorbid with other psychiatric conditions that have overlapping symptoms, or it may be part of another affective disorder such as bipolar disorder. In addition, as examined in closer detail elsewhere in this supplement, an accurate differential diagnosis may also be confounded by coexistent medical ill-

ness, psychological problems due to life stressors, personality disorders, and/or substance abuse.

For example, depression may easily be misdiagnosed as an anxiety disorder, particularly when agitation is a more predominant symptom than fearfulness or worry. Studies of families with strong histories of bipolar depression suggest that patients who present with agitated depression may actually have bipolar disease.<sup>2,3</sup> Furthermore, depression and anxiety occur more often comorbidly than alone.<sup>2</sup> According to the National Comorbidity Survey of more than 8000 adults, 58% of respondents with lifetime major depression have also had an anxiety disorder.<sup>4</sup> Comorbidity not only makes diagnosis more difficult, it also increases the chances of resistance to treatment.

### The Role of Managed Care

The challenge of diagnosing depression is difficult enough without the time constraints imposed by managed care. Primary care physicians have been given the role of medical gatekeeper without being taught how to meet that challenge with new organizational skills. As a

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## Checklist

- Partial response
- Prior augmentation strategies
- Dosing
- Duration of therapy
- Side effects
- Comorbid medical disorders
- Comorbid anxiety disorders
- Comorbid bipolar disorders
- Comorbid psychotic features
- Comorbid personality disorders

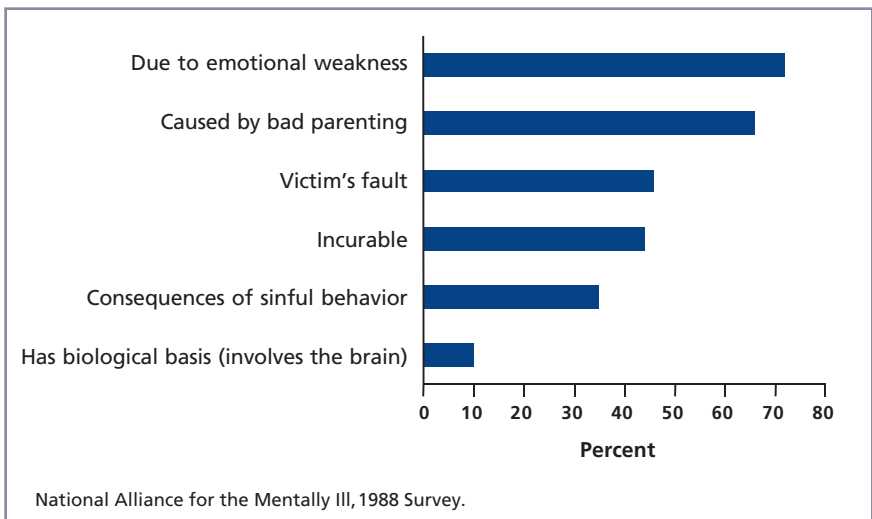
**Figure 1.** Factors that may prevent timely and proper diagnosis and contribute to “treatment resistance.” (Source: Montano CB, Montano MB. A new paradigm for treating depression in the primary care setting [Medscape Web site]. September 18, 2002. Available at: <http://www.medscape.com/view-program/2022>. Accessed September 25, 2002.)

result, many physicians merely try to accomplish what they have been taught in smaller increments of time. Instead, what is needed is a fresh approach in the way physicians conceptualize and apply their skills and direct other health professionals.

Under the current system, physicians have little choice but to focus heavily on somatic complaints and their organic etiologies. Many somatic symptoms, however, including sleep disturbances, fatigue, back pain, weight changes, headache, or gastrointestinal complaints, may be symptoms of either depression, a medical disorder, or both (Figure 2). In a 3-year study of common somatic complaints, no organic cause could be determined in most patients.<sup>5</sup> Even if one assumes that 50% of those missed had an organic basis and the rest had a psychological cause, the impact of missing the latter diagnosis has a significant impact on a physician’s time and cost of services. Primary care physicians in particular need to keep depression high on the diagnostic index when patients report somatic complaints that overlap with those associated with depression.

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**Figure 2.** Physical complaints with and without organic causes. (Adapted with permission from Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. *Am J Med.* 1989;86:262-266.)



**Figure 3.** How the general public views mental illness. (Source: National Alliance for the Mentally Ill, 1988 Survey.)

### Diagnosis Based on Somatic Complaints

Somatic complaints may be the only way some groups of patients know how to express the presence of an emotional problem, especially if it carries a cultural or group stigma (Figure 3). Depression is described as “masked” by the somatic focus in seniors who simply may not know any other way to express the feeling. For other patients from families where mental illness is a virtual taboo, somatization is a way to get attention, caring, and acceptance. These individuals and their families may avoid and

resist any psychiatric diagnosis. Physicians who treat patients from these groups need to make sure they—and other office personnel—respond to such complaints in a way that is effective. This response may include not using psychological terminology and keeping explanations medically focused.

### Physician Bias in Diagnosis

Finally, physicians may have their own conscious and unconscious biases. The thought of facing a depressed patient in the midst of a busy day and the concern that a simple inquiry can open an unwel-

**Primary Care Rapid Assessment Scale (PCRAS)**  
**While you are waiting for the doctor, please answer the following questions**  
**so that we can better serve you.**

**1 = Not at all.**  
**2 = A little from time to time.**

**3 = I have this a lot, but I can handle it.**  
**4 = This really gets in the way.**

1. Headaches	1	2	3	4	32. Feeling fearful/hurt	1	2	3	4
2. Indigestion/nausea	1	2	3	4	33. Excessive sexual feelings/activity	1	2	3	4
3. Dizziness	1	2	3	4	34. Excessive eating	1	2	3	4
4. Constipation/diarrhea	1	2	3	4	35. Other excessive behavior (gambling, shopping, cleaning, etc)	1	2	3	4
5. Pains in neck	1	2	3	4	36. Uneasy in crowds	1	2	3	4
6. Back pain	1	2	3	4	37. Trouble falling asleep	1	2	3	4
7. Muscle pain/soreness	1	2	3	4	38. Suddenly scared	1	2	3	4
8. Chest discomfort	1	2	3	4	39. Fear of leaving home	1	2	3	4
9. Joint pain/stiffness	1	2	3	4	40. Thoughts racing	1	2	3	4
10. Rapid heart	1	2	3	4	41. Life limited by fear	1	2	3	4
11. Body numbness or tingling	1	2	3	4	42. Impulsive spending	1	2	3	4
12. Short of breath	1	2	3	4	43. Concerns about sexuality	1	2	3	4
13. Trembling	1	2	3	4	44. Decreased need for sleep	1	2	3	4
14. Frequent urination	1	2	3	4	45. Work-related problems	1	2	3	4
15. Hot/cold spells	1	2	3	4	46. Health is a concern	1	2	3	4
16. Stomach pain	1	2	3	4	47. Family problems associated with alcohol/drugs	1	2	3	4
17. Weakness in your body	1	2	3	4	48. Health problems associated with alcohol/drugs	1	2	3	4
18. Low energy/fatigue	1	2	3	4	49. Legal problems associated with alcohol/drugs	1	2	3	4
19. Restless/disturbed sleep	1	2	3	4	50. Decreased sexual interest	1	2	3	4
20. Irregular periods (females)	1	2	3	4	51. Easily distracted	1	2	3	4
21. Painful periods (females)	1	2	3	4	52. Memory problems	1	2	3	4
22. Impotence (males)	1	2	3	4	53. Recent trauma or loss (past, present, or anticipated)	1	2	3	4
23. Poor appetite	1	2	3	4	54. Recent weight change	1	2	3	4
24. Early AM awakening	1	2	3	4	55. Rapidly shifting mood	1	2	3	4
25. Feeling future is hopeless	1	2	3	4	56. Easily startled	1	2	3	4
26. Feeling blue/sad	1	2	3	4	57. Trouble maintaining relationships	1	2	3	4
27. Trouble concentrating	1	2	3	4	58. Nightmares	1	2	3	4
28. Frequent worrying	1	2	3	4	59. Not able to make decisions	1	2	3	4
29. Irritable/annoyed	1	2	3	4					
30. Tense/keyed up	1	2	3	4					
31. Restlessness	1	2	3	4					

Information assessed by \_\_\_\_\_

Date \_\_\_\_\_

◀ **Figure 4.** Primary Care Rapid Assessment Scale developed by Murray H. Rosenthal, DO, as an assessment tool for the primary care physician. Reprinted courtesy of Murray H. Rosenthal, DO. Web site available at: <http://www.bmrhealthquest.com>

come “Pandora’s box” is not completely unfounded. Although modern psychopharmacology has made depression safer and easier to treat, how do you allow for the time required? Gathering the necessary diagnostic information, educating the patient, and initiating treatment can be a different process compared with that for treating medical illnesses. Without fresh approaches to the problem, the bias will continue to be that of responding to the immediacy of the moment. As a consequence, untreated or undertreated depression will continue to complicate the treatment of any associated medical conditions and compliance with medical regimens.<sup>6</sup> The consequence to patient care is obvious; less so is the added burden to physicians and their staffs and the ultimate cost of providing care.

### A Potential Tool for Diagnosis

Disease management tools provided by pharmaceutical companies have not been widely accepted or proven useful, possibly owing to the fact that these companies relied on physicians to perform all or most of the data collection tasks. Our center in San Diego has used a team model for conducting clinical trials. This model may have utility for primary care physicians.

Although no cookbook answers to patient management exist, some fundamentals do apply. Physicians must never abdicate their role as diagnosticians; instead, they can learn to delegate the task of information gathering to trained personnel. A variety of rating scales and database questionnaires are available to the practicing physician. Although time is needed for initial training of personnel, the physician’s time ultimately can be reduced to assessing the collected data and focusing on more specific diagnostic issues.

An unvalidated rating scale (primary care rapid assessment scale, the

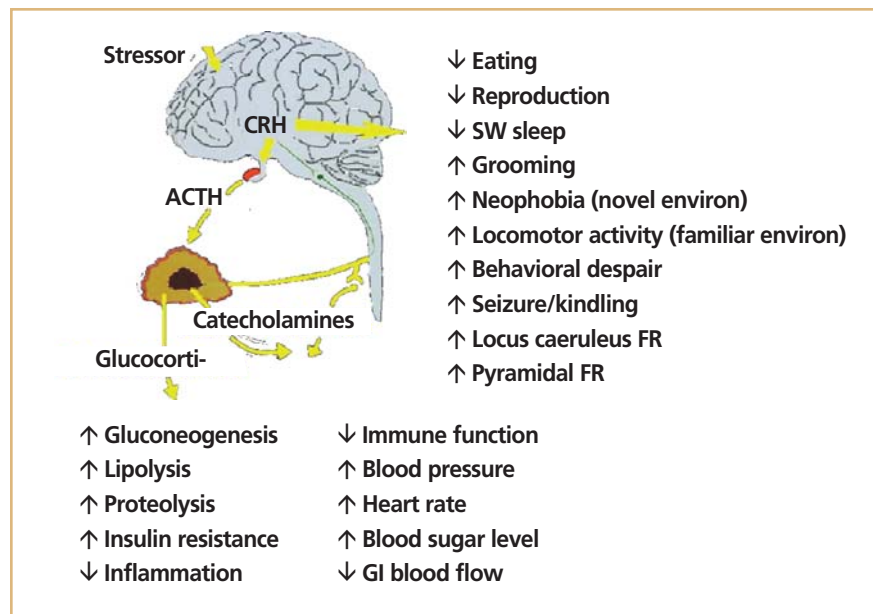
Table In Vitro Inhibition of Human Cytochrome P-450 Enzymes by Selective Serotonin Reuptake Inhibitors					
	P-450 Enzymes				
	1A2	2C9	2C19	2D6	3A
<input type="checkbox"/> Escitalopram oxalate	0*	0	0	0	0
<input type="checkbox"/> Citalopram hydrochloride	+	0	0	+	0
<input type="checkbox"/> Fluoxetine hydrochloride	+	++	+ to ++	+++	++
<input type="checkbox"/> Fluvoxamine maleate	+++	++	+++	+	++
<input type="checkbox"/> Paroxetine hydrochloride	+	+	+	+++	+
<input type="checkbox"/> Sertraline hydrochloride	+	+	+ to ++	+	+
<input type="checkbox"/> Venlafaxine hydrochloride	0	0	0	0	0

\*0 = minimal or zero inhibition; +, ++, +++ = mild, moderate, or strong inhibition, respectively.  
**Sources:** Von Moltke LL, Greenblatt DJ, Giancarlo GM, Granda BW, Harmatz JS, Shader RI. Escitalopram (S-citalopram) and its metabolites in vitro: cytochromes mediating biotransformation, inhibitory effects, and comparison to R-citalopram. *Drug Metab Dispos.* 2001;29:1002-1009; and Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Drug interactions with newer antidepressants: role of human cytochromes P450. *J Clin Psychiatry.* 1998;59(Suppl 15):19-27.

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**Figure 5.** Efficacy of escitalopram oxalate versus citalopram and placebo in depressed patients (pooled results from three trials) as measured by mean change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) scores. (Reprinted with permission from Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectr.* 2002;7(Suppl):40-44.)

**Figure 6.** Working hypothesis of limbic-hypothalamic-pituitary axis interactions in anxiety and depressive disorders. CRH indicates corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GI, gastrointestinal; SW, slow wave; FR, firing rates.



PCRAS [Figure 4]) that combines somatic and psychological questions to lessen the resistance of confronting psychological questions was developed by the author (M.H.R.). The PCRAS and other informational tools are used regularly by the staff to present patient information to BMR HealthQuest physicians, allowing them to focus on diagnostic issues.

Controversy exists concerning whether self-report scales underreport or overreport information, but it is a place to start. Combining information such as that from the PCRAS with comprehensive personal and family history assists primary care physicians in making an informed decision regarding diagnosis and treatment and whether to refer a patient if more specialized help is needed.

### Current Antidepressant Therapeutic Modalities

The 1950s and 1960s began a revolution in the treatment of depression with the advent of tricyclic antidepressants and monoamine oxidase inhibitors, giving many people hope. These treatment options, however, were often difficult to tolerate. The subsequent development of the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitor venlafaxine hydrochloride in the past decade and a half has greatly enhanced the treatment of depression by offering patients medications that have similar response rates (60% to 70%) as the older agents but are generally more tolerable and safer in an overdose.<sup>7,8</sup>

The addition of atypical antidepressants, such as bupropion hydrochloride, nefazodone hydrochloride, and mirtazapine, has substantially increased the choices available for treating depressed patients. Despite these advances, rates of remission (treatment to full recovery) continue to be low and the risk of relapse and recurrence remains high.<sup>9-11</sup>

The choice of the most appropriate medication varies with individual patient needs. Each class of antidepressant has slightly different modes of action; however, the overall response rates are similar between classes (60% to 70%).<sup>10</sup> For example, a patient receiving multiple medications for a variety of comorbid medical illnesses would be a good candidate for an agent that did not interact significantly with the cytochrome P-450 enzymes, the enzymes responsible for the oxidative biotransformation of many drugs used in clinical practice.<sup>12,13</sup> The inhibitory effects of various SSRIs on specific enzymes in this metabolic pathway are listed in the *Table*.<sup>12,14</sup>

### Understanding Rating Scales

Antidepressant efficacy is typically measured in clinical trials by standard rating scales. Two commonly used scales include the Montgomery Asberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HAMD).

The MADRS is administered by an interviewer. This scale evaluates 10 depressive symptoms. Each area is rated on a 7-point scale (0 to 6) from mild to severe symptoms. Developed by Asberg and Montgomery<sup>15</sup> in 1979, this scale is especially effective for measuring change in symptoms with treatment over time.

The HAMD also provides an indication of a patient's level of depression.

The higher the total HAMD score, the more severe the depression. The original HAMD contained 17 items, but many versions now exist. It was first introduced by Hamilton<sup>16</sup> in 1960, and was developed to measure the outcome of treatment, not for use as a depression screening or diagnostic tool.

### New Antidepressants Escitalopram

Two new antidepressants may provide improved antidepressant efficacy. Escitalopram oxalate, the S-isomer of the SSRI citalopram, offers antidepressant efficacy with potential reduction in the side effects associated with the R-isomer of the parent compound. As shown in *Figure 5*, pooled data from three randomized, multicenter trials confirm that 8 weeks of treatment with escitalopram oxalate (10 mg to 20 mg daily) is significantly more effective than placebo in alleviating depression, as measured by a change from baseline scores on the MADRS.<sup>17</sup> The onset of action and magnitude of clinical effect associated with escitalopram may be superior to that observed with citalopram hydrobromide, demonstrating statistically significant efficacy relative to citalopram on changes in mean MADRS total scores at weeks 1 and 8.<sup>17</sup>

Another study focused on the efficacy and tolerability of escitalopram in a population of moderately to severely depressed patients who had had intolerable

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erable adverse events during 8 weeks of treatment with either citalopram, fluoxetine hydrochloride, paroxetine hydrochloride, or sertraline hydrochloride. These patients were switched to treatment with escitalopram, and 85% were able to continue treatment; MADRS scores continued to decline.<sup>18</sup>

### Duloxetine

Duloxetine hydrochloride is a dual norenergic and serotonergic reuptake inhibitor that is expected to receive Food and Drug Administration approval in 2003. A controlled, multicenter, double-blind study documents the efficacy and safety of duloxetine (titrated over 3 weeks to 120 mg/d) in the treatment of depression as measured by the 17-item HAMD.<sup>19</sup> Another controlled, multicenter study indicates that in addition to its antidepressant properties, duloxetine hydrochloride (60 mg/d) may also provide significant relief from painful physical symptoms.<sup>20</sup> The drug was also well-tolerated, with rates of discontinuation comparable to those observed for other SSRIs.<sup>20</sup>

### Novel Therapeutic Targets Corticotropin-releasing Factor in Depression

The core physiologic response to stress involves the hypothalamic-pituitary axis (HPA) and the sympathetic nervous system.<sup>21</sup> Figure 6 illustrates a working

hypothesis to explain interaction between the limbic system and the HPA. An abbreviated explanation of these interactions is as follows: A stressor activates the hypothalamus to secrete corticotropin-releasing factor (CRF), a neuropeptide that in turn stimulates production of adrenocorticotropin hormone (ACTH) from the anterior aspect of the pituitary gland. The increased production of ACTH is associated with a corresponding surge in release of glucocorticoids from the adrenal gland. This chain of events is a physiologically appropriate adaptation to acute stress. However, chronic elevations of either of these two groups of compounds have negative effects on metabolic, vegetative, and immune function in susceptible individuals and may exacerbate or cause anxiety and mood disturbances.<sup>21</sup>

The massive body of work exploring the relationship between stress, CRF, and depression confirms a link between clinical manifestations of depression in adults and a dysfunctional endocrine response to stress.<sup>22</sup> For example, cerebrospinal fluid levels of CRF are higher in depressed patients than they are in control subjects or patients with schizophrenia.<sup>23</sup>

Furthermore, it is hypothesized that early stressful life events may sensitize children to later depression and anxiety by inducing a cascade of long-term neuroendocrinologic responses. One result of

◀ **Figure 7.** Efficacy of the NK1 antagonist MK-869 in outpatients with major depressive disorder (MDD) and moderately high anxiety: Mean change from baseline in the 21-item Hamilton Depression Rating Scale (HAMD) scale. (Adapted with permission from Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, et al. *Distinct mechanism for antidepressant activity by blockade of central substance P receptors.* *Science.* 1998;281:1640-1645. Copyright 1998 American Association for the Advancement of Science.)

this phenomenon is hypersecretion of CRF, which is consistent with the observation that the hypothalamic-pituitary-adrenal axis is hyperactive in individuals with depression.<sup>24</sup> Although this relationship requires further long-term longitudinal studies, it does offer an attractive and novel pharmacologic target for new antidepressant drugs. Multiple manufacturers have already developed CRF antagonists, that is, agents that ultimately inhibit glucocorticoid release by binding to CRF receptors in the brain. Early studies in animals as well as in patients with depression and anxiety are promising.<sup>21</sup> Although long-term glucocorticoid suppression is not feasible, an agent that provides neurohormonal balance rather than blockade may theoretically be of great benefit in, for example, depressed or anxious patients with diabetes or cardiovascular disease.

### The Role of Substance P

Substance P, neurokinin A, and neurokinin B are three related peptides that play a role in the stress response. Substance P is the most profuse neurokinin (NK) in mammals and the receptor with the greatest affinity for it (NK1) is concentrated in regions of the brain that regulate the stress response and affective behavior.<sup>25,26</sup> The NK1 receptor also interacts in a complex fashion with noreadrenergic and serotonergic systems<sup>25</sup>; experimental work indicates that administration of antidepressants that act along these pathways may down-regulate production of substance P, suggesting its potential role in the pathophysiology of depression and providing another potential mechanism of action for antidepressant agents.<sup>25,27</sup>

Drugs that antagonize the NK1 receptor may be the novel antidepressant agents of the future. The first non-peptide NK1 antagonist was described in 1991,<sup>28</sup> and since then, multiple agents with increasing selectivity have been synthesized and advanced toward clinical development. In one multicenter, well-controlled clinical trial in outpatients with major depressive disorder and moderately high anxiety, the NK1 receptor antagonist MK-869 (300 mg/d) was significantly more effective than placebo and comparable to paroxetine hydrochloride (20 mg/day) in lowering scores on the 21-item HAMD Scale and the Hamilton Anxiety Scale after 6 weeks of treatment (*Figure 7*).<sup>25</sup> Adverse events associated with MK-869 in this trial were comparable to those of placebo and significantly less troublesome than the increased fatigue, nausea, and sexual dysfunction reported by patients receiving paroxetine.<sup>25</sup>

### Transcranial Magnetic Stimulation

The use of magnets to stimulate healing and positive medical effects has a long history, dating as far back as 2000 years.<sup>29</sup> Transcranial magnetic stimulation (TMS) has received particular attention during the past several years. It is a noninvasive technique that applies alternating magnetic fields to generate an electrical current that is sent through cortical tissue in various parts of the brain and thereby increases or decreases cortical excitability, blood flow, receptor density, or hormone concentrations. The ensuing behavioral or cognitive effects have provided researchers with a tool for linking specific neurologic structures to function and, most recently, for developing a possible strategy for treating psychiatric disorders such as major depression, bipolar disorder, obsessive-compulsive disorder, posttraumatic stress syndrome, and others.<sup>30</sup>

Results from a variety of open and controlled clinical trials have been promising. A meta-analysis of open TMS trials suggests that this technique does offer antidepressant activity of uncertain clinical effect, whereas a meta-analysis of 23 controlled (TMS vs sham) studies found significantly superior antidepressant activity of little meaningful clinical

magnitude.<sup>30</sup> The investigators hypothesize that TMS may offer clinical benefit when used in combination with antidepressant agents.<sup>30</sup>

### Psychotherapeutic Treatment

Physicians need to give careful thought to their selection of antidepressants, especially for those patients on multiple medication regimens. More information is available than ever before about drug-drug interactions and side effect profiles of newer-generation antidepressants. Although several classes of newer-generation drugs now available are generally equally effective, they offer differing advantages and disadvantages based on modes of action and side effect profiles. Patients who are more psychologically minded may be offered additional non-drug treatment options earlier than patients who may be resistant to such ideas.

Many nondrug modes of therapy are available; two that have shown utility are cognitive-behavioral therapy and interpersonal therapy. Cognitive behavioral therapy can be effective at modifying self-destructive/defeating lifestyles and behaviors, as well as treating the residual symptoms of depression following antidepressant therapy.<sup>31</sup>

Interpersonal therapy is based on the supposition that depression is a medical illness that can be triggered or exacerbated by interpersonal difficulties; treatment therefore is devoted to identifying and modifying interpersonal problems resulting from life's stressors such as grief, role disputes, role transitions, or interpersonal deficits.<sup>32</sup>

### Push to Remission, Not Response

What is the most appropriate end point for evaluating the efficacy of an antidepressant treatment? Typically, researchers and clinicians tend to identify a response as a greater than or equal to 50% fall from baseline values in the HAMD or other rating scales. Even significant improvement, however, does not necessarily imply complete relief of symptoms. For example, if the patient's baseline score was extremely high, even a 50% decrease associated with treatment could still leave the patient with residual symptomatology that may impair psychosocial function

or leave the patient vulnerable to yet another depressive episode in the future.

Therefore, it is far more effective to push for a greater therapeutic response, that is, remission. The criteria for remission include minimal or no symptoms, a return to functionality, and the absence of positive diagnostic criteria for depression. Remission is often measured quantitatively as a HAMD score of 7 or less.

It is not appropriate to assume that patients who fail to achieve remission or even partial response are resistant to treatment. Factors that may compromise a therapeutic response (*Figure 1*) should be addressed before concluding that a treatment failure has occurred. In particular, augmentation strategies that allow the combination of different mechanisms of action should be considered, as should the combination of an SSRI antidepressant or noradrenergic reuptake inhibitor with an anxiolytic agent if the patient is experiencing anxiety disorders.

### Comments

The combination of the pressures of an office practice and the prevalence of comorbid disorders leads many physicians to miss the diagnosis of depression, particularly in patients who present with somatic rather than psychological symptoms. More accurate differential diagnosis may be achieved by paying meticulous attention to somatic complaints, the possibility of comorbidity, and its relationship to depression and by developing strategies in the office for being more efficient at gathering data. Trained personnel can collect important information, allowing the physician to focus on the crucial and often complex task of diagnosis.

New pharmacologic and nonpharmacologic interventions are rapidly becoming available to primary care physicians. Use of these treatment modalities until a patient achieves remission is critical to the long-term care of depressed patients, because response without remission can lead to noncompliance, poorer management of coexistent medical conditions, and the reappearance of disabling depressive symptoms.

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