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. 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 illness, 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. Furthermore, depression and anxiety occur more often comorbidly than alone. According to the National Comorbidity Survey of more than 8000 adults, 58% of respondents with lifetime major depression have also had an anxiety disorder. 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
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. 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.

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.

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

Date ___________
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. 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

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<tr>
<td><strong>In Vitro Inhibition of Human Cytochrome P-450 Enzymes by Selective Serotonin Reuptake Inhibitors</strong></td>
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<tr>
<th>P-450 Enzymes</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A</th>
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<tr>
<td><strong>Escitalopram oxalate</strong></td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Citalopram hydrochloride</strong></td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fluoxetine hydrochloride</strong></td>
<td>+</td>
<td>+</td>
<td>+ to ++</td>
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<tr>
<td><strong>Fluvoxamine maleate</strong></td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
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<tr>
<td><strong>Paroxetine hydrochloride</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Sertraline hydrochloride</strong></td>
<td>+</td>
<td>+</td>
<td>+ to ++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Venlafaxine hydrochloride</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
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*0 = minimal or zero inhibition; +, ++, +++ = mild, moderate, or strong inhibition, respectively.


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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.7,8

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.9,11

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%).10 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.12,13 The inhibitory effects of various SSRIs on specific enzymes in this metabolic pathway are listed in the Table.12,14

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 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 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.17 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 8.17

Another study focused on the efficacy and tolerability of escitalopram in a population of moderately to severely depressed patients who had had intol-
erable adverse events during 8 weeks of
treatment with either citalopram, fluoxetine
hydrochloride, paroxetine hydrochloride, or sertraline hydrochlo-
ride. These patients were switched to
treatment with escitalopram, and 85% were able to continue treatment; MADRS
scores continued to decline.18

Duloxetine
Duloxetine hydrochloride is a dual na-
drenergic and serotoninergic 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 depres-
sion as measured by the 17-item
Hamilton Depression Rating Scale (HAMD).
Another controlled, multi-
center study indicates that in addition to
its antidepressant properties, duloxetine
hydrochloride (60 mg/d) may also pro-
vide significant relief from painful phys-
ical symptoms.20 The drug was also well-
tolerated, with rates of discontinuation
comparable to those observed for other
SSRIs.20

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.21 Figure 6 illustrates a working
hypothesis to explain interaction between
the limbic system and the HPA. An
abbreviated explanation of these inter-
actions is as follows: A stressor activates
the hypothalamus to secrete corti-
cotropin-releasing factor (CRF), a neu-
ropeptide that in turn stimulates pro-
duction of adrenocorticotropic hormone
(ACTH) from the anterior aspect of the
pituitary gland. The increased produc-
tion of ACTH is associated with a cor-
responding surge in release of glucocor-
ticoids from the adrenal gland. This chain
of events is a physiologically appropriate
response 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 individ-
uals and may exacerbate or cause anxiety
and mood disturbances.21

The massive body of work exploring
the relationship between stress, CRF, and
depression confirms a link between clini-
cal manifestations of depression in adults
and a dysfunctional endocrine response
to stress.22 For example, cerebrospinal
fluid levels of CRF are higher in
depressed patients than they are in con-
tral subjects or patients with schizo-
phrenia.23

Furthermore, it is hypothesized that
early stressful life events may sensitize
children to later depression and anxiety
by inducing a cascade of long-term neu-
roendocrinologic responses. One result of
this phenomenon is hypersecretion of
CRF, which is consistent with the obser-
vation that the hypothalamic-pituitary-
adrenal axis is hyperactive in individ-
uals with depression.24 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 ulti-
mately 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.21 Although long-term gluco-
corticoid suppression is not feasible, an
agent that provides neurohormonal bal-
cance rather than blockade may theoreti-
cally be of great benefit in, for example,
depressed or anxious patients with dia-
betes or cardiovascular disease.

The Role of Substance P
Substance P, neurokinin A, and neu-
rokinin B are three related peptides that
play a role in the stress response. Sub-
stance P is the most profuse neurokinin
(NK) in mammals and the receptor with
the greatest affinity for it (NK1) is con-
centrated in regions of the brain that reg-
ulate the stress response and affective
behavior.25,26 The NK1 receptor also inter-
acts in a complex fashion with nor-
adrenergic and serotoninergic systems25;
experimental work indicates that admin-
istration of antidepressants that act along
these pathways may down-regulate pro-
duction of substance P, suggesting its
potential role in the pathophysiology of
depression and providing another poten-
tial mechanism of action for antidepress-
ant agents.25,27
Drugs that antagonize the NK1 receptor may be the novel antidepressant agents of the future. The first nonpeptide NK1 antagonist was described in 1991, 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).

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.

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. 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.

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. The investigators hypothesize that TMS may offer clinical benefit when used in combination with antidepressant agents.

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.

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.

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.
References


