DEPRESSION IN PRIMARY CARE

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Depression is common in primary care settings, affecting at least 10% of primary care patients. It carries medical and psychiatric comorbidity, increasing the risk of cardiovascular disease, diabetes, hypertension, stroke, medically unexplained (functional) symptoms, chronic pain, anxiety disorders, and substance abuse. Diagnosis and treatment are straightforward for many patients. The greatest current challenge is to recognize and relieve symptoms of treatment-resistant depression. This article reviews current approaches to diagnosing and treating depression, especially treatment-resistant forms of depression. (*Ethn Dis*. 2007;17[suppl 2]:S2-28–S2-33)

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INTRODUCTION

Depression is common, has serious medical and social consequences, and is generally undertreated. Approximately 50% of depression is treated in primary care settings, and improving our ability to recognize and treat depression in primary care settings is an important step to addressing this public health concern. The aims of this paper are:

- to review the epidemiology and consequences of depression, especially as it presents in primary care settings;
- to discuss practical approaches to treating depression in primary care settings; and
- to present findings on newer approaches to treating depression, including findings from the STAR*D study, which might guide further thinking on the treatment of resistant forms of depression.

EPIDEMIOLOGY AND CONSEQUENCES OF DEPRESSION

Depression is common in the general population, with a point prevalence of ≈5% and a lifetime prevalence of 16%. Among women, the lifetime prevalence is >20%. In primary care ambulatory settings, prevalence of depression consistently runs around 10%–12%, while in subspecialty clinics such as oncology, renal, and cardiology clinics, as many as 30%–40% of patients meet the criteria for a clinically significant form of depression. A somewhat dated but still useful overview of depression in primary care can be found in the Depression in Primary Care monographs published by the US Department of Health and Human Services.[1]

The medical and social consequences of depression are underappreciated. Having a history of depression roughly doubles the risk of developing coronary artery disease and increases the risk of developing hypertension or stroke by at least 50%. Das et al recently reported findings from the Interheart study, which showed that psychosocial stress was responsible for ≈30% of the attributable risk of acute myocardial infarction.[2] In particular, a sense of hopelessness appeared to be strongly correlated with adverse cardiovascular outcomes. Similarly, Yusuf et al found that psychosocial factors represented the third greatest risk factor for acute myocardial infarction, after smoking and elevated ApoB/ApoA1 ratios.[3]

Not only does depression roughly double the risk of developing new heart disease, it worsens the prognosis for existing heart disease. For example, Lesperance and Frasure found that patients with depression one week after myocardial infarction had a six-fold greater risk of dying within 18 months compared with non-depressed patients, even after controlling for other risk factors.[4]

The explanations for the relationship between depression and heart disease are not entirely understood but probably include behavioral changes such as reduced compliance with medication, reduced activity, and dietary indiscretion. In addition, much evidence has accumulated linking altered platelet aggregation (''stickiness'') in depression with increased risk of cardiovascular morbidity and mortality. This has therapeutic implications as well, since platelets release serotonin as part of the platelet activation pathway, and platelet serotonin reuptake transporters are affected by the same serotonin reuptake inhibitors that are effective in treating depression and anxiety dis-

Table 1. DSM-IV Diagnostic Criteria for Major Depressive Episode[25]

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change in functioning; with at least one of the symptoms either depressed mood or loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
  (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty or observation made by others (eg, appears tearful). Note: In children and adolescents can be irritable.
  (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others).
  (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
  (4) Insomnia or hypersomnia nearly every day.
  (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  (6) Fatigue or loss of energy nearly every day.
  (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
  (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, without a specific plan, or a suicide attempt or a specific plan to commit suicide.
B. The symptoms do not meet criteria for mixed episode (manic and depressive symptoms).
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
E. The symptoms are not better accounted for by bereavement, ie, after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

orders. For further information on the relationship between depression and cardiovascular disease, the review by Whooley is recommended.[5]

In addition to being a risk factor for cardiovascular disease, depression has been linked to an increased risk for type 2 diabetes mellitus, osteoporosis among women, and decreased immune functioning. Further, depressed patients are more likely to present with medically unexplained somatic symptoms, are more likely to present with chronic nonmalignant pain syndromes, and are at greater risk of overutilizing medical services. The last finding suggests a possible medical cost offset effect whereby the cost of improved diagnosis and treatment of depression in medical settings may be offset by a reduction in usage of other medical services. Although results of controlled trials are not consistent, there seems to be some agreement that, while short term cost savings (cost offsets) may not always be apparent, costs for enhanced depression recognition and treatment programs are generally no greater than those seen for usual care. An especially interesting study comparing a simple assessment/education/monitoring intervention to usual care suggested cost effectiveness greater than that for pneumococcal vaccine and smoking cessation programs and comparable to cost effectiveness of treating severe hypertension.[6]

Three nonmedical consequences of depression are of special importance: disability, suicide, and psychiatric comorbidities. The seminal World Health Organization report on disability and medical conditions predicted that depression will soon, if it has not already, become the leading cause of disability among women, leading to impaired ability at work, school, home, and in relationships.[7]

Almost one half of people who commit suicide, the 11th leading cause of death among adults, saw their primary care physician in the month preceding suicide. This figure compares with only 15% of patients who saw a mental health professional and underscores again the importance of primary care practitioners in the treatment of depression and the prevention of suicide.[8]

Other psychiatric disorders contribute to medical morbidity and unnecessary healthcare utilization. Approximately 50% of depression patients suffer from other serious psychiatric conditions such as panic disorder, somatization disorder, substance abuse, and pain disorder, complicating the job of the primary care clinician.[9]

RECOGNIZING AND TREATING DEPRESSION IN PRIMARY CARE

The diagnostic criteria for a major depressive episode are listed in Table 1, but a better guide to recognizing depression in primary care settings consists of a simple two-question screen:[10]

1. "During the past month, have you often been bothered by feeling down, depressed, or hopeless?"
2. "During the past month, have you often been bothered by little interest or pleasure in doing things?"

The two-question screen is >90% sensitive if either question is answered in

Table 2. First-line antidepressants for treating depression in primary care

Generic name	5-HT	NE	Average half life (hrs)	P450 inhibition	Usual dosages, mg	Comments
Fluoxetine	+	0	84	2D6, 3A4, 2C9	10 – 60	Generic available
Sertraline	+	0	25	Minor 2D6	25–200	Generic available
Paroxetine	+	0	21	2D6, 3A4	10 – 60	Weight gain
Citalopram	+	0	35	Minor 2D6	10 – 60	
Escitalopram	+	0	35	Minor 2D6	10 – 40	
Venlafaxine[b]	+	+	5	Minor 2D6	75 – 450	Hypertension
Duloxetine	+	+	12	2D6	20 – 60	Contraindicated in hepatic impairment; hypertension
Bupropion[a,b]	0	+	12	2D6	150–450	Seizures
Mirtazapine	+	+	30	None	15 – 60	Agranulocytosis

5-HT = effect on serotonin
NE = effect on norepinephrine
a. mechanism of action of bupropion less clear, but also affects dopamine
b. extended-release form available

the affirmative, making longer questionnaires unnecessary. The second question (anhedonia) is especially important as a measure of treatment outcome. As will be seen in the last section of this paper, most depressive episodes are not treated to full remission of symptoms, and a failure to resume enjoyment of previously pleasurable activities is an important indicator of incomplete treatment.

Despite the utility of the two-question screen, many depressed patients who fear the stigma associated with a mental disorder will deny depressive changes except for changes in somatic symptoms. For such patients, additional history from a significant other may be helpful in clarifying the diagnosis. In some cases, however, the diagnosis remains unclear and treatment may begin based on a high index of suspicion, in the belief that the favorable risk-benefit ratio associated with newer antidepressants is sufficient justification. The use of an antidepressant in these instances can be explained to the patient who denies depressive changes on grounds of effects on somatic symptoms (eg, pain, sleep, energy).

Asking about suicidal thoughts requires a sensitive, indirect approach for many patients, for whom thoughts of suicide, or even of depression itself, are interpreted as signs of personal or moral weakness.[11] Such patients, who are in the likely majority, will deny having thoughts of wanting to die. Thus, rather than asking directly about suicidal thoughts, such patients should be asked questions relating to hopelessness or lack of a meaningful future. For example, a clinician might express empathy for the patient's situation and ask about whether she/he is feeling overwhelmed: "It's got to be tough, with things at home the way they are, and now with this new medical situation. Does it get to be too much sometimes? Do you feel like you'd like to crawl in bed and pull the covers over your head? Do you sometimes think it wouldn't be so bad if you never got up? If you just passed away in your sleep? Does it go beyond that? Do you ever think about taking things into your own hands?" By this point, patients usually have indicated one way or the other whether they are feeling hopeless or suicidal and appropriate action can be taken.

Once a diagnosis of depression is strongly suspected, a brief physical assessment should be carried out to rule out other conditions masking as depression. The screening does not need to be exhaustive, but screening for thyroid disease and sleep apnea and looking for a possible link between medications and symptoms of depression may be useful.[12–16] Medications commonly associated with depressive changes include corticosteroids, interferon, and perhaps beta-blockers (which may cause exercise intolerance and lethargy but rarely true depression). Many other medical conditions and medications have been associated with depression, but their consideration is usually suggested by other findings in the history and examination.

Treatment most often begins with a selective serotonin reuptake inhibitor (SSRI) or mixed serotonin-norepinephrine reuptake inhibitor (Table 2). The advantages of SSRI antidepressants include favorable risk/benefit ratio, with few medically serious adverse effects, low risk of serious complications following overdose, efficacy in common co-morbid conditions such as anxiety disorders and premenstrual syndrome, and availability of generic alternatives in some cases. The selection of a specific antidepressant may be made on the basis of prior response, family history of successful response, and patient preference.

With the high co-morbidity between depression and anxiety, antidepressants should be started at a low dose to prevent exacerbation of anxiety symptoms during the first two weeks of

treatment. It is preferable to start at the lowest dose possible and increase weekly to the desired target dose, using a benzodiazepine such as clonazepam for several weeks or months if emergent anxiety symptoms such as panic attacks threaten compliance.

While SSRI antidepressants are the overwhelming choice for initial treatment, other antidepressants are useful, especially when concomitant effects are desirable (eg, antismoking effects with bupropion or treatment of chronic pain with nortriptyline).

Along with an antidepressant, short-term prescription of a hypnotic may be useful in the initial stages of treatment. Use of a hypnotic should be accompanied by advice on sleep hygiene, including reduction of caffeine (it is not unusual in my clinics to see patients who drink liters of caffeine-containing tea or soda daily), avoidance of naps longer than 30 minutes, and efforts to get out of bed at a desired time.

''Psychotherapy'' in primary care settings is an essential component to treating depression in primary care settings; it consists primarily of psychoeducation and will promote compliance and improve outcomes. Key elements of office-based primary care psychoeducation include:

1. Educating the patient, and partner when possible, about the biomedical nature of depression. This helps to reduce stigma associated with this mental disorder and reduces the patient's sense of guilt due to a false belief that depression is caused by personal failure. It also helps partners to understand their critically important role in supporting the patient while treatment is getting started;
2. Educating the patient and partner about the nature of antidepressant treatment. It is a common belief that antidepressants are addictive, that they act as stimulants similar to amphetamines, and that the use of an antidepressant represents a failure on the part of the patient. It should be explained that using an antidepressant is similar to using an antihypertensive, insulin, or any other common medication with which the patient and partner are familiar;
3. Suggesting, encouraging, and monitoring behavior change, including changes related to sleep hygiene, modest exercise, and food intake, all of which may contribute to antidepressant effects.
4. Advising patients and partners on the expected treatment course and outcome. Most patients will want to know how long treatment will take (several months for full effect), and how long they will continue on medication. The best advice on the length of antidepressant treatment, based on relapse data, is one year when the episode is the first and ''indefinitely'' for subsequent episodes of depression.

An underappreciated area for many physicians is the effect of race and culture on diagnosis and treatment of mental illness, including attitudes toward mental illness, access to medical care, ethno-phamarcologic differences, and availability of alternative sources of support.[17] Individuals from different backgrounds may interpret depression in various ways – as a medical condition, spiritual failure, or punishment. Similarly, cultural attitudes toward treatment will vary. Continuing education in this area, as well as a willingness on the part of the physician to explore personal and patient attitudes, is strongly encouraged.

Additional treatments and therapies may be used to treat depression that does not respond with primary care approaches, but these are most often carried out in specialized mental health settings. These therapies include electroconvulsive therapy (ECT), the most effective treatment for depression, mania, and catatonia.[18] Unfortunately, ECT is underutilized, in part due to media portrayals and public perception. Older movies such as *One Flew Over the Cuckoo's Nest* portrayed ECT as it was practiced more than 30 years ago, practices barely resembling ECT as it is administered today. Current standards for ECT usually require the treatment to be delivered in a site such as a recovery room, which has adequate medical emergency equipment and personnel, with an anesthesiologist present in addition to the attending psychiatrist. Oxygen, a short-acting barbiturate, and a muscle relaxant are administered prior to the ECT, so that the risks of fracture, uncontrolled seizures, or prolonged hypoxia are greatly reduced. An intracranial mass or increased intracranial pressure remain relative contraindications, but ECT has been administered safely even in the presence of these complications. Electroconvulsive therapy (ECT) treatment for a depressive episode is usually given three times a week for two to three weeks, and an antidepressant is often started after ECT is completed to reduce the risk of relapse. Cognitive changes invariably include memory loss around the time the treatments are administered and some loss of memory for events occurring in the days prior to treatment, but long-term memory changes are unusual and controversial. Given that depression is associated with reductions in the size of hippocampi (responsible for long-term potentiation of memory), most depressed patients will likely experience an improvement in laying down new memories after treatment.

NEWER APPROACHES TO TREATING DEPRESSION

Newer approaches to treating depression of which primary care physicians might have heard include the selegiline patch, vagus nerve stimulation (VNS), and repetitive transcranial mag-

netic stimulation (rTMS). The role of each of these is limited to treatment-resistant depression, and rTMS is limited to research settings pending US Food and Drug Administration (FDA) approval.

The selegiline patch is applied daily at a dose of 6 mg/24 hours. It is an irreversible inhibitor of the monoamine oxidase (MAO)-B enzyme responsible for degradation of dopamine and phenylethylamine (and, to a lesser degree, serotonin and norepinephrine) in the central nervous system and platelets. Because the MAO-A form present in the gut and liver is not inhibited, dietary tyramine restrictions are not needed for the 6-mg dose. However, drug interactions with meperidine, dextromethorphan, other antidepressants, St. John's wort, and other stimulating medications must be observed.

VNS involves the implantation of a silver dollar-sized stimulator in the left upper chest, with the electrodes wrapped around the vagus nerve.[19] A stimulus is given for ≈30 seconds every 5 minutes, but patients may activate or deactivate the device. It is currently approved for the treatment of partial seizures and depression, though lack of a placebo control made FDA approval for treatment of depression controversial. Common side effects (other than postsurgical complications) include hoarseness and difficulty swallowing.

rTMS involves placing a magnetic stimulus over an area of the brain (eg, left fronto-temporal) where a stimulus at a frequency of 1–2 Hz is applied.[20] This induces an electrical stimulus in underlying neurons, which, depending on the frequency of the stimulus, may be either activating or inhibitory. Earlier rTMS occasionally produced a generalized seizure, but current use finds this to be a rare complication. Data supporting the efficacy of rTMS over sham treatments has not been conclusive, and the treatment is still considered experimental.

THE SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION STUDY (STAR*D)

Little data has been available to guide clinicians in the treatment of depression, except what has been published with support from pharmaceutical companies. Since the aim of these companies is to win FDA approval with minimum expense, studies have excluded patients less likely to respond (eg, those with co-morbid medical and psychiatric conditions), have used response (eg, a 50% reduction in symptoms) rather than remission (a nearly complete resolution of symptoms) as the primary outcome, and have limited the length of studies to just the length of time in which statistically significant separation occurs between drug and placebo.

To address these shortcomings, the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) was initiated, and the first results have recently been published.[21] This study is aimed at answering questions about treatment choices and outcomes for depression and is important for its design as well as its findings. Design features include:

1. funding from the National Institutes of Mental Health, not the pharmaceutical industry;
2. selection of patients who are more representative of patients seen in ordinary clinical settings (eg, patients who have concomitant medical and psychiatric disorders, patients with chronic or recurrent depression);
3. focus on patient outcomes that are more meaningful to patients and families – remission of most or all symptoms, not just response to treatment; and
4. emphasis on approaches to patients whose symptoms do not remit after the first treatment with an SSRI.

The last design feature is especially important, as more than half of patients treated for depression with an antidepressant do not meet criteria for remission, and a variety of additional treatment choices might be considered by the clinician and patient. Until now there has been little to guide decision-making from among these options.

In the study design, the initial phase of treatment (level 1) enrolled >4000 patients with nonpsychotic depression, during which patients received the SSRI citalopram at flexible dosages up to 60 mg (41 mg mean) for up to 14 weeks.[22] Only 27.5% of patients met criteria for remission, with no difference between patients treated in primary care or psychiatric settings. Those who could not tolerate citalopram or whose symptoms failed to remit entered level 2 of the study and were offered the choice between switching to another antidepressant (extended-release venlafaxine, sertraline, or sustained-release bupropion) or adding an augmenting agent (bupropion, buspirone, or cognitive behavior therapy) to the citalopram.[23,24] Level 3 included patients who did not achieve remission or could not tolerate the treatment received at level 2. These patients were randomly assigned to mirtazapine or nortriptyline.

Results from the switching strategy in level 2 showed remission rates of 18%–24%, with no differences between sertraline (18.1%), venlafaxine (24.4%), and bupropion (21.3%). For the augmentation strategy, results were remission rates of 29.7% for citalopram plus bupropion and 30.2% for citalopram plus buspirone. These were not statistically different, but buspirone was less well tolerated. Results for the cognitive behavior group have not yet been published.

These results differ from current clinical practice, in which the most common approach to treating a depression that has not remitted with an SSRI is to switch to an antidepressant with

another mode of action (dual actions on norepinephrine and serotonin or actions on dopamine and norepinephrine). STAR*D seems to suggest that switching to another SSRI may be just as effective a strategy.

The data from level 2 seem to suggest that augmenting the SSRI may be more effective than switching to another antidepressant. Though the study was not designed to compare different strategies, so no firm conclusion can be drawn about switching versus augmenting, it seems reasonable to try switching if the SSRI was not tolerated or if the response was minimal. If the response was at least 50% reduction in symptoms, perhaps the better strategy might be to add bupropion or buspirone.

In level 3, patients were randomly assigned to mirtazapine (up to 60 mg/day) or to nortriptyline (up to 200 mg/day) for up to 14 weeks of treatment. Remission rates (12.3% with mirtazapine and 19.8% with nortriptyline) did not differ statistically between the treatment options and the treatments did not differ in tolerability. However, one wonders if the results suggest that tricyclic antidepressants ought to be used more often.

Several limitations of the STAR*D study should be mentioned. There was no placebo comparison, different strategies cannot be compared directly, and a number of popular treatments were not included (eg, mood stabilizers, atypical antipsychotics, hypnotics, and benzodiazepines). Nevertheless, useful data have been published, and more results are forthcoming.

CONCLUSIONS

Depression is a major public health concern and is associated with significant medical and psychiatric co-morbidity and disability. Its treatment can and, in most instances, should be started in primary care settings with a brief psychoeducational approach and prescription of an SSRI or related medication. However, at least 50% of patients will have a less-than-satisfactory response, and the greatest challenge will be to learn how to treat treatment-resistant forms of depression. Given a frequent lack of access to psychiatric resources, this will require primary care physicians to become more familiar with alternative approaches to treating depression, guided by the results of the STAR*D study.

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AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Elliott
Manuscript draft: Elliott