The Evaluation and Management of Depression in Primary Care: An Evidence-Based Review

PART 2: Treatment

Case Study and Commentary: Rohn S. Friedman, MD, and Christopher T. Clancy, MD

Abstract
Depression is a common, treatable disorder that remains underdiagnosed and undertreated. The primary care physician must be alert to the symptoms of depression and be aware that depression may present in somatic guise in primary care. Once the diagnosis of depression is made, the physician must evaluate for psychiatric and medical factors that bear on etiology and management, including the need for hospitalization or psychiatric consultation. Psychiatric and medical comorbidities are common in depressed patients. Treatment options for depression include psychotherapy, pharmacotherapy, and alternative treatments. Psychotherapy has demonstrated effectiveness as monotherapy for the treatment of mild to moderate depression and is beneficial as conjoint treatment with biological therapy for moderate and severe depression. Among available antidepressant medications, the preponderance of evidence favors equal efficacy among medications. There is no good evidence to support the use of alternative treatments for depression in primary care at this time. Problems in evaluating the literature on the efficacy of therapies are discussed.

Instructions
The following article, “The Evaluation and Management of Depression in Primary Care: An Evidence-Based Review,” is a continuing medical education (CME) article. To earn credit, read the article (Part 1 and Part 2) and complete the CME evaluation form on page 119.

Objectives
After participating in the continuing education activity, primary care physicians should be able to:
1. Be familiar with the epidemiology and clinical presentations of depression
2. Know how to screen for and diagnose depression in primary care
3. Evaluate the evidence for efficacy of treatments of depression
4. Know the phases of pharmacologic treatment of depression and the standards for monitoring treatment and seeking consultation

Depression is a common disorder that often goes unrecognized and untreated. In Part 1 of this paper, we discussed the etiology, diagnosis, and evaluation of depression in the primary care setting. In Part 2, we will discuss treatment of depression.

Case Study
Initial Presentation
In Part 1, a 50-year-old woman presented to her primary care physician with complaints of hot flashes, palpitations, left arm numbness, chest pain, and a feeling of impending doom. After talking further with the patient, the physician determined that she met the diagnostic criteria for major depressive disorder as well as for generalized anxiety disorder, panic disorder, and caffeine abuse. There is no evidence of psychosis, suicidal or homicidal ideation, or inability to care for herself. The physician considers which treatment to recommend.

What are problems in evaluating the literature on efficacy of depression treatments?
Problems in Evaluating the Literature
Some caveats must be borne in mind when evaluating the literature on the efficacy of therapies for treatment of depression in primary care.

Study Setting
Many medications and therapies have not specifically been tested in primary care populations, especially in randomized controlled clinical trials (RCTs). This is especially true of trials in patients with dysthymia, minor depression, and subtypes other than pure uncomplicated major depression. Often, trials of medications in psychiatric settings exclude patients with preexisting medical or psychiatric conditions, even though both are common in primary care.

Misleading Negative Results
The treatment effect size in published studies of depression is typically on the order of 18% improvement over placebo. The placebo effect itself is strong (30% on average), and only 50% of the placebo-controlled RCTs of newer agents that are ultimately approved by the FDA demonstrate statistically significant effects despite adequate power. This effect size appears to be a reduction from that in trials of first-generation antidepressants, which may reflect shifts from inpatients to ambulatory (less severely depressed, less “classical”) patients, decreased numbers of treatment-naive subjects, shift to an intention-to-treat analysis, and less unintended “unblinding” because of the milder side effects of the selective serotonin reuptake inhibitors (SSRIs). The differential treatment effect between 2 effective agents is likely to be even smaller than with comparison to placebo, meaning that the power of most studies (typically fewer than 100 subjects per arm) to detect a superior treatment is very low [1].

Much of the concern in relation to the treatment of depression in primary care is directed toward health policy and the structure of health care systems. To address such health policy and systems issues, outcome measures need to move beyond symptom improvement to examine direct and indirect costs, functioning, and health-related quality of life. Such studies require sample sizes in the hundreds per cell for cost-effectiveness studies and in the thousands for cost-effectiveness studies [2]. These considerations make it very difficult to interpret negative results, since the studies are so likely to be underpowered; negative results include not just failing to find one medication effective, but perhaps more significantly, failing to find one medication superior or inferior to another. To put it differently, failing to find a medication or treatment superior or inferior to another is not the same as proving that they are equivalent.

Misleading Positive Results
Publication and commercial bias means that studies that have positive results and studies that favor a medication under patent are likelier to be reported. Sometimes studies are set up in a biased fashion, such as comparing a new medication to a subtherapeutic dose or duration of a known medication. These biases inflate the effect size in published studies and magnify the problems discussed above in terms of effect size. Moreover, they mean that any meta-analysis limited to published studies will exaggerate the effect size.

The issue of “efficacy” (whether a treatment is effective under carefully controlled conditions) has been distinguished from “effectiveness” (how treatments that have been proven efficacious actually affect outcome in non-research, real-world settings) [3]. In the research setting, subjects are usually followed with a frequency and intensity that is not practicable in real-world primary care settings, where a typical office visit lasts 15 minutes or less. In the non-research setting, there are no “exclusion” criteria, and pure cultures of a psychiatric diagnosis without comorbidities are unlikely; moreover, in this setting, “usual care” may be a more appropriate control condition than placebo.

Death of Nonmedication Studies
There is a dearth of RCTs of various forms of psychotherapy that meet the same stringent standards expected of medication studies. The lack of an interested funding source has meant that most studies are underpowered with small sample size; moreover, only recently have longer-term studies emerged that look beyond acute response and at a wider variety of quality-of-life variables. Studies looking specifically at primary care settings are even more limited.

- What are treatment options for depression and what is their evidence base?

Psychotherapy

Summary

- Psychotherapy has demonstrated effectiveness as monotherapy for the treatment of mild to moderate depression.
- Psychotherapy has demonstrated a benefit as conjoint treatment with biological therapy for moderate and severe depression and for chronic or recurrent depression.
- The best studied therapies are cognitive behavioral therapy and interpersonal therapy, 2 forms of well-described and operationalized short-term therapy. There is inadequate data to evaluate the efficacy of other forms of psychotherapy.
Evidence
In studies not specific to primary care settings, one meta-analysis found that cognitive therapy was superior to waiting list or placebo control conditions and to antidepressants in patients with mild to moderate depression [4]. When the American Psychiatric Association and Agency for Healthcare Research and Quality (AHRQ) first released their practice guidelines for the treatment of depression, they were criticized for underestimating the efficacy of psychotherapy as a first-line treatment for depression, even in cases of more than mild-to-moderate severity [5]. A meta-analysis and analysis of pooled data by DeRubeis reanalyzed the severely depressed subgroups of 4 major RCTs and found comparable effect size between antidepressants and cognitive behavioral therapy [6]. A large “mega-analysis” (a meta-analysis of pooled original data of 595 patients with major depression in 6 standardized treatment protocols) in which subjects were treated with cognitive behavioral therapy alone, interpersonal therapy alone, or interpersonal therapy plus antidepressant pharmacotherapy found that psychotherapy alone was equally effective in milder depressions, but the combined therapy had a highly significant advantage in more severe recurrent depressions [7]. A second large study in the treatment of chronic depression found that the rate of response (48%) was equal in the patients randomized to psychotherapy or to antidepressant alone but was significantly improved (73%) in those randomized to combined treatment [8]. Other studies have found more modest benefit to combined therapy, though “at least nonsignificant differences favoring the combined modality were apparent in virtually every relevant comparison examined” [9]. While the need for further large RCTs across a range of severity levels is evident, the evidence supports the recommendation to consider psychotherapy (cognitive therapy, behavioral therapy, or interpersonal therapy) as monotherapy for mild to moderate depression in patients who prefer that approach (with monitoring so that worsening or failure to respond can be quickly addressed) and as part of combination treatment of severe or chronic or recurrent depression.

If we look specifically at RCTs of psychotherapy in the primary care setting, we find weaker but similar data. Brown and Schulberg reviewed RCTs in primary care settings and concluded that while the studies generally supported the efficacy of psychosocial treatments in primary care, the methodological deficiencies in the trials limited their generalizability [10]. One meta-analysis of counseling in primary care found that counseling provided modest short-term improvement over “usual care” but no long-term advantages [11]. Another RCT found similar results specifically in a population of depressed primary care patients [12].

A few studies have tried to compare medication and psychotherapy in the primary care setting. For the treatment of major depression, in a 4-arm study of amitriptyline prescribed by a psychiatrist versus cognitive behavioral therapy from a psychologist versus counseling and case work by a social worker versus routine care by a general practitioner, Scott et al found that there was marked improvement in all treatment groups over 16 weeks and any superiority of specialist treatment was not sufficient to justify the doubled costs [13]. In a 3-arm RCT comparing amitriptyline, problem-solving therapy (a 6-session behaviorally oriented approach designed to be used in primary care settings in Britain by nonpsychiatrists), and placebo, Mynors-Wallis found that problem-solving therapy was as effective as amitriptyline and had fewer dropouts [14]. Interestingly, in a subsequent report, the authors reported that the combination of antidepressant and problem-solving treatment was no more effective than either one alone in a primary care population [15]. Shulberg and colleagues conducted an RCT in primary care patients with major depression comparing nortriptyline within operationalized AHCPR guidelines, interpersonal psychotherapy, and usual care. Among treatment completers, approximately 70% responded to either full pharmacotherapy or psychotherapy compared to 20% of the usual care patients [16]. Less severely depressed patients who received the nortriptyline improved significantly more rapidly in the first 3 months than patients assigned to interpersonal therapy [17]. When cost-effectiveness of these interventions was examined, both therapies led to better outcomes but higher costs than usual care, though the pharmacotherapy group did slightly better in terms of quality-of-life outcomes and cost [18].

For the treatment of dysthymia and minor depression, Barrett and colleagues in the Treatment Effectiveness Project, an offshoot of the MacArthur Foundation’s Depression and Primary Care Initiative, compared paroxetine to problem-solving therapy in a 3-arm RCT. The remission rate was 80% for paroxetine and 57% for problem-solving therapy, both significantly higher than the 44% remission rate for placebo for dysthymia; for minor depression the remission rate of 64% was similar in all 3 groups [19]. In elderly primary care patients they found moderate benefit for paroxetine but not for problem-solving therapy over placebo in symptom resolution [20].

Pharmacotherapy
Summary

- For the treatment of moderate and severe major depression, medication should be included in the treatment recommendations; for the treatment of mild depression, alternative forms of treatment alone may be considered.
- Among the available antidepressants (Table), the preponderance of the evidence favors equal efficacy among medications. There is some evidence
that tricyclic antidepressants (TCAs) are more effective than SSRIs for severe depressions. There is even slighter evidence that so-called dual action (norepinephrine and serotonin) newer agents, specifically venlafaxine and mirtazapine, may be more effective than pure serotonin reuptake inhibitors for severe depressions and may have more rapid onset of response. The choice of antidepressant therefore is predominantly based on side effects, interactions with medications, effects on comorbid medical illnesses, and cost.

- The preponderance of evidence favors reaching and maintaining a full therapeutic dose and duration of antidepressant treatment, whether treating major or minor depression. This conclusion applies to primary care and geriatric populations as well as to patients seen in psychiatric settings.
- Anxiolytics may be useful ancillary medications in depressions with prominent anxiety.

Evidence

The literature comparing TCAs and SSRIs is extensive. Hotopf and colleagues reviewed all RCTs, meta-analyses, and cost-effectiveness studies comparing SSRIs and TCAs in 1996 and concluded that there was no evidence to suggest that SSRIs were more cost-effective than TCAs. They made some important points to keep in mind in reviewing the literature, including (1) most studies grossly overestimated the cost of dropouts and treatment failure, for example, by ignoring the likelihood that patients who drop out would likely try an alternative medication; and (2) studies funded by the drug industry may produce conflict of interest and introduce bias. They found that SSRIs were safer in overdose, but that suicide was such a rare event that it was impossible to study in RCTs. They also found that SSRIs had a very slight advantage in tolerability, in so far as 3% more patients on TCAs will drop out of treatment; better tolerance may lead to better compliance even short of dropping out. However the cost of SSRIs is disproportionately high and they conclude that TCAs should remain the first-line treatment for depression, with SSRIs reserved for patients with a medical contraindication, intolerance, or high suicide risk [21].

In another meta-analysis in 1997, Steffens and colleagues found that in intention-to-treat studies, TCAs and SSRIs were equally efficacious, while in studies that looked only at subjects who completed treatment, TCAs were statistically significantly more efficacious, implying that the TCAs were more effective in those who could tolerate and complete the full course of treatment. But as more people dropped out, the overall efficacy in all patients who started TCAs was equivalent to those who started SSRIs [22]. Anderson found that in 25 inpatient studies, TCAs were significantly more effective (in one subanalysis the difference was accounted for entirely by TCAs with dual action on noradrenaline and serotonin as opposed to those with predominantly noradrenergic action) but had significantly higher rates of discontinuation [23]. In a larger review of 102 RCTs not limited to inpatients, Anderson found that there was no overall difference in efficacy between SSRIs and TCAs, though TCAs appeared more effective in inpatients and amitriptyline was more effective than SSRIs; again, the TCAs had higher rates of discontinuation [24].

A review of meta-analyses found with high confidence that there was little difference in efficacy between new and old antidepressants, that there was superior efficacy of dual action serotonin and noradrenaline reuptake inhibitors over SSRIs, and that there was superior tolerability of SSRIs over TCAs; with lower confidence the review concluded that TCAs were more efficacious in inpatients and that amitriptyline was superior to SSRIs [25].

The San Antonio Evidence-based Practice Center evaluated the efficacy of treatment of major depression and dysthymia using a modified intention-to-treat analysis that produces conservative estimates of treatment effect. They found valid evidence that SSRIs, serotonin and norepinephrine reuptake inhibitor (SNRI), reversible monoamine oxidase inhibitors (MAOIs), serotonin receptor antagonists, and St. John’s wort were all superior to placebo, with an average treatment response difference of 25% (20% in the elderly). For dysthymia, SSRIs were superior to placebo. No clinically or statistically significant differences were found within the SSRIs or between SSRIs and TCAs in the treatment of major depression. Dropout rates were slightly higher for tertiary TCAs than SSRIs, but equivalent between secondary TCAs and SSRIs [26–28].

Geddes and colleagues for the Cochrane Depression, Anxiety, and Neuropysis Group reviewed 98 RCTs with comparator antidepressants that involved 5044 subjects treated with SSRIs or related drugs and 4510 subjects treated with alternative antidepressants and concluded that there was no clinically significant difference in efficacy, even when they did sub-analyses comparing individual SSRIs. They did find a small but significant advantage for TCAs in inpatients, and a small but significant decrease in dropouts in the SSRI-treated patients (25 patients would need to be treated with SSRI rather than comparator to prevent a single dropout). They cite other cost reviews to conclude that the most cost-effective strategy would seem to be to use TCAs as a first-line treatment and reserve SSRIs for those who have medical contraindications, significant difficulty tolerating side effects, or failure to respond [29].

There is one meta-analysis of adverse effects in tricyclics versus SSRIs [30]. The authors found some side effects with
## Table. Pharmacotherapy Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacodynamics and Side Effect Profile</th>
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<tbody>
<tr>
<td><strong>Tricyclics (tertiary amines)</strong></td>
<td>Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision), antidiadrenergic (orthostasis, erectile dysfunction), antihistaminic (sedation, weight gain), lower seizure threshold, type IA (quinidine-like) effects on cardiac conduction</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
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<td>Clomipramine</td>
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<td>Doxepin</td>
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<td>Imipramine</td>
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<tr>
<td>Trimipramine</td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclics (secondary amines)</strong></td>
<td>Less anticholinergic, antihistaminic, antidiadrenergic than tertiary amines; less sexual dysfunction</td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
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<tr>
<td>Nortriptyline</td>
<td></td>
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<tr>
<td>Protriptyline</td>
<td>Most stimulating of tricyclics, but most anticholinergic of secondary amine tricyclics</td>
</tr>
<tr>
<td><strong>Tetracyclics</strong></td>
<td>Side effects similar to secondary amine tricyclics</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Has D₂ blocking properties, so may treat psychotic depression, but risk of extra-pyramidal syndrome, tardive dyskinesia, hyperprolactinemia</td>
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<tr>
<td>Maprotiline</td>
<td>Lowers seizure threshold, especially at high doses or with rapid escalation of dose</td>
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<tr>
<td><strong>SSRIs</strong></td>
<td>Selective serotonin reuptake inhibitors. Serotonergic activity may cause GI distress, agitation, insomnia, anxiety, delayed orgasm and decreased libido, and headache initially (though also prevent migraines over time). Discontinuation syndrome of dizziness, confusion, malaise, fatigue, aches, chills, nausea, anxiety, irritability, crying spells, and vivid dreams, especially with paroxetine.</td>
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<tr>
<td>Citalopram</td>
<td>Most anticholinergic of SSRIs</td>
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<tr>
<td>Escitalopram</td>
<td>Most dopaminergic and adrenergic of SSRIs</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Dopamine, norepinephrine, and serotonin reuptake inhibitor. Can cause GI upset, agitation, insomnia, sexual dysfunction similar to SSRI</td>
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<tr>
<td>Fluvoxamine</td>
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<td>Paroxetine</td>
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<td>Sertraline</td>
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<tr>
<td>DNSSRI</td>
<td>Dopamine, norepinephrine, and serotonin reuptake inhibitor. Can cause GI upset, agitation, insomnia, sexual dysfunction similar to SSRI</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Above 225 mg can cause sustained elevation of blood pressure. Can have discontinuation syndrome.</td>
</tr>
<tr>
<td><strong>DNRI</strong></td>
<td>Dopamine and norepinephrine reuptake inhibitor. Major side effects are GI upset, activation, insomnia, may exacerbate psychosis; neutral to prosexual</td>
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<tr>
<td>Bupropion</td>
<td>Lowers seizure threshold especially with rapid escalation or high dosage; most activating antidepressant available; may exacerbate anxiety</td>
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<tr>
<td><strong>SSRI/5-HT₂ antagonists</strong></td>
<td>Increases serotonin while blocking 5-HT₂ receptor, hence less sexual side effect, less agitation</td>
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<tr>
<td>Trazodone</td>
<td>Also causes orthostasis, rarely priapism; very sedating</td>
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<tr>
<td>Nefazodone</td>
<td>Black box warning of rare cases of fulminant hepatic failure; fewer sexual side effects</td>
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<tr>
<td>α₂ Antagonist/5-HT₂ and 5-HT₃ antagonist</td>
<td>Increases both noradrenergic and serotonergic activity by antagonizing feedback inhibition; weight gain and sedation (especially at lower doses); fewer sexual side effects</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td>Monoamine oxidase inhibitors. Orthostasis, insomnia, headache.</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>Weight gain, sexual dysfunction</td>
</tr>
<tr>
<td>Phenelzine</td>
<td></td>
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<tr>
<td>Tranylcypromine</td>
<td>Most activating; weight loss</td>
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</table>

<table>
<thead>
<tr>
<th>Pharmacokinetics, Interactions, and Comments</th>
<th>Average Wholesale Price, Monthly*</th>
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<tbody>
<tr>
<td>Do not combine with MAOI because of risk of hypertensive crisis May also be used for headache and chronic pain</td>
<td>$0.98 for 50 mg/d $60.68 for 100 mg/d $3.65 for 75 mg/d $2.29 for 100 mg/d $84.01 for 100 mg/d</td>
</tr>
<tr>
<td>Also used for sleep apnea</td>
<td>$25.43 for 100 mg/d $63.77 for 75 mg/d $35.96 for 15 mg/d</td>
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<td>Long half-life (especially fluoxetine) keeps steady levels; cytochrome P-450 enzymes inhibited with paroxetine, fluvoxamine, and fluoxetine; citalopram and sertraline less likely to cause clinically significant interactions. Do not combine with MAOI because of risk of serotonin syndrome Drug interactions uncommon</td>
<td>$66.98 for 40 mg/d N/A $68 for 20 mg/d Prozac $88.05 for 100 mg/d $66.02 for 20 mg/d $64.55 for 50 mg/d</td>
</tr>
<tr>
<td>Drug interactions uncommon: low protein-binding</td>
<td>$78.71 for 150 mg/d Effexor; $69.65 for 75 mg/d Effexor XR</td>
</tr>
<tr>
<td>Drug interactions uncommon</td>
<td>$86.45 for 300 mg/d bupropion; $79.75 for 300 mg/d Wellbutrin SR</td>
</tr>
<tr>
<td>Powerful cytochrome P-450 3A3/4 inhibitor</td>
<td>$6.53 for 150 mg/d $74.42 for 300 mg/d</td>
</tr>
<tr>
<td>Drug interactions uncommon</td>
<td>$73.21 for 15 mg/d</td>
</tr>
<tr>
<td>Needs low-tyramine diet; avoid indirect-acting sympathomimetics, TCAs, SSRIs, meperidine; good for anxious depressions, treatment-resistant depressions, “atypical” depressions</td>
<td>$42.40 for 20 mg/d $42.37 for 45 mg/d $57.80 for 30 mg/d</td>
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</tbody>
</table>
no statistically significant differences between SSRIs and TCAs (headache, tremor, urinary disturbance, and hypotension), some side effects more common with TCAs than with SSRIs (dry mouth, constipation, dizziness, sweating, and blurred vision—mainly anticholinergic symptoms), and some more common with SSRIs (nausea, anorexia, diarrhea, insomnia, nervousness, anxiety and agitation—generally speaking hyperarousal symptoms). Patients receiving SSRIs had 11% fewer discontinuations than patients receiving secondary amine tricyclics, 3% fewer than those receiving tertiary or quaternary amines; overall there were 3% fewer amongst the SSRI group, but none of these numbers reached statistical significance. Only in a subanalysis restricted to adult outpatient trials was statistical significance reached: there were 2% fewer dropouts due to adverse events in the SSRI group. The authors conclude that the burden of adverse events was comparable in the 2 groups, but that the specific adverse events were different: patients on SSRIs dropped out because of gastrointestinal side effects, anxiety, and agitation; patients on TCAs dropped out because of dry mouth, constipation, and dizziness.

Primary Care Patients
Generalizing from tertiary care psychiatric research settings or community mental health settings to the primary care setting requires many assumptions that we have already indicated there may be reason to question. Therefore it is important to review the evidence that is specific to these settings. Mulrow reviewed a total of 28 RCTs involving 5940 primary care patients with major depression, dysthymia, or minor depression in a meta-analysis. Average response rates were 63% for the newer agents, 60% for TCAs, and 35% for placebo. Response rates were similar in the different depressive diagnoses. Dropout rates were 8% with newer agents and 13% with tricyclics. They conclude that antidepressants are more effective than placebo in primary care settings for major depression, dysthymia, and minor depression; dropout rates are lower for the newer agents [31].

Special Populations
Medically ill patients. An important question is whether antidepressants are effective in patients with medical illness, patients likelier to be seen in primary care settings. Gill and Hatcher reviewed this topic for the Cochrane Collaboration and found 18 trials involving 838 patients that met their inclusion criteria. They concluded that antidepressants are more likely than placebo to produce short-term improvement in the depressed medically ill patient. About 4 patients would need to be treated to produce 1 recovery that would not have occurred with placebo; about 10 patients would need to be treated to produce one dropout that would not have occurred with placebo. They grouped all antidepressants in the analysis based on past studies that suggest equal efficacy for all antidepressants; they found the homogeneity of their outcome analysis supported this decision. Although they found a statistically nonsignificant trend for higher efficacy in studies using TCAs than those using SSRIs and a greater tendency to dropout with TCAs than SSRIs, they concluded that TCAs and SSRIs have approximately equal effectiveness and acceptability in the medically ill [32].

The elderly. Another population of importance to primary care are the elderly. A Cochrane review of antidepressants versus placebo in the depressed elderly found that TCAs, SSRIs, and MAOIs are all effective in both outpatient and inpatient populations, with both major and minor forms of depression, with odds ratios of 0.32, 0.51, and 0.17 and numbers needed to treat of 3.97, 8.45, and 3.14, respectively. All classes had similar discontinuation rates [33]. Gerson and colleagues in a meta-analysis of both pharmacologic and psychologic treatments in the elderly found that antidepressants were significantly better than placebo (average reduction in symptom severity of 48.0% versus 31.3%) with no difference in efficacy or tolerability between classes of antidepressant. Data on the outcomes of psychological treatments were too limited to conclude anything more than that cognitive-behavioral, behavioral, and psychodynamic therapies were better than placebo [34]. Mittman and colleagues examined the efficacy and tolerability of antidepressants in late-life moderate to severe major depression (Hamilton Depression Rating Scale score ≥ 15) and found a response rate (50% or greater reduction in score) of 57.7% for SSRIs, 63.1% for TCAs, and 27.2% for placebo; there were no significant differences between classes in efficacy, safety, or dropouts [35]. McCusker and colleagues excluded studies in inpatient settings to try to get a population more similar to ambulatory geriatric patients with mild to moderate depression who might be seen in primary care; they found that heterocyclic antidepressants reduced Hamilton Depression Rating score by an average of 5.78 points; other drugs had nonsignificantly smaller effects; psychological treatment that was cognitive-behavioral in nature reduced scores 7.25 over “no treatment” controls but did not reduce scores significantly over controls who received nonspecific similar attention; psychological treatments that were based on expressing feeling (interpersonal and psychodynamic therapy) did not show statistically significant superiority to no treatment [36]. A complicating issue in the elderly is that of comorbid dementia.

Patients with nonmajor depression. As mentioned, dysthymia (chronic depression) and minor depression are prevalent in primary care settings and costly. A meta-analysis of placebo-controlled RCTs of antidepressant treatment in dysthymia
found that the treatment response was similar for TCAs, SSRIs, and MAOIs, although patients on TCAs were more likely to report adverse events. There were no differences between dysthymia, dysthymia plus major depression (double depression), or minor depression in response [37,38]. The results of the Treatment Effectiveness Project cited above address the efficacy of both therapy and medication for dysthymia in the primary care setting; for minor depression there was not a clear benefit over nonspecific clinical management [19].

**Patients with anxiety.** Since anxiety is a frequent comorbidity with depression, as with the case patient, the role of anxiolytics is often considered in the treatment of depression. Multiple trials have shown that benzodiazepines are inferior to the usual antidepressants as monotherapy for the treatment of depression; however, they may have a role as adjunctive medication in anxious depression. A review of 9 studies with 679 subjects found that the combination therapy group had a lower dropout rate and an increased response rate at early points in the trials (though the difference in response rate disappeared after 4 weeks); the authors note that the risk of abuse and discontinuation syndromes require individualizing recommendations [39].

An alternative to benzodiazepines is the anxiolytic buspirone. Unlike benzodiazepines, which have immediate onset and can be used on an as needed basis, buspirone takes 3 to 5 weeks of ongoing treatment for response. Therefore, buspirone is not useful for acute anxiety but only for chronic anxiety; on the other hand, buspirone may potentiate antidepressant response even beyond its effect on anxiety, especially in the higher-dose ranges of 40 to 60 mg/day divided into 2 or 3 doses [40]. The question of concomitant treatment of anxiety may be especially important in primary care, since at least one study has found that depressed primary care patients with comorbid anxiety prematurely terminate treatment more frequently than patients with depression alone; so the treatment of anxiety may be essential to enable compliance with the full course of treatment for depression [41].

**Dose**

In primary care in particular, there is evidence that patients are often treated with lower-than-guideline-recommended doses of antidepressants, so the relation of dose to effect is important to examine. A meta-analysis of 33 trials that compared 2 or more doses of the same antidepressant found that a dose equivalent to 100 to 200 mg of imipramine showed a 53% response rate under intention-to-treat analysis; higher doses did not increase efficacy, while lower doses showed modestly but significantly reduced efficacy (46%) [42]. Despite some controversy, it remains the current recommendation to aim for the usual therapeutic doses, even in the primary care setting.

**Electroconvulsive Therapy**

**Summary**

- ECT is the most effective treatment for severe depression or depression with psychotic features, catatonia, or depression accompanied by refusal to take food or fluids. It may also be used for severe depression that has failed 2 or more adequate trials of medication, or in someone with a history of prior good response.
- Because of the medical issues and likelihood of transient confusion, it usually is best provided or at least begun in an inpatient setting.
- Maintenance treatment, usually pharmacotherapy, occasionally maintenance ECT, is recommended following acute treatment because of a relatively high rate of recurrence if no maintenance treatment is provided.

**Evidence**

There are no good studies of ECT specifically in primary care settings. There is one major meta-analysis of ECT; done in 1985, the comparator antidepressants were somewhat limited. ECT was superior to placebo (41% more effective), simulated ECT (32% more effective), tricyclics (estimated superiority 20%), and MAOIs (estimated superiority 45%) [43]. A review of more recent literature focused on depression in the elderly found 12 studies; the overall conclusion was that ECT was efficacious and well-tolerated [44]. In particular, ECT may have efficacy for specific variants of depression such as delusional depression and catatonia [45].

**Alternative Treatments**

**Summary**

- There is no good evidence to support the use of alternative treatments for depression in primary care at this time.

**Evidence**

Transcranial magnetic stimulation (TMS) is a technique that allows noninvasive stimulation of the cortex; low frequency repetitive TMS tends to inhibit cortex while high frequency repetitive stimulation tends to activate cortex. Most studies to date have involved small sample size and are single-blinded and lead to the conclusion that there is no strong evidence of efficacy, though the weaknesses of the studies also do not allow the rejection of the possibility of efficacy [46]. There are no studies of TMS in primary care.

There is one study of light therapy in primary care; it randomized patients with seasonal affective disorder to bright white light treatment or sham dim red light treatment; both
groups improved equally [47]. However, in the general psychiatric population there are a number of studies that suggest efficacy in patients with seasonal affective disorder: remission rates of 54% to 60% for morning light and 28% to 33% for evening light as compared with placebo controls (11% to 16%) [48–50]. A meta-analysis of 39 studies found a dose-response relationship between light intensity and reduction of typical symptoms of depression (though not atypical symptoms) [51]. Replication studies in primary care would be of potential significance, in so far as the literature suggests that patients with seasonal affective disorder are heavy users of health care services [52] and show functional impairment comparable to that seen with chronic medical conditions [53].

St. John’s wort (hypericum) has been used in herbal treatments for a long time. Most trials have been short-term and involved mild to moderate depression; in this population, hypericum preparations were more effective than placebo but the evidence is insufficient to determine whether they are as effective as standard antidepressants [54,55]. Since that review, a large double-blind study failed to find an effect of hypericum, but also failed to find an effect for sertraline [56].

Vagal nerve stimulation is a new modality of treatment for treatment-resistant depressions involving the implantation of electrodes in the vagal nerve. Initial small studies, largely in treatment-resistant depressed patients, have found antidepressant efficacy; in one multicenter trial a response rate of 40% to 50% was reported in patients who had failed multiple prior treatment trials [57]. There is no data on its use in primary care.

- What is the role of patient preference?

In making a treatment recommendation it is critical to ask about patient preferences. In general, primary care patients may prefer counseling over medication [58]. Where there are equally effective options (eg, in the treatment of mild depression), honoring the patient’s preference is likelier to foster compliance. Where there is scientific evidence for another approach, learning about the patient’s preference will alert the physician to the need to provide the patient with data. Finding out what the patient knows about depression and its treatment, what his or her hopes and concerns are, and what his or her preferences are allow the primary care physician to direct his or her educational efforts, to collaborate, and to include the patient in medical decision making.

**Initial Treatment**

The physician tells the patient that after talking with her, he is concerned that she has a number of symptoms that suggest she is feeling depressed, including her crying spells, her difficulty sleeping, her weight gain, and her lack of interest or pleasure in her life. He also notes that she has generalized anxiety as well as panic attacks, which may be exacerbated by her heavy use of caffeine. He explains that depression is a treatable illness, not a personal weakness, and that a number of treatments have proven effective. Anxiety is also a treatable disorder, and he suggests she cut back her caffeine consumption. He asks her whether she would like to speak to a therapist; she declines. He then suggests that medications may be helpful. In view of her weight gain, panic attacks, and anxiety, he chooses sertraline 25 mg and adds oxazepam 15 mg per night as needed for her insomnia.

After starting the sertraline, the patient develops headache, nausea, and a tremor in her upper extremities that does not remit until she stops the sertraline after 2 weeks. The physician switches her to citalopram, increasing to a dose of 30 mg over 3 weeks despite mild headache and nausea that remits after a few days. Three weeks later at a follow-up visit, the patient tells the doctor, “You saved my life.” She says that her mood is improved and she feels “more lively.” She is sleeping 6 solid hours a night and is returning to her usual activities. Her panic attacks have disappeared.

Two months later, she returns to the clinic reporting that the fear and depression have returned; she reveals that after she “got better,” she cut back her dose of citalopram to 20 mg.

- What is the typical course of treatment?
- How should treatment be monitored?

**Course of Treatment**

Nonpharmacologic treatments are typically managed by specialists rather than the primary care doctor; here we focus on the course of pharmacologic treatment. The treatment of depression is often divided into acute phase, continuation phase, and maintenance phase (Figure 1). The acute phase of treatment is from the initiation of pharmacotherapy to complete resolution of symptoms (ie, no longer meeting diagnostic criteria or Hamilton Depression Rating Scale score < 7); typically this takes about 6 to 12 weeks. It is critically important to achieve full remission, since residual symptoms predicts relapse. At this point in an uncomplicated case, a patient no longer meets diagnostic criteria for depression, but the patient remains at somewhat higher risk of relapse (about 25% within 2 months) if medication is discontinued [59]. Therefore, medication is usually continued for 6 to 12 months at the full therapeutic dose that was required for resolution of symptoms. There is no support for lowering the dose once the patient is feeling better. After this continuation phase, the
patient and doctor must decide whether a maintenance phase medication is necessary to prevent recurrence. Depression is a recurrent illness; fewer than 50% of patients will suffer a single episode of depression. There is now good evidence that for those patients who have 3 or more episodes of major depression, maintenance therapy for at least as long as 3 years decreases both the incidence of recurrent depression and its severity if it does recur [60]. For a first uncomplicated episode of depression, a recommendation to finish the continuation phase but then slowly taper the antidepressant (to avoid withdrawal reactions which have been reported with both tricyclics and SSRIs) over a couple of weeks is usually made. However, in a patient with high-risk factors (a very severe depression, a depression with significant suicidal ideation, a strong family history, residual symptoms), consideration of maintenance therapy after a single or second episode of depression is a matter for informed discussion with the patient [61]. In any event, continued monitoring for symptoms of depression so that treatment can be resumed at the earliest indication should be part of the treatment plan.

A significant proportion of depressed patients do not respond in the typical 6- to 12-week period. Twenty percent to 35% of patients will have residual symptoms, 15% to 20% will relapse (ie, become depressed again after remitting but before achieving extended recovery), and 50% to 85% will have a recurrent depression (ie, after fully recovering) [59,62]. In one study in a primary care setting, the rate of relapse during the first year of treatment of depression was 27.1%; the best predictors of relapse were persistence of sub-threshold symptoms and history of recurrent or chronic depression [63]. This finding underlines the importance of active monitoring to detect failure in adherence or response and to adjust treatment as needed.

**Treatment Monitoring**

Patients being started on antidepressant medications should have frequent brief monitoring to minimize side effects and monitor symptoms, since compliance is a major ingredient of efficacy and residual symptoms predict treatment failure. Particular attention should be paid to any suicidal ideation, exploring whether or not it is present, whether it is active or passive in nature, whether there is intent to act, whether there are the means to act (eg, weapons, medications), and whether there is a plan or a deadline to act. Any shift in the direction...
of more intense, active, or planful suicidal thinking requires evaluation of safety and whether hospitalization may be necessary. Initially, contact weekly or biweekly with the patient is recommended by the AHRQ guideline; a brief telephone contact often is sufficient to monitor the patient and encourage compliance. Once the patient is showing signs of response, the treatment can be continued and checked again at 6 and 12 weeks; if at 6 weeks the patient shows no improvement, either a switch of medication or an augmentation strategy should be initiated with continued close follow-up. If at 12 weeks there is no improvement, referral to a psychiatrist should be considered. Figure 2 summarizes this approach in a decision flowchart.

Follow-up

The physician explains to the patient that she needs to continue taking the 30-mg dose of citalopram. She agrees to do so, but she complains at her next visit 2 weeks later of a lack of improvement in her mood, energy, concentration, motivation, and anxiety, as well as of craving sweets and continued weight gain. The physician increases the citalopram to 40 mg. She complains 4 weeks later that she still has not improved, and the physician again suggests a referral to a therapist. The patient is reluctant to go, fearing that once she starts talking, she will not be able to stop crying. After a lengthy discussion, she agrees to try a cognitive behavioral approach. The therapist teaches her some relaxation techniques, which she practices daily with some improvement in mood and sleep; however, she discontinues the therapy after 3 weeks. The physician suggests increasing the citalopram, but whenever the dose gets above 40 mg, the patient develops a severe upper extremity tremor. The physician suggests a referral to a psychiatrist to help evaluate her medication regimen as well as why she is finding it so difficult to adhere to treatment recommendations.

The physician’s experience with this patient and others in his practice leads him to ask whether there are ways his practice could better structure the care of primary care patients to have a better rate of detection and successful treatment of depression.

• How can compliance be optimized?
• When should a referral or consultation be made?

Compliance

As with the case patient, continued compliance is frequently an issue, especially as a patient may be feeling better psychologically and feeling more troubled by side effects or the stigma of taking medications. Up to 50% of patients stop antidepressants in the first month [64]. Factors that are important to consider in evaluating compliance are the side effect burden, cost, complexity of the regimen (once daily dosing is much more likely to be followed than 3-times daily dosing), and the possibility of cognitive impairment. It may be helpful to present a medical model of depression: depression is an illness, the prognosis is good, the goal is remission and full recovery, but the risk of recurrence is high. It is important to anticipate possible side effects, to underline the importance of continuation at the optimal dose, and to ask about side effects at each encounter. Some of the side effects that may not seem crucial to the physician but may be extremely distressing to the patient include sexual dysfunction and weight gain. Developing an alliance that allows open communication about compliance and addresses patient concern is critical, since noncompliance is the strongest predictor of recurrence in recurrent depressions [65].

Criteria for Psychiatric Consultation

It is difficult to establish universal criteria for psychiatric consultation, since consultation is influenced by such nonclinical concerns as available resources, insurance coverage, and a practitioner’s experience and comfort with dealing with psychiatric issues. However, the following criteria are generally cited as reasons for referral:

• Psychosis
• Significant suicidal ideation or any suicide attempt
• Significant comorbid medical illness (including pregnancy) or complex medication regimen
• History of noncompliance or poor response
• Failure of 1 or 2 adequate trials or failure to respond within 12 weeks
• Bipolar depression/mania
• Depression with comorbid substance abuse
• Depression with comorbid dementia
• Diagnostic uncertainty
• Patient preference

It is important for patient care that there be good communication about the medical aspects of the patient’s treatment between the psychiatrist and primary care doctor.

• Do systems-based interventions improve depression treatment?
Figure 2. Depression flowchart.
A number of studies have attempted to address the issue of whether systems interventions increase the quality of care (accurate diagnosis and treatment that meets current guidelines). Interventions that were limited to education of and brief feedback (diagnosis, treatment algorithms, case review) to primary care doctors have not been successful [66]. Katon and colleagues at the University of Washington and the Group Health Cooperative of Puget Sound developed a “collaborative care” program for primary care patients that included physician and patient education, initial consultation with an on-site psychiatrist followed by “co-management” visits every 1 to 2 weeks, with the psychiatrist alternating with the primary care doctor. The intervention group showed greater adherence to treatment guidelines, better response, and improved satisfaction with care [67]. Another program they developed involved a psychologist integrated into the primary care setting who provided 4 to 6 sessions of psychoeducation, symptom monitoring, and short-term cognitive behavioral therapy; the psychologist would also discuss the case with a psychiatrist who would communicate any medication recommendations to the primary care doctor. In this study too they found improved adherence, outcome, and satisfaction [68]. However, longer-term follow-up failed to show better clinical outcome at 19 months [69]. In a third study, they followed treated depressed patients with either usual care or an intervention program consisting of patient education, 2 follow-up visits with a mental health clinician, and 3 telephone checkups over the course of a year; the intervention patients had improved adherence and outcomes [70]. In a fourth study from the Group Health Cooperative, feedback and algorithm-based recommendations alone did not affect outcomes; only when care management (systematic follow-up of patients, detailed feedback and medication recommendations to doctors) was added was there an improvement in adherence to guidelines and outcome at an incremental cost of $80 per patient [71].

Katzelnick and colleagues developed a program of patient and physician education, telephone-based treatment coordination, and pharmacotherapy for depressed high utilizers and demonstrated improved outcomes over usual care [72]. Sturm and Wells at RAND and UCLA did a cost-effectiveness analysis and simulations based on the Medical Outcomes Study and concluded that increased counseling and more appropriate medication use improves functional outcome despite increasing the cost of care [73]. The results of the studies show an effect of at least short-term duration of multimodal interventions that are costly and not easily generalizable.

Conclusion
Depression is a common disorder that frequently presents in the primary care setting. While there is a need for more studies specific to this setting and focused on “effectiveness” rather than “efficacy,” there is substantial evidence to guide the primary care physician in the evaluation and management of their patients with depression.

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I was provided with new information pertinent to my practice. □ □ □ □ □
I reaffirmed a specific skill or knowledge. □ □ □ □ □
This article will help with clinical decision making. □ □ □ □ □
Relevant clinical outcomes are addressed. □ □ □ □ □
The case is communicated in a manner that kept my interest. □ □ □ □ □
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Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

☐ see no need to change my practice.
☐ will seek more information before modifying my practice.
☐ intend to change the following aspect(s) of my practice: (Briefly describe)

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