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## Newly diagnosed hypertension and depressive symptoms: How would you treat?

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**A 56-year-old man** who has had borderline hypertension for 2 to 3 years presents at a regularly scheduled office visit with blood pressure of 149/91 mm Hg.

### Medical history

- No other significant medical or psychiatric problems
- Married, with 2 teenaged children
- Employed as an administrator for an insurance company (>50 hrs/wk)
- Drinks 3 to 4 alcoholic beverages/wk
- Does not smoke
- Enjoys fishing and other outdoor activities
- Both parents had hypertension; father also had peripheral vascular disease

### Examination

- Patient is in no acute distress
- Approximately 30 pounds over ideal body weight
- Other vital signs are normal
- Normal retinal examination, no carotid bruits, and clear lungs. Cardiac rate and rhythm are regular; no abdominal bruits
- Laboratory studies reveal normal renal function; cholesterol, 184 mg/dL; low-density lipoprotein (LDL) cholesterol, 129 mg/dL; high-density lipoprotein (HDL) cholesterol, 55 mg/dL; triglycerides, 163 mg/dL. Electrocardiogram shows no current or

prior evidence of ischemia or left-ventricular strain.

Additional information is required in a number of domains. Blood pressure readings should be repeated to make an accurate diagnosis of hypertension. While the patient may have hypertension, only a single blood pressure reading is elevated. The Joint National Committee on Blood Pressure (JNC 7) specifications<sup>1</sup> state that 2 such readings on different days are needed to confirm a diagnosis of hypertension. The symptoms of claudication should be investigated. Physical examination should focus on auscultation for bruits and on the examination of eye grounds to further investigate the possibility of peripheral vascular disease (PVD). In addition, a lipid profile should be drawn. While guidelines are conflicting, consideration should be given to assessing a fasting glucose, potassium, and renal function. Other tests, such as a C-reactive protein, are more controversial.<sup>2</sup>

The patient opts for drug treatment of his hypertension, and begins taking atenolol 50 mg/d (in addition to aspirin 81 mg/d). He is scheduled to follow-up by phone in 1 week to assure compliance and in 3 months in the office.

**■ FOLLOW-UP CARE**

On a return visit to the office 3 months later, the patient reports the recent onset of fatigue.

**Q:** What is the differential diagnosis of the patient's symptoms? What additional information might you like to know?

**A:**

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On further questioning he reports that he initially tolerated the beta-blocker without problem, but more recently has experienced low energy and poor sleep (with early morning awakening); he acknowledges decreases in libido, interest in pleasurable activities (eg, hunting, fishing), and his ability to concentrate. He has gained 5 to 10 pounds in the last month.

Although he denies feeling "sad," he says his emotions seem "flat." He denies having thoughts of suicide, increased anxiety, symptoms of hypomania, or psychotic symptoms. He describes a mild increase in stress at work, and he feels that the process of preparing for his son to go to college had been "a big burden." He says there are no other stressors.

The patient's alcohol use has not changed significantly, and he reports being compliant with his new medication regimen.

When his father died 6 years earlier, he experienced similar symptoms; at no other time have such symptoms occurred. The patient reports no other new physical symptoms, and his physical examination is essentially unchanged from the exam conducted 3 months earlier. His vital signs are normal, including a blood pressure of 128/84 mm Hg.

Consider the differential diagnosis of the patient's abnormal mood and neurovegetative symptoms. In the primary care setting, the differential diagnosis of depressed mood is broad (**Table 1**), including medical disorders and a variety of psychiatric syndromes.

**TABLE 1**

**Partial differential diagnosis of depressed mood and neurovegetative symptoms**

**General medical conditions**

*Endocrine:* hypothyroidism, Cushing's syndrome

*Hematologic:* anemia

*Nutritional:* vitamin B12 deficiency

*Neurologic:* movement disorders (eg, Parkinson's disease, Huntington's disease), head trauma, seizure disorders

*Vascular:* peripheral vascular disease, cerebrovascular accident

*Sleep disorders:* sleep apnea, narcolepsy

*Neoplastic:* pancreatic, lung, central nervous system neoplasms

**Substance abuse disorders**

Alcohol, benzodiazepine, or barbiturate dependence

Cocaine or amphetamine withdrawal

**Psychiatric disorders**

Major depressive disorder

Dysthymia

Adjustment disorder with depressed mood

Bipolar disorder

Medical conditions to consider include a medication induced side effect, hypothyroidism (a metabolic masquerader of depression), anemia, sleep disorder (eg, sleep apnea), and alcohol abuse. PVD should also be considered—his symptoms may be secondary to poor perfusion of the cerebral cortex.

**Q:** When are depressive symptoms serious enough to warrant treatment? What effects might beta-blockers be having on his mood, energy level, and libido? You call a psychiatrist colleague for an informal consultation.

TABLE 2

### Major depression, minor depression, and adjustment disorder

#### Major depressive disorder

Requires depressed mood or loss of interest/pleasure (anhedonia) most of the day, nearly every day for 2 weeks, with a total of 5 (out of 9) depressive symptoms, and resulting in functional impairment.

#### Minor depression (research criteria)

Requires depressed mood or loss of interest/pleasure (anhedonia) most of the day, nearly every day for 2 weeks, with a total of 2 to 4 depressive symptoms, and without history of major depressive disorder.

#### Adjustment disorder

Mood or anxiety symptoms occur within 3 months of a stressful life event. Such symptoms are in excess of the symptoms that would normally be expected as a result of the event or impair function. The symptoms do not meet criteria for major depressive disorder, bereavement, or another major psychiatric disorder.

Source: Adapted from *DSM-IV*.<sup>14</sup>

## ■ PSYCHIATRIST'S COMMENTS

It is important to distinguish major depression from other, less severe depressive syndromes. In major depression, 5 out of 9 symptoms (including depressed mood or anhedonia) are present most of the day nearly every day for 2 weeks.

With adjustment disorder and so-called minor depression, symptoms are fewer or less persistent (Table 2).

This distinction is important, as antidepressants are effective for major depression, but they have not yet been shown effective for adjustment disorders or minor depression. Major depression is the “hypertension of mental illness in primary care”—common, often undiagnosed, and associated with poor outcomes. Therefore, accurate diagnosis and appropriate treatment for major depression are essential.

Given the possibility of a depressive syndrome, gather further information to determine the duration of ongoing symptoms, and obtain answers to a short questionnaire (eg, the Beck Depression Inventory [BDI]<sup>3</sup> or the PHQ-9<sup>4</sup>). Elicit a family history of mood disorder, or personal history suggestive of thyroid dysfunction, a sleep disorder, or alcohol or drug abuse. Order a complete blood count (CBC) to evaluate for anemia, a thyroid-stimulating hormone (TSH) to evaluate for hypothyroidism, and, if indicated by history, a sleep study.

**Beta-blockers and depression.** The patient's symptoms developed in the context of beta-blocker therapy. From the 1970s through the 1990s, the lore was that beta-blockers caused depression and should be avoided in patients with a history of depression. Because of this, many patients with myocardial infarction (MI) and congestive heart failure (CHF) have been denied treatment with beta-blockers when otherwise indicated.

Fortunately, a recent rigorous academic study of this issue was conducted by Ko and colleagues<sup>5</sup> to rationally guide treatment. This study involved a meta-analysis of 15 randomized controlled trials of beta-blocker therapy in patients with MI, CHF, or hypertension; the authors found that beta-blockers were associated with a slight (though statistically significant) increase in fatigue and sexual dysfunction, and that their use was not associated with depressive symptoms. This is the best review to date of beta-blockers and depression, and it debunks the myth that beta-blockers cause depression—a myth that has prevented many post-MI patients from receiving much-needed beta-blocker therapy. In short, although idiosyncratic reactions are possible, it is unlikely the patient's use of atenolol caused his apparent depressive symptoms.

■ **FURTHER PRIMARY CARE EVALUATION**

The patient has no cold intolerance or other symptoms of thyroid dysfunction. He does report a long history of snoring, confirmed by his wife. However, he did not notice feeling more fatigued after starting atenolol. Nonetheless, you switch his antihypertensive

medication from atenolol to hydrochlorothiazide. In addition, you order a CBC, serum chemistries, a thyroid panel, and a sleep study. The patient is told to return for a follow-up appointment in 2 weeks and to call before that if symptoms worsen.

**Q:** Is this recommended course of treatment reasonable? What other options are available for the patient?

**A:** \_\_\_\_\_  
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In this situation, the evidence (depressive symptoms in the context of good blood-pressure control) was insufficient to justify a switch from a beta-blocker to hydrochlorothiazide. One could argue that the switch was reasonable regardless of his depressive symptoms; the most recent guidelines from JNC 7<sup>1</sup> indicate that thiazide diuretics are first-line therapy for hypertension in patients without CAD, and that beta-blockers are not the first-line agent in the patient's clinical situation.

But discontinuing atenolol because of ongoing depressive symptoms is not supported. The patient may well need a beta-blocker in the future (eg, if he were to develop CAD). By prematurely concluding that the beta-blocker caused adverse effects, we may be denying him an important treatment down the road.

**Option 1: 2-week drug holiday**

If there was concern that the patient was having an idiosyncratic reaction to atenolol, or if he developed substantial fatigue or sexual dysfunction, a 2-week drug holiday could be conducted while carefully monitoring blood pressure and depressive symptoms. Atenolol

could then be restarted to identify a temporal relationship between the symptoms and the medication.

**Option 2: Treat for depression**

Another option would be to treat the patient as if his symptoms represented depression. Exhibiting 4 of the necessary diagnostic criteria, the patient nearly qualifies for a diagnosis of current major depression. An antidepressant could be started, exercise could be prescribed, or a referral could be made for psychotherapy. However, again there is insufficient evidence that his subsyndromal depression will respond to standard treatments designed for major depressive disorder.

The patient returns as scheduled 2 weeks later. He has tolerated the change in blood pressure medications without difficulty, but he is experiencing persistent anhedonia, terminal insomnia, and low levels of concentration, energy, and libido. He has felt increasingly hopeless and worthless over the past 2 weeks, though he denies having thoughts of suicide. Results on CBC, serum chemistries, thyroid panel, and sleep study are all unremarkable.

The patient now clearly meets criteria for a major depressive episode. As a first step, he should be educated about depression. An excellent self-help book is *Getting Your Life Back* by Wright and Basco.<sup>6</sup> The patient should be taught to monitor his symptoms with the BDI<sup>3</sup> or the PHQ-9<sup>4</sup> to better assess the severity of the current episode, to monitor changes in his symptoms, and to rapidly identify relapses.

Most physicians would start an antidepressant, unless the patient had significant objections. Other treatment options, alone or in concert with antidepressant treatment, include exercise or psychotherapy. The patient is an excellent candidate for exercise, given that he has 3 risk factors for CAD: hypertension, a sedentary lifestyle, and obesity (4, if you include depression). Exercising for at least 30 minutes, 2 to 3 times per week, would likely benefit his physical and mental health. In addition to its cardiac benefits, exercise 3 times weekly was found in at least one trial to be as effective as sertraline in treating major depression in outpatients.<sup>7</sup>

**Choosing an antidepressant.** A number of factors should be considered in choosing antidepressants, including efficacy, side effect profile, and cost. **Table 3** outlines some of the main considerations in the choice of antidepressants for this patient. Note that tricyclic antidepressants are not listed, being contraindicated in CAD because of their tendency to contribute to arrhythmias in the post-MI period. In this patient's case, mirtazapine should be avoided because of the possibility of weight gain; venlafaxine should be avoided because of hypertension. Sertraline would be an appropriate choice, given that it has been relatively well-studied in persons with CAD.

The patient begins treatment with fluoxetine (10 mg/d, which is then increased to 20 mg/d after several days). His depressive symptoms gradually diminish; he achieves a "50%" reduction of symptoms at follow-up visit 3 weeks later. Two months after fluoxetine was initiated, the patient is nearly euthymic, reporting only 2 depressive symptoms, and is again engaging in usual recreational activities.

## ■ CONCLUSIONS

**Q:** Is depression, like hypertension, a risk factor for the development of coronary artery disease (CAD)?

**A:** \_\_\_\_\_  
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Whether depression is a risk factor for CAD depends on how one defines a risk factor and whether one is discussing "major" or "minor" risk factors. At least 15 narrative reviews have been written on the relationship between depression and heart disease, but none has examined the epidemiologic evidence for depression as a major risk factor for CAD (**Table 4**).<sup>8</sup>

In looking at the 7 main epidemiologic criteria for a risk factor, depression does very well on 4: strength of association, consistency, dose-

response effect, and predictability. Numerous studies have shown that depression is clearly and consistently associated with the development of CAD, and that clinical depression appears to predict CAD more robustly than does depressed mood alone.<sup>9-12</sup>

On 2 of the criteria, specificity and biological plausibility, there is fair evidence for depression as a CAD risk factor. We do not yet know the relative importance of recurrent major depression, dysthymia, BDI scores of 10 or greater, or some

TABLE 3

### A comparison of antidepressants in the treatment of depressed patients in cardiac populations

Medication	Class/mechanism	Risks/side effects	Benefits
Citalopram	SSRI		Low cost, minimal drug-drug interactions
Escitalopram	SSRI	Newest/least studied agent	Low cost, minimal drug-drug interactions, possibly faster onset and fewer side effects
Fluoxetine	SSRI	Long half-life, more drug-drug interactions	
Paroxetine	SSRI	Sedation, mild anticholinergic effects	
Sertraline	SSRI	Sedation, mild	Best studied in CAD; few drug interactions
Mirtazapine	Atypical antidepressant (5HT <sub>2</sub> , 5HT <sub>3</sub> , and alpha <sub>2</sub> receptor blockade)	Sedation, weight gain, possible elevation of lipids	No sexual dysfunction
Venlafaxine	Selective serotonin and norepinephrine receptor blockade	Elevated blood pressure in 13% at doses of 300 mg or greater	
Bupropion	Increases noradrenergic and dopaminergic activity	Initial anxiety	No sexual dysfunction

SSRI, selective serotonin reuptake inhibitor; CAD, coronary artery disease

other marker of depression as predictors of CAD.

Because mild depressive symptoms may predict CAD, it is unclear what levels of depression increase the risk of CAD and require intervention. Excellent work exists regarding the development of plausible mechanisms by which depression may lead to CAD; however, these mechanisms have yet to be proven. Therefore, the evidence in this domain can only be rated as fair.

Finally, the evidence is incomplete for one important criterion: response to treatment. Only one study has been designed to examine the

effect of depression treatments on cardiac risk reduction. This study (the ENRICHD trial<sup>13</sup>) was a treatment study of post-MI depression that found that cognitive-behavioral therapy did not have a significant impact on reducing recurrent cardiac events.

Based on the most stringent epidemiologic criteria, depression is almost, but not quite, a *major* risk factor for CAD. However, depression is a minor risk factor for CAD, and may someday be considered a major risk factor. While the mechanisms by which depression may lead to CAD have not yet been established, the association between depression and subsequent CAD likely occurs via 2 pathways.

## Family physician commentary

**This case illustrates several important points** in the management of depressive symptoms in the family practice setting.

First, patients may present with subsyndromal depressive illness; there is, as yet, no evidence that antidepressants are beneficial in this population, and they expose patients to side effects such as sexual dysfunction.

Second, practitioners in general should not shy away from using beta-blockers where indicated for patients with cardiovascular disease and depression; the link between beta-blockers and depression seems minimal at best.

Third, when patients do present with the syndrome of major depression, it is important to evaluate potential medical contributors (eg, obstructive sleep apnea) when appropriate, and to treat with adequate doses of antidepressants for an adequate duration.

Fourth, the potential effects of depression on the development of CAD give family physicians yet another reason to remain vigilant for the presence of depression in all patients.

**Should the FP treat independently?** This discussion then leads to the question of when an informal or formal psychiatric consultation is indicated for the treatment of a depressed patient, and when the FP may wish to handle the case independently. The short answer is, of course, "it depends." As with all areas of medical specialty, FPs will have varying levels of comfort, knowledge, and experience in the treatment of psychiatric disorders, and this will often affect the threshold for obtaining consultation. Furthermore, the number of psychiatric consultants—and thus the opportunity for consultations—varies widely depending on practice location.

**Value of informal consultations.** In general, FPs are well-equipped to handle patients with uncomplicated major depressive disorder or dysthymia without suicidal ideation or psychotic

features. Informal consultation may be useful in cases (as in this case) when it is difficult to distinguish whether the patient meets criteria for major depressive disorder (and therefore requires treatment) or has subthreshold depressive symptoms. In addition, informal consultation can be useful when there is a question about antidepressant agent selection in a specific clinical situation. Finally, informal consultation may be of benefit when there are comorbid psychiatric illnesses, for example, coexisting panic disorder, generalized anxiety disorder, and major depressive disorder.

**Opting for formal consultation.** Formal psychiatric consultation is often useful when there is a mood disorder with suicidal ideation or psychotic features, when the disorder has been refractory to 2 or more adequate trials of an antidepressant, when there is a question of bipolar disorder (for which monotherapy with antidepressants is contraindicated) or substance use disorder, or for progressively worsening depression despite treatment.

**Billing and coding.** The logistics of billing for the treatment of comorbid psychiatric disorders by primary care physicians vary with the type of payer and from state to state. Because it is often impractical to modify billing procedures with each patient, it is useful for each practice to develop general billing guidelines for psychiatric disorders billed to Medicaid, Medicare, and the most common managed care organizations in the practice. In general, the physician caring for the patient described in this report would bill for hypertension and depression and get paid under the primary diagnosis of hypertension. When in doubt about whether to bill for a psychiatric disorder, primary care clinicians may include the relevant physical symptom in the billing codes, such as fatigue, headache, insomnia and bill under that code.

TABLE 4

### Depression as a risk factor for CAD: a “report card”<sup>8</sup>

Risk factor	Strength of evidence
Strength of association	Good
Predictability	Good
Specificity	Fair
Consistency	Good
Dose-response effect	Good
Biological plausibility	Fair
Response to treatment	Incomplete

The first pathway is behavioral. Patients with depression have diminished self-care, possibly increasing other CAD risk factors such as smoking, poor diet/hyperlipidemia, diabetes, physical inactivity, and obesity.

The second pathway by which depression may lead to CAD is neuroendocrine. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and hyperactive sympathomedullary activity may result in elevated cytokine levels, platelet activation, and vascular damage, thereby contributing to CAD.<sup>8</sup>

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#### DRUG BRAND NAMES

- Atenolol • Tenormin
- Bupropion • Wellbutrin
- Citalopram • Celexa
- Escitalopram • Lexapro
- Fluoxetine • Prozac
- Hydrochlorothiazide • Esidrix, HydroDIURIL, Oretic
- Mirtazapine • Remeron
- Paroxetine • Paxil
- Sertraline • Zoloft
- Venlafaxine • Effexor