REVIEW

A Generalist's Guide to Treating Patients With Depression With an Emphasis on Using Side Effects to Tailor Antidepressant Therapy

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This review provides a guide to the primary care physician for diagnosing and managing depression. To identify relevant articles, a PubMed search (ending date parameter, October 15, 2009) was conducted using the keywords *depression*, *antidepressants*, *side effects*, *adverse effects*, *weight gain*, *sexual dysfunction*, and *sleep disturbance*, and the reference lists of relevant articles were hand searched. This review explores the challenges in diagnosing depression that will and will not respond to antidepressants (ADs) and describes the value of 2-question screening instruments followed by in-depth questioning for positive screening results. It underscores the implications of veiled somatic presentations in which underlying depression is missed, leading to fruitless and expensive medical work-ups. Following this survey of the difficulties in diagnosing depression, the 4 options generalists have for treating a patient with depression are discussed: watchful waiting, antidepressant therapy, psychotherapy, and psychiatric referral. This review proposes that physicians, once they decide to prescribe, use AD side effects to advantage by selecting medications to minimize negative and maximize positive possibilities, thereby improving adherence. It focuses on the 3 most troubling adverse effects—sleep disturbance, sexual dysfunction, and weight gain. It provides AD-prescribing principles to assist primary care physicians in successfully managing depression and appropriately referring patients to a psychiatrist. Antidepressant therapy is not a panacea for treating patients with depression. An approach blending enlightened observation, medications, and psychotherapy often helps depressed patients recover to their former baselines.

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AD = antidepressant; CYP = cytochrome P450; GABA = γ-aminobutyric acid; 5-HT$_2$ = 5-hydroxytryptamine (serotonin) receptor 2; NO = nitric oxide; PDE-5 = phosphodiesterase 5; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

The lifetime risk of developing major depressive disorder in the United States is 16.2%, making it among the most common conditions physicians encounter.[1] Up to 10% of outpatients treated by generalists meet criteria for major depression.[2] Yet primary care physicians have an abysmal record of inquiring about depression. In a survey of patients with chronic or recurrent depression, family practice physicians asked about depressive symptoms only 34.0% of the time and internists only 27.3% of the time.[3] In a nationally representative survey, only 41.9% of depressed patients reported receiving adequate treatment for their depression from their primary care physicians.[4]

For treatment of major depressive disorder, generalists currently have watchful waiting, initial psychopharmacological treatment, psychotherapy, and psychiatric referral in their armamentarium. This review surveys these management options, emphasizing the most problematic adverse effects associated with the use of antidepressants (ADs) and offering suggestions—if medication is indicated—on how to tailor a side-effect profile to a particular patient's presentation. It offers parameters within which to define appropriate treatment length and other principles for prescribing ADs. Finally, it provides specific guidance on when to recommend psychotherapy and when to refer the patient to a psychiatrist.

To identify relevant articles for this review, a PubMed literature search (ending date parameter, October 15, 2009) was conducted using the keywords *depression*, *antidepressants*, *side effects*, *adverse effects*, *weight gain*, *sexual dysfunction*, and *sleep disturbance*, and reference lists in the identified articles were hand searched for additional relevant publications.

DIAGNOSING MAJOR DEPRESSIVE DISORDER

Major depression is described as "a heterogenous disorder with a highly variable course, an inconsistent response to treatment, and no established mechanism."[5] Adding to its protean complexity are its multiple symptom domains (eg, emotional, somatic, and behavioral), which may be variably expressed in conjunction with dysregulation of appetite, sleep, energy, and concentration.[6] When somatization is particularly prominent, as it is in two-thirds of depressed patients presenting to primary care, blindsided physicians may focus on working up physical symptoms and fail to probe for their depressive underpinnings. This is a primary reason why generalists miss the depression diagnosis.[7]

Conversely, much of what at first glance looks like major depression may turn out with further examination to fit criteria for another entity, such as adjustment disorder, bereavement, cognitive disorder, personality style, or dysthymia (Table 1). The first 2 entities either fail to rise to the level of

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major depression or have not been present long enough to meet criteria. The third and fourth entities are characterized by patterns of interacting with the world that have become pervasive rather than episodic. The last, a chronic form of mild depression, consists of depressed mood and 2 or more depressive symptoms present for at least 2 years. If a patient lacks a medical or psychiatric comorbid condition, a physician should be even more reluctant to assume the presence of major depression. In a Finnish sample of 137 patients with major depression, only 12% had neither additional psychiatric diagnoses nor chronic physical illness. The investigators concluded that "treatment of depression in primary care should not rest on an assumption of short-lived, uncomplicated mild disorders."[9]

Major depression is strictly a clinical diagnosis made on clinical grounds. Initial screening is easily accomplished with a 2-question case-finding instrument, the Patient Health Questionnaire 2, which has proven as effective as much more complex instruments in establishing the diagnosis. With their references to time frame, depressed mood, and anhedonia, the 2 queries contain the sine qua non criteria for establishing the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) diagnosis: "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?" Positive answers to both are associated with a sensitivity of 96% and a specificity of 57%.[10,11] Negative answers to both make clinically relevant depression unlikely and alternative diagnoses more likely.[12]

Having screened positive on at least 1 of the 2 items in the case-finding instrument, patients should be asked additional questions to see whether they meet the major depression threshold, particularly because 2-question instruments identify 8 of 10 cases of depression but have a false-positive rate of 60%.[13] Endorsement of at least 4 more symptoms for at least 2 weeks along with social and occupational impairment is required to make the diagnosis (Table 1).

MANAGING DEPRESSION

In managing suspected depression, the generalist has 4 treatment options: watchful waiting, psychopharmacological treatment, psychotherapy, and referral to a psychiatrist. The vigorous marketing of ADs and the availability of more than 2 dozen of them on the US market may encourage physicians to opt for psychopharmacological therapy, but even in this age of the "Prozac Nation," reflexively prescribing an AD on flimsy grounds is certainly contraindicated. An initial, more conservative approach of watchful waiting may be appropriate.

TABLE 1. **Differential Diagnosis of Depressive Syndromes**

Depressive symptoms
1. Depressed mood
2. Decreased pleasure
3. Weight loss or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or reduced energy
7. Preoccupation with feelings of worthlessness or guilt
8. Poor concentration or indecisiveness
9. Morbid or suicidal thoughts
10. Substantial social or occupational impairment
Major depressive disorder
Either 1 or 2; at least 4 items from 3-9 for at least 2 wk; 10
Dysthymia
1; at least 2 items from 2-9 for at least 2 y; 10
Adjustment disorder with depressed mood
Identifiable stressor but symptoms out of proportion to what is expected
Not enough symptoms to meet major depressive disorder criteria
Substantial social or occupational impairment
Stressor within 3 mo, impairment not longer than 6 mo
Bereavement
Specific stressor: death of a loved one
Symptoms resemble major depressive disorder, but patient considers them appropriate
Major depressive disorder diagnosis is not given unless symptoms persist longer than 2 mo or include guilt not related to the dead, a preoccupation with worthlessness, marked psychomotor retardation, suicidal ideation, and prolonged and marked functional impairment

From *Quick Reference to the Diagnostic Criteria From DSM-IV-TR*,[8] with permission.

WATCHFUL WAITING

With adverse effects of ADs common and prescription costs high, Ackermann and Williams[14] favor watchful waiting with frequent face-to-face contact to assess whether symptoms have resolved or more aggressive treatment is indicated.

Ackermann and Williams[14] note the tendency of primary care physicians to prescribe ADs reflexively for what they label *minor depression*, ie, depressive syndromes that fail to rise to the standard of 4 or more distinct symptoms beyond depressed mood and anhedonia. A scanty literature does not support AD efficacy in this population. The physician's judgment about whether symptoms will spontaneously resolve in 2 to 4 weeks should determine whether medication is prescribed.[10]

Other diagnoses for which ADs are inappropriate are normal bereavement and adjustment disorders, which by definition cannot meet criteria for another acute depressive or anxiety disorder. "Current data suggest that clinicians should consider active treatment only for those individuals with more severe functional impairment," these psychotropic minimalists opine, recommending "[a] 4-to-8 week trial of support, education, and when appropriate, exercise, ... for all others."[14]

Despite a burgeoning literature purporting to show the therapeutic efficacy of AD medications, prescribers will do well to proceed with appropriate skepticism. First, AD re-

TABLE 2. **Commonly Used Antidepressants**

Antidepressant	Dose (mg/d)		
	Starting	Therapeutic	Maximum
Selected first-generation antidepressants			
Tricyclics			
Tertiary amine			
Amitriptyline	25	50-200	300
Clomipramine (Anafranil)	25	50-200	300
Doxepin (Sinequan)	25	50-200	300
Imipramine (Tofranil)	25	50-200	300
Secondary amine			
Desipramine (Norpramin)	25	50-200	300
Nortriptyline (Pamelor)	25	50-150	150
Selected second-generation antidepressants			
SSRIs			
Citalopram (Celexa)	10	10-60	80
Escitalopram (Lexapro)	10	10-20	40
Fluoxetine (Prozac)	10	20-60	80
Paroxetine (Paxil)	10	20-50	60
Sertraline (Zoloft)	25	25-200	200
SNRIs			
Desvenlafaxine (Pristiq)	50	50-100	100
Duloxetine (Cymbalta)	30	30-90	120
Venlafaxine (Effexor XR)	37.5	37.5-375	
Serotonin antagonist			
Mirtazapine (Remeron)	7.5	15-45	45
Norepinephrine and dopamine reuptake inhibitors			
Bupropion SR (Wellbutrin)	100	100-400	400
Bupropion XL (Wellbutrin)	150	150-450	450

SNRI = serotonin and norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; XL = extended release. All doses are for oral preparation taken once daily except for bupropion SR, which is taken twice daily, and venlafaxine (Effexor SR), which can be taken once a day or in divided doses.[6,10,19-21]

sponse, defined as a 50% reduction in depressive symptoms, is not the same as depression remission. Only about a third of patients achieve full symptom resolution after 3 months of treatment with an initial AD, and only two-thirds achieve full remission, even after trials of 3 additional ADs.[15] Second, by the time several ADs have been tried, the episode might be expected to resolve on its own. In the Baltimore Epidemiological Catchment Area Study, the median length of a first depressive episode was 20 weeks, with subsequent episodes typically somewhat shorter. Only half of the first-episode group had a recurrence during 15 years of follow-up.[16]

Yet another justification for waiting to diagnose depression in equivocal cases is the tendency of generalists—when they inquire about depressive symptoms at all—not only to underdiagnose actual depression but also to diagnose depression when it is not actually there. A meta-analysis that pooled more than 50,000 cases found that generalists achieved a positive predictive value of 42% and a negative predictive value of 86%. Given the relative rarity of the depressed vs nondepressed condition, what this means is that in a sample of 100 patients, 10 patients with depression will be correctly identified, 10 will be missed, and 15 patients who are not depressed will be falsely given the diagnosis.[17]

Psychopharmacological Treatment

It [medicine] always is directly hurtful; it may sometimes be indirectly beneficial.

Oliver Wendell Holmes Sr
Currents and Counter-Currents in Medical Science

The person who takes medicine must recover twice, once from the disease and once from the medicine.

Attributed to William Osler, MD

Both Holmes and Osler speak truths that apply to patients in whom ADs have been newly prescribed. Not only can patients with depression develop medication-induced adverse effects long before mood improvement can be expected, but they can also experience the treatment as being as noxious as the illness being treated. The proof of these statements' validity is that as many as 70% of primary care patients fail to adhere to either short- or long-term AD treatment, citing adverse effects as the main reason for discontinuing use of their medication.[18]

Choosing among the many ADs currently on the US market (Table 2) presents a challenge to primary care physicians, who write more than 75% of the prescriptions for

these drugs.[22] That choice is complicated by clinical trial data whose applicability to real-life practice is brought into question by unrepresentative patient populations, the fact that all available medications are predicated on an understanding of the underlying mechanism in depression that is outdated, and the impact of vigorous marketing claims that are not borne out by the research.

Pharmaceutical studies that guide physicians' treatment decisions are frequently based on individuals not typical of patients in most practices. Zimmerman et al[23] wanted to know what proportion of depressed patients in their Rhode Island outpatient psychiatric practice would be eligible for such studies. They distilled inclusion and exclusion criteria from 31 studies that appeared in 5 major psychiatric journals in the mid-1990s. Ruled ineligible were patients with bipolar depression, recent substance abuse, suicidal ideation, and comorbid Axis I disorders, including anxiety, borderline personality disorder, and depression that had lasted either too long or not long enough. Only 41 (12%) of 346 patients would have made the cut. Prescribers should assume that criterion standard randomized controlled trials are at best general guides for how to medicate actual patients, most of whom will have 1 or more inconvenient comorbid conditions rendering them ineligible for most research trials.

Antidepressant treatment strategies are based nearly exclusively on the half-century-old monoamine hypothesis, which posits that depressive symptoms are driven by noradrenergic, serotonergic, and dopaminergic system abnormalities that will be corrected with drugs that raise brain monoamine levels.[24] All ADs in current use are thought to work through monoaminergic manipulation, even as the mechanisms by which this occurs remain incompletely defined.[25] Depression is increasingly understood to derive not only from perturbations in monoamine circuits—a so-called chemical imbalance in the brain—but also from "the cumulative impact of genetics, adverse events in childhood and ongoing or recent stress" that affect brain-derived neurotrophic factor levels, hypothalamic-pituitary-adrenal axis function, and glutamate-mediated toxicity in multiple brain regions.[25] With only half of depressed patients responding to monoaminergic ADs, Rapaport[24] cites evidence for multiple pathophysiologic processes that may contribute to what he calls the *complex heterogeneous syndrome of depression* that may not respond to available ADs. "Our most recent consensus suggests that the depressive disorders reflect the interplay between these biological systems and psychosocial experiences, such as early-life trauma and current life stressors," Rapaport writes.[24]

Although all AD classes demonstrate comparable efficacy in treating depression,[26-28] second-generation ADs have become first-line treatment as a result of vigorous marketing claims that they promote better adherence and are safer in overdose than the cardiotoxic first-generation tricyclic antidepressants (TCAs).[29] Although patients have reported tolerating second-generation ADs—so-called modern or atypical ADs—better than first-generation drugs,[30] assertions of improved tolerance belie patient actions. An 84-study meta-analysis by Trindade et al[31] showed no difference in dropout rates between those taking TCAs and selective serotonin reuptake inhibitors (SSRIs), although the same study found distinct differences between the 2 drug classes in terms of adverse effects that patients considered unacceptable. Although the 2 classes did not differ in the prevalence of headache, tremor, urinary disturbance, or hypotension, TCAs were substantially more likely to induce such anticholinergic symptoms as dry mouth, constipation, dizziness, sweating, and blurred vision, and SSRIs were associated with substantially more nausea, anorexia, diarrhea, insomnia, nervousness, agitation, and anxiety.[31]

Knowing that all ADs have similar efficacy, the generalist faced with choosing an appropriate AD would do well to base rational treatment decisions on differences in side effects among the available ADs (for prescribing principles, see Table 3). Aggressive side-effect management can improve adherence, enhance comfort and function, and obviate premature discontinuation.[40] Side effects can even be harnessed for their therapeutic value, as this review illustrates.

Working with side effects means seeking to minimize the noxious and maximize the beneficial while also targeting specific depressive symptoms. In a sense, with divergent side-effect profiles for first- and second-generation drugs, the patient and physician can "pick their poison," choosing between the potential anticholinergic and antihistaminic effects prominent with TCAs and the serotonergic and noradrenergic effects with SSRIs and such atypical ADs as mirtazapine, venlafaxine, and duloxetine. Drugs within a particular class may also have divergent tolerability. Paroxetine, for example, causes more sedation, constipation, sexual dysfunction, and weight gain than other SSRIs,[41] whereas escitalopram and sertraline appear to be the best tolerated in terms of efficacy and acceptability.[42] One class of drugs may even be safer than another. For suicidal or impulsive patients, SSRIs are a better choice than TCAs with their cardiac toxicity in overdose.

Side effects are by no means always problematic. For example, a TCA or mirtazapine can provide beneficial sedation to patients in whom insomnia figures prominently, whereas bupropion may energize a patient who is experiencing lassitude. Moreover, any drug may potentially prove a double-edged sword, with consequences intoler-

TABLE 3. **Prescribing Principles for Antidepressant Therapy**

1. Do not rush to prescribe ADs for mild depressions, adjustment disorders, or depressive syndromes that do not meet full criteria for major depression; watchful waiting, combined with supportive visits with the physician, may cause the symptoms to remit[14]
2. Inform patients of potential side effects and how they will be managed (early ones will be transient and bearable; late-developing or persistent effects may necessitate dosage adjustment or other antidote)
3. Warn patients that adverse effects will likely occur before substantial benefit, which may not arrive for several weeks[26,31,32]; set realistic expectations for small, incremental improvements in target symptoms rather than for simultaneous departure of the entire panoply of symptoms; track progress by chronicling improvement in specific target symptoms that are most bothersome (eg, difficulties with sleep, concentration, and appetite regulation) rather than depression per se; in some patients, depression resolution will not occur with the first AD that is tried and a second or even third AD trial may be necessary
4. Frame side effects as neither good nor bad, but choose a medication whose side-effect profile could prove salutary to the patient, such as a sedating AD for anxiety and sleep difficulties or an activating one for sluggishness and lack of motivation; ask how important sexual and/or weight concerns are to the patient and factor the answer into the medication choice
5. Begin with a low dose of AD and increase gradually every 5-7 d to the desired therapeutic dose, particularly if adverse effects are tolerable. The typical TCA dose effective against depression may be an order of magnitude or more higher than the dose for indications such as neuropathic pain or pruritus. The starting dose of an SSRI or SNRI may be as little as one-tenth the maximum that can be given. Electrocardiographic findings of patients taking AD doses of TCAs should be intermittently checked for QRS-complex widening beyond 100 ms, a sign of TCA toxicity[33]
6. Avoid combining multiple serotonergic agents that could precipitate serotonin syndrome, an acute toxic state manifesting in mental status changes, neuromuscular signs, and autonomic dysregulation. The most specific signs of excessive serotonin stimulation are clonus, hyperreflexia, agitation, diaphoresis, and tremor[34]
7. Plan on at least 3 follow-up visits during the 3 mo after the initial appointment to increase AD adherence.[35] The first should be within 7-10 d and focus on how the patient is tolerating the medication rather than on symptom alleviation; SSRI-induced agitation or akathisia that has raised concerns about driving suicidal behavior is most likely to occur soon after initiating treatment and constitutes a medical emergency.[36] Patients should be encouraged to contact the physician with any concerns
8. Consider adjunctive therapies, such as PDE-5 inhibitors for sexual concerns and soporifics for sleep, particularly when they may improve adherence; adjunctive anxiolytics or soporifics may be especially helpful during the early weeks of treatment before the AD has begun to take effect
9. Taper gradually when discontinuing AD use to avoid discontinuation syndromes, which can include neuropsychiatric, emotional, and physical symptoms that may be confused with physical illness or depression relapse.[34,37] Reduce dose by no more than 25% per week; taper more slowly the longer the patient has been taking the AD and the shorter the AD's half-life. For mild and transient withdrawal symptoms, reassurance may be enough; however, severe reactions may necessitate slowing the rate of taper or reinstituting the original AD dose[38]
10. Do not abruptly discontinue use of ADs, particularly SSRIs. Such inappropriately sudden discontinuation can occur when the patient is admitted to a hospital for a nonpsychiatric problem and the admitting team elects to stop AD use to reduce confounders in diagnostic dilemmas or fails to order them because they do not understand their importance. As Papadopoulos and Cook,[39] 2 pharmacologists, point out, SSRI withdrawal typically starts within 3 d and can last up to 3 wk, with symptoms including dizziness, paresthesias, tremors, anxiety, nausea, emesis, lethargy, and headache. Withdrawal from venlafaxine and duloxetine, which modulate serotonin and norepinephrine levels, can also precipitate these symptoms
11. Remember that pharmacotherapy and psychotherapy can prove synergistic, particularly for patients with recurrent depressive episodes. After a first depressive episode, the chance of recurrence is 50%[16]; by the third episode, recurrence is virtually guaranteed. Much like diabetes mellitus or hypertension, therefore, depression becomes a chronic medical condition to manage rather than an acute, time-limited condition to cure. The use of AD medication should be continued for 6 to 12 mo after remission with a first episode, 3 y after a second episode, and indefinitely after ≥3 recurrences

AD = antidepressant; PDE-5 = phosphodiesterase 5; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

able for one patient, being salutary for another. An example is sertraline, an SSRI, which, like other drugs in its class, can induce a plethora of sexual difficulties when prescribed for depression but can also delay male orgasm in men with premature ejaculation.[43] One man's curse becomes another's boon.

Side Effects of ADs. Among the pharmacological characteristics of the ideal AD, Richelson[44] included "no side effects" and "rapid onset of action." Unfortunately, no available medication meets either criterion. Insult compounds injury when adverse effects dominate the clinical picture well before the AD can be expected to exert therapeutic benefit.

Treatment with ADs occurs in 3 phases: initiation, continuation, and maintenance. During initiation, the goal of triggering remission is achieved through gradual up-titration of the AD dose. Although achievement of remission is far from universal, when it does occur, the AD should be taken throughout this "continuation phase," defined as a period that is the typical length of an untreated episode. For a first episode, treatment continues for 6 to 12 months. After a second episode, a year or more of treatment is rec-

ommended. With 3 episodes or more, lifelong maintenance treatment is recommended in hopes of limiting the intensity and frequency of future episodes or forestalling them altogether.[6]

Paralleling the 3 stages of AD treatment, side effects occur in 3 overlapping but roughly sequential phases, each requiring active management to maximize chances that patients will continue taking medications long enough to reap benefits. Indeed, a recent background article from the American College of Physicians emphasizes that it is not the specific AD but the length of time an AD is taken that is key. An adequate treatment trial consists of the maximum tolerable dose of a particular medication taken for at least 8 weeks.[29]

The traditional distinction between short-term and long-term side effects appears to be artificial and misleading.[45] A more useful classification includes those effects that arrive early—sometimes within hours—and are self-limiting, such as nausea or headache; those that arrive early and persist, such as sexual dysfunction or fatigue; and those that emerge gradually and accrue, such as weight gain. Early side effects result from AD synaptic effects on neurotransmitter reuptake and receptor blockage, whereas those emerging later stem from such slow-to-develop neuroplastic adaptations as receptor desensitization and downregulation that are hypothesized to reverse depression.[25,27]

During the first phase, long before an AD effect is expected, receptor-mediated synaptic side effects dominate the clinical picture. Examples include nausea or dull headache with SSRIs or jitteriness with bupropion. Because these typically diminish or disappear with time, prescribers can reassure patients in whom ADs have been recently prescribed that at least some of the unpleasantness of these early days will dissipate with continued drug exposure. With fluoxetine, activation in the form of nervousness, anxiety, agitation, and insomnia was more likely to wane during the first few weeks than sedation manifesting as daytime somnolence, low energy, and fatigue.[46] In a carefully reasoned meta-analysis of AD-benzodiazepine combination therapy, Furukawa et al[47] found that fewer patients taking the combination dropped out of treatment than those taking AD alone, although they advised judicious consideration of the potential for developing dependence or precipitating accidents.

"Start low and go slow" is good advice for limiting the noxiousness of these early adverse effects, and patients are more likely to tolerate them if given the expectation that they will be self-limiting. In addition, warn Kelly et al,[40] "side effects sometimes exacerbate or masquerade as residual depressive symptoms." Fatigue, cognitive impairment, apathy, agitation, irritability, sleep disturbances, sexual dysfunction, and gastrointestinal distress are among depressed patients' many concerns that could be attributed to ADs if clinicians are not careful to tease out what was already present before the patients started taking medications. If a patient has out-of-proportion adverse effects in response to low AD doses or no AD response to high doses, cytochrome P450 (CYP) genotypic testing for variations that cause slow or rapid metabolism may be indicated, particularly because many ADs are metabolized through either the CYP2D6 or CYP2C19 subsystems. Physicians should be aware of the potential for drug-drug interactions, particularly with long half-life drugs such as fluoxetine and agents that alter CYP activity.[48,49]

The second phase is noticeable as the ephemeral activating side effects dissipate and the AD begins to kick in. Classic examples can be found in the sexual realm. Just as individuals whose libido may have flagged as a function of their depression become interested in sex again, their bodies refuse to perform in accustomed ways. This paradox can be so upsetting that patients discontinue use of the ADs just as they are starting to help. Because ultimate treatment success depends on physicians doing whatever they can to ensure adherence, prescribers will do well to anticipate potential sexual side effects with their patients, reassuring them that, if problems emerge, effective strategies and adjunctive therapies are available.[50]

Weight gain exemplifies the third side effect phase, the late-emerging stage. Through changes in metabolism, eating patterns, exercise, or all 3, weight may stealthily increase until it is impossible to ignore. Again, paradoxically, mood may have greatly improved when weight gain becomes noticeable, and ironically it appears that some individuals—those already at risk for obesity—may be prone to outsized gain.

In an influential study of 401 patients interviewed 2.5 to 3.5 months after initiating AD therapy, Hu et al[22] found that 86% reported at least 1 adverse effect and 55% had an adverse effect bothersome enough to challenge their willingness to continue use of their AD. Although dry mouth, drowsiness, and sexual dysfunction were most common, it was the latter 2 plus weight gain that the patients studied by Hu et al judged most bothersome. Following the lead of Hu et al, this review will consider each of these in turn.

Sleep Disturbances and Sedation. Neurotransmitters associated with wakefulness and cortical arousal include histamine, acetylcholine, norepinephrine, and serotonin, among others. The most prominent neurotransmitter promoting sleep is γ-aminobutyric acid (GABA), and the most prominent neurotransmitter promoting awakeness is histamine. Strategies for inducing sleep thus most frequently focus on either increasing GABA function through allosteric activation of GABA-A receptors or blockage of histamine receptors. Benzodiazepines and the benzo-

diazepine receptor agonist "Z drugs" (zolpidem, zaleplon, and eszopiclone) work through modulating different components of the GABA-A receptor complex in the hypothalamic sleep-promoting center. Over-the-counter antihistamines, such as diphenhydramine and/or doxylamine, or ADs with strong antihistaminic side effects, such as trazodone and doxepin, block histamine receptors, particularly H_1, in the hypothalamic wake-promoting center.[51]

Disturbed sleep is a cardinal sign of depression, with difficulty falling asleep, trouble staying asleep, and early-morning wakening each potentially present and problematic. As the AD acts, sleep will ideally normalize. In the first few weeks after starting use of ADs, however, a benzodiazepine or Z-drug may be used to induce sleep while awaiting the AD's salutary effects. Because benzodiazepines induce tolerance, their use for sleep induction is not recommended beyond a month. Although intermediate-acting benzodiazepines may be more likely to facilitate sustained sleep, short- to intermediate-acting benzodiazepines (temazepam, estazolam, and triazolam) are preferred if daytime sleepiness, dizziness, or incoordination becomes a problem. Long-acting benzodiazepines, such as clonazepam, can induce a hangover sensation when used for sleep alone and are best reserved for patients with a strong anxiety component, present not only at bedtime but throughout the day. In these patients, benzodiazepines may slow racing thoughts or reduce muscular tension, making sleep more likely to follow. In elderly patients with reduced hepatic and renal clearance, lower doses of any benzodiazepine are advised to reduce the risk of falls and hip fractures.[52]

Although data beyond 6 months of use are lacking, the soporific effects of Z-drugs appear less likely to wear off, making them viable options for longer periods.[52] Many studies during the past 15 years have shown that Z-drugs do not interfere with AD response. Recently, Fava et al[53] have shown in a large placebo-controlled study that eszopiclone prescribed simultaneously with fluoxetine may not only immediately improve sleep but also enhance the speed of onset and magnitude of response of AD effect.

For some patients, ADs, particularly highly serotonergic ones, may relieve all neurovegetative signs of depression except poor sleep. An antihistamine strategy can prove helpful, augmenting ADs with low doses of highly antihistaminic-sedating ADs, such as doxepin or trazodone, at bedtime.[52] Stahl[51] warns, however, that most commonly used antihistamines are not selective for histamine receptors alone. Over-the-counter antihistamines, for example, are typically highly anticholinergic and can induce confusional states, particularly in elderly patients.

The TCAs with high affinity for histamine receptors work best for sleep induction in doses that are 1 to 2 orders of magnitude less than typical AD doses of 100 mg or more. With an AD dose, a TCA such as doxepin is associated with dry mouth, postural hypotension, cardiac arrhythmia, drowsiness, and weight gain, among other side effects. In a study of doxepin in ultralow doses of 1 to 6 mg, in which it is highly selective only for H_1 receptors, anticholinergic effects, memory impairment, and next-day hangover effects occurred no more often than with placebo, thus minimizing myriad other neurotransmitter actions and concomitant adverse effects that occur with full dosing.[54]

Trazodone causes hypotension, constipation, and rarely priapism.[52] Intolerable for most in a full AD dose (150-600 mg), trazodone effectively induces sleep in doses of 25 to 150 mg.[51] The dose may need to be titrated down if daytime sedation or a hangover sensation occurs or up if early morning awakening continues to be a problem. Reports published soon after trazodone's introduction more than a quarter century ago associated it with ventricular arrhythmias and idiopathic peripheral edema with substantial weight gain. Janowsky et al[55] challenged 20 patients with preexisting cardiac problems or histories of adverse cardiac reactions to trazodone doses ranging from 150 to 600 mg. Two of 20 had increased premature ventricular contraction frequency, and 1 of 20 had a reduction in frequency. Premature ventricular contraction frequency returned to baseline when the trazodone dose was decreased or use of the medication discontinued. Barnett et al[56] reported 10 cases of peripheral edema associated with trazodone in doses ranging from 150 to 600 mg. In all cases, edema resolved with dose reduction or discontinued use of the medication. Of note, patients taking trazodone for its soporific properties rarely require doses within the ranges used in the studies by Janowsky et al and Barnett et al. Case reports implicate trazodone in acute overdoses (exceeding 1.5 g) as causing QT prolongation and delayed atrioventricular nodal conduction in a first case[57] and a potentially lethal ventricular arrhythmia in a second case.[58]

With its prominent 5-hydroxytryptamine receptor 2 ($5\text{-}HT_2$)–blocking properties, the tetracyclic AD mirtazapine specifically counteracts SSRI-induced nonspecific stimulation of serotonin receptors. Blockade of $5\text{-}HT_2$ is associated with eventual shortened sleep-onset latency, increased total sleep time, and improved sleep efficiency.[59] Mirtazapine also has histaminic effects prominent soon after initiation, which dissipate as tolerance to the sedating effect develops.[60] By then $5\text{-}HT_2$ sleep-promoting influences predominate, with the added advantage of there being no hangover effect.[60,61] A subtherapeutic AD dose of 15 mg or less is recommended for long-term treatment of insomnia.[61]

As mentioned, TCAs can be sedating, particularly in higher doses, and are therefore usually given in a single

dose at bedtime. In contrast, SSRIs are typically considered energizing, possibly through their 5-HT_2–stimulating properties, and are usually taken once daily in the morning. With its greater tendency to cause sedation than other SSRIs, paroxetine is the exception and is often taken at night.[41] For unclear reasons, a few patients may experience daytime sedation while taking any of the SSRIs. For them, a first strategy is to switch the morning dose to evening. If this fails to relieve the grogginess, a trial of another AD may be necessary.

Sexual Dysfunction. First-generation ADs (TCAs) certainly cause sexual dysfunction along with a host of other adverse effects. Introduced in a more sexually repressed age, the 1950s, and causing constipation, urinary retention, blurry vision, and cognitive clouding, among other antihistaminic and anticholinergic effects, these drugs did not draw attention to sexual performance in the way that so-called modern ADs (eg, SSRIs, serotonin and norepinephrine reuptake inhibitors [SNRIs], and bupropion) have. By the late 1980s, Americans were speaking more freely about their sex lives and their dissatisfaction with medications that interfered with their intimate activities. Even so, self-reports of medication-induced sexual dysfunction, at 2% to 16%, have always lagged behind rates elicited by direct questioning,[62] which can range up to 70%, even as problems uncovered through deliberate querying may not be clinically important for many experiencing them.[63]

As a result of substantial serotonin reuptake blockade, second-generation ADs (SSRIs and SNRIs, such as venlafaxine) have been associated with reduced libido in both men and women, as well as genital arousal problems (erection in men and lubrication in women) and delayed or absent orgasm in up to 40% of both men and women.[64] The extent of these problems was not recognized until reports began to appear in the medical literature in the 1990s, years after these medications had been hailed as wonder drugs free of the adverse effects that had made TCAs so difficult for many to tolerate.

Although the details of SSRI-induced sexual dysfunction remain unknown, one culprit may be elevated synaptic levels of serotonin, which are theorized to improve mood centrally while indirectly contributing to compromised genital function peripherally. Although details of the specific interaction between serotonin and nitric oxide (NO) remain uncertain, NO is a direct mediator of arousal, with levels increasing in response to sexual stimulation. At least one SSRI (paroxetine) has been shown in the laboratory to interfere with NO synthase, thereby reducing NO levels.[65]

Ultimately, NO is responsible for triggering production of cyclic guanosine monophosphate, the agent that relaxes smooth muscle, including that found in genital vasculature, a process that allows blood to engorge sexual organs in both men and women. Although varied strategies, such as drug switching, dose reduction, drug holidays, and antidotes, have been tried to reverse sexual dysfunction, only 3 pharmacological strategies have been shown in double-blind trials to have efficacy against these adverse effects.[64] To maintain dopamine levels thought necessary for optimal sexual functioning, the first 2 strategies consist of adding to the SSRI regimen either high daily doses of buspirone (60 mg/d), an anxiolytic that prevents serotonin's damping effect on dopamine, or therapeutic daily doses of bupropion (300-450 mg/d), a dopaminergic AD in its own right. Taken only in anticipation of intercourse, the third option, phosphodiesterase 5 (PDE-5) inhibitors (eg, sildenafil, vardenafil, and tadalafil), have become the standard of care.[18,40,63] The PDE-5 inhibitors are thought to act through inhibiting the enzyme that inactivates cyclic guanosine monophosphate, thus permitting greater NO effect. In men, these drugs facilitate improved erections and greater orgasmic satisfaction, with nearly 60% of men needing an antidote for SSRI-induced dysfunction reporting "much" or "very much" improved sexual performance in all spheres.[18] In women, sildenafil has shown promise for reversing the inadequate lubrication and delayed orgasm induced by SSRIs.[66]

It is critical to emphasize that PDE-5 inhibitors do not directly enhance libido but only exert their effects in response to sexual stimulation. One second-generation AD in particular appears to spare NO function. Patients taking bupropion alone report one-fourth to one-sixth the rate of sexual dysfunction in all spheres (desire, arousal, and orgasm) compared with patients taking SSRIs or SNRIs, with bupropion rates indistinguishable from placebo.[67] This sparing of sexual function is likely the result of bupropion's negligible effects on serotonin levels and appreciable effects on dopamine levels, the neurotransmitter associated with enhancing sexual function.[62] Like bupropion, nefazodone has minimal impact on sexual function, but it has carried a Food and Drug Administration black box warning since 2002, the only AD with such a warning for hepatotoxicity. Although most ADs have the potential to cause idiopathic liver injury, nefazodone seems to inflict the most serious damage, although at a rate of only 1 case per 250,000 to 300,000 treatment-years. Of 9 cases of liver failure in the literature up until 2007, 4 resolved on their own, 3 resolved after liver transplant, and 2 resulted in death, with 1 of the deaths occurring after liver transplant.[68]

Distinguishing AD effects from depressive symptoms can be challenging. Labbate[63] emphasizes that sexual dysfunction is frequently both premorbid and multifactorial,

resulting from medical factors, such as vascular disease and cardiac medications, and psychological factors, such as marital dissatisfaction. Assessing sexual function before starting use of an AD may prevent false attribution of preexisting dysfunction to the AD. If sexual adverse effects develop after starting use of ADs, however, active intervention is advised rather than waiting for improvement because tolerance to these adverse effects rarely develops.[64] Although decreased libido and erectile dysfunction are common in patients with depression, the ejaculatory delay and anorgasmia frequent with SSRIs are not.[69]

As with many of the side effects attributed to ADs, low libido is for some patients a depressive symptom that may actually be relieved as the AD begins to take effect. Others may experience side effects as changes in familiar body responses that they can readily tolerate, particularly if prescribers have alerted them in advance to these possibilities. Some patients are not particularly concerned about their sex lives. Others may be willing to increase foreplay to overcome reduced libido or take a drug such as a PDE-5 inhibitor to enhance genital engorgement, particularly if their depression is relieved. Like men taking SSRIs for premature ejaculation, some depressed men may actually find delayed orgasm advantageous and desirable. For women, estrogen creams applied directly to the genitals may be helpful. In addition, nonpharmacological means, such as vaginal lubricants, can obviate adding a medication. Physicians and patients should talk about sexual issues before they become problems, preferably introducing the topic when AD therapy is initiated.

Weight Gain. Antidepressants differ in their capacity to induce weight gain. Even in low doses, tertiary amine TCAs (eg, amitriptyline, imipramine, and doxepin) are more likely to cause weight increase than secondary amine TCAs (eg, nortriptyline and desipramine). Bupropion is linked to the least weight gain of any AD.[40] Among the SSRIs, paroxetine has the greatest potential for inducing weight gain. Mirtazapine carries a reputation for being a particularly potent appetite stimulant, even though it is far from clear that it is any more of a culprit than any other AD. The exact mechanism is disputed, but these drugs' antihistaminic qualities are often implicated. Consistent with their having greater antihistaminic potency than secondary amine TCAs, the greater tendency of tertiary amine TCAs to induce weight gain supports this hypothesis.

Recent publications have challenged simplistic earlier formulations linking weight gain exclusively to histamine receptor antagonism, while also undermining initial hopes that SSRIs would prove weight neutral. "Despite their claimed selectivity," write Harvey and Bouwer,[70] "SSRIs still interact, either directly or indirectly, with various critical neurotransmitter systems." Norepinephrine, dopamine, serotonin, cholecystokinin, corticotropin-releasing factor, endogenous opioids, neuropeptide Y, and various hormone-like peptides, including leptin, interact in complex ways to regulate appetite and related behaviors. Exquisitely regulated hormonal and metabolic feedback mechanisms involving ingested nutrients, adipose tissue, and hypothalamic nuclei govern energy expenditure, food intake, and ultimately weight gain or loss.[71] Specifics of these interactions remain elusive, with many potential sites for pharmaceutical interferences.

Referencing both TCAs and SSRIs, Malone[72] emphasizes that all drugs within each class are not created equal: "The tendency to cause weight gain is often related to differential specificity and sensitivity of binding to receptors involved with appetite regulation." Moreover, a given AD does not identically affect everyone; people may vary not only in their response to any particular AD but also in their genetic predisposition to weight gain and obesity more generally.[73] Healthy people gain a kilogram a year during adult life, independent of medication effects.[74] Depression is associated with reduced food intake in some patients and increased intake in others, and therefore resolution of depression will be associated with weight gain in the former and weight loss in the latter.

Nonetheless, a frequently confusing and contradictory literature sheds some light on what to expect when starting AD therapy, which ADs are comparatively weight neutral, and what to advise patients about weight in advance of taking these drugs. A study by Sussman et al[75] illuminates both the extent and scale of the problem with SSRIs. Observed during 16 to 46 weeks, 13.8% of patients taking SSRIs (1 in 7) gained 7% or more of body weight, although the study did not report possible differences among sertraline, fluoxetine, and paroxetine. In a recent review, Papakostas[45] singled out paroxetine over other SSRIs as being particularly problematic. He cited a 26- to 32-week study in which a weight increase of 7% or more occurred in 25.5% (1 in 4) of paroxetine-treated patients vs only 6.8% of fluoxetine-treated patients and 4.2% of sertraline-treated patients. A meta-analysis of studies of escitalopram purports it to be weight neutral.[76]

In the study by Sussman et al,[75] 24.5% of imipramine-treated patients gained 7% or more of body weight. A study comparing patients taking imipramine and mirtazapine showed weight gain of 7% or more in 22% of the former but also 13% of the latter patients. Interestingly, average body weight increases overall were only 1.7 kg and 1.4 kg for imipramine and mirtazapine, respectively, suggesting that a few of the patients gained most of the weight. The same phenomenon of most of the weight gain concentrated in a few patients occurred in a 34-week

study comparing duloxetine and paroxetine. Although the overall average weight gain was only 1.0 kg and 1.3 kg for the duloxetine- and paroxetine-treated patients, respectively, 10.8% of the duloxetine and 13.8% of the paroxetine groups recorded gains of at least 7% of body weight.[77] The only AD on the market that is consistently cited as being weight neutral is bupropion, prescribed not only as Wellbutrin (GlaxoSmithKline, Ann Arbor, MI) for depression but also as Zyban (GlaxoSmithKline, Ann Arbor, MI) for smoking cessation.[67,78,79]

In summary, it appears that all ADs except bupropion and possibly escitalopram are associated with weight gain of at least a few pounds. In a notably few patients, large weight gain is possible, regardless of the particular AD, and typically occurs gradually over many months. Some ADs are more likely than others to induce marked weight gain, and patients already susceptible to obesity may be more prone to this effect. In a trial with patients with eating disorders, bupropion in its immediate-release form had a 4-fold risk of inducing seizures compared with SSRIs. In the sustained-release preparation, the rate of inducing seizures proved to be the same as for the SSRIs.[80] Prudent practice indicates that bupropion should be prescribed warily, if at all, in patients with elevated seizure risk or a history of an eating disorder.

When to Refer for Psychotherapy

When is psychotherapy a better choice than pharmacotherapy? In encouraging physicians to characterize the quality of the depressive presentation, Markowitz[81] outlines 3 broad strategies for determining the appropriate modality, asserting that "the patient's symptoms and psychosocial context are crucial guides to treatment selection." Severe loss of pleasure combined with overwhelming neurovegetative symptoms calls for psychotropic medications, including ADs. A "barrage of negative thinking," underpinned by automatic, dysphoria-perpetuating thoughts that "are more catastrophic than their actual lives," may respond to a cognitive behavioral therapy approach.[81] A severe life crisis (eg, marital strife, job loss, or death of a loved one) lends itself to exploration in interpersonal therapy, a treatment that helps generate new skills for asserting personal needs and engaging more constructively, even confrontationally, with significant others at work and at home.

Other approaches include behavioral therapies that encourage participation in rewarding activities and discourage involvement in those that reinforce depressive thoughts. Problem-solving therapy helps patients break overwhelming issues into bite-sized, manageable pieces.[10] Common to all these therapeutic approaches is a set of principles that includes caregivers (1) sharing their conceptualizations of the diagnosis with their patients, (2) using treatment techniques in logical sequences, (3) encouraging the development of skills useful in daily life, and (4) attributing improvement to patient efforts.[82]

Medication rarely does all the work of dispelling unconstructive thought patterns or maladaptive relationship styles. In Markowitz' opinion, psychotherapy offers new skills that "can transform functioning" even after an acute depressive episode has passed.[81] Such cognitive behavioral therapy–related approaches facilitate a greater capacity to tolerate ingrained negative or uncomfortable effects that might otherwise be confused with major depression. When mild to moderate depression is present, head-to-head studies have found pharmacotherapy and brief psychotherapy to be equally effective. If psychotherapy is elected instead of medication, improvement should be obvious after 6 to 8 weeks of weekly sessions, with full remission within 12 weeks. Otherwise, adding ADs should be considered.[10] The converse is likely true as well.

In a landmark 2000 study, Keller et al[83] showed that in chronic depression, pharmacotherapy and psychotherapy were equally effective in gaining response or remission in 52% to 55% of patients but that the combination of the 2 was substantially more effective, with an 85% response rate. The same group demonstrated that combined therapy leads to more rapid remission of depression than either therapy alone.[84]

When to Refer to a Psychiatrist

For some patients, it is best for psychiatrists to assume their care. With others, a one-time consultation can help a generalist sort out complex medication or diagnostic considerations. Psychiatrists favor an approach that consists of (1) avoiding specific adverse effects, (2) targeting particular clinical symptoms, (3) taking into account previous positive or negative responses to specific ADs, and (4) managing comorbid psychiatric disorders.[85] Generalists will do well to incorporate the first 3 principles into their practice and refer a patient with prominent comorbidity to a psychiatrist.

Consider psychiatric referral if the patient fails to respond to an adequate initial AD trial (defined as a therapeutic dose of 1 or more medications for at least 8 weeks each),[86] describes a strong family history of psychiatric illness or substance abuse, portrays a labile or recurrent illness course of his/her own, or provides a history consistent with past episodes of mania. Depressed patients with bipolar disorder in family members or themselves may be candidates for combination therapy—a mood stabilizer in addition to an AD.[32]

Psychiatric referral should also be considered when the patient experiences only adverse effects without relief

from depressive symptoms or sustains neither adverse effects nor depressive improvement. The psychiatrist may question the depressive diagnosis and propose alternative diagnoses or approaches, including CYP genotyping. In the first instance (maximal adverse effects and minimal benefit), a CYP abnormality could explain that the patient is a poor metabolizer in at least 1 depleted enzyme subsystem. In the second instance (neither adverse effects nor benefit), the patient could be an ultrarapid metabolizer, and excessive CYP activity could result in the active agent being metabolized before it can have an effect either good or bad.[48,49]

The patient who reports that nothing has ever helped, despite multiple trials of medications from many classes, should also be referred to a psychiatrist. Such patients could have unappreciated bipolar disorder or ongoing substance abuse. They may have personality styles not amenable to pharmacological manipulation, require trials of adjunctive medications, or be candidates for psychotherapy rather than pharmacology.

The patient who has complex medical comorbid conditions that, by masquerading as psychiatric phenotypes, complicate assigning accurate psychiatric diagnoses should be treated by a psychiatrist. If depression is judged to be present, aggressive treatment is indicated to reduce sensitivity to somatic symptoms, enhance self-care efforts, and potentially improve prognosis.[10]

The patient who takes a complex combination of medications that the primary care physician is not comfortable continuing to prescribe should also be referred to a psychiatrist. Such a patient may be taking medication combinations from within a single class or from multiple classes, and it may not be readily apparent how or why this polypharmacy has evolved.

The patient who has psychotic symptoms, demonstrates active suicidality, or appears to have manic and depressive symptoms simultaneously, a so-called depressive mixed state that is associated with an elevated risk of all forms of suicidal behavior, should also be treated by a psychiatrist.[7,87] When a physician observes or suspects these particularly dangerous conditions, collateral history from family and other associates may be especially useful in fleshing out the presentation.

CONCLUSION

Antidepressant therapy is not a panacea for depressive presentations but is one element in a generalist's armamentarium, which also includes watchful waiting, psychotherapy, and psychiatric referral. With the right mix of medications and psychotherapy, patients with severe psychiatric illness can and do become stable. Two-question case-finding instruments have high sensitivity in identifying potential cases of major depression, supplemented with devices likely to flesh out the diagnosis. Given similar efficacy among AD classes, side-effect profiles can guide prescribing practices, with the twin goals of minimizing noxious effects and maximizing potential benefits. Particularly problematic adverse effects include sleep disturbance, sexual dysfunction, and weight gain. Bupropion appears to have the most favorable balance of noxious and beneficial side effects, being both weight neutral and sexual function–sparing,[19,79,88] with the important caveat that it is contraindicated in patients at elevated seizure risk, especially in its immediate-release preparation. In the United States, generalists write three-quarters of AD prescriptions. Psychiatric referral is indicated when patients have complex medical or psychiatric comorbid conditions, when initial AD trials have failed to achieve desired results, or when the primary care physician is uncomfortable managing a complicated medication regimen.

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