Rational Antidepressant Selection: Applying Evidence-Based Medicine to Complex Real-World Patients

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ABSTRACT ~ Every clinician faces the daily question of which antidepressant is best for a particular depressed patient. Double-blind studies submitted for U.S. Federal Drug Administration marketing approval include only the "purest" population of patients, and the American Psychiatric Association and other treatment guidelines often do not adequately address the complexities of developmental, family history, psychosocial, medical, and psychiatric comorbidity, and treatment-refractory issues that are seen in routine clinical practice. Long-term trends in depression treatment include ever-expanding choices among drugs, highly specific psychotherapies, and attempts to treat chronic and/or mild cases, with the goal of remission for all patients. We performed literature reviews and attempted to synthesize factors that may be useful in the application of evidence-based medicine in office-based psychiatric practice. We have found that factors influencing antidepressant selection include drug factors (including tolerability, interactions, and cost), depression subtype, psychiatric and medical comorbidity, and stage of life. In addition, patient preference for avoiding certain side effects and personal and family history of treatment response are helpful information. Most patients in the community would not fit strict antidepressant study criteria. Biologic markers predicting treatment response are not yet widely available, so the optimal choice of medication must be guided by detailed history. Psychopharmacology Bulletin. *2006;39(1):38-104.*

INTRODUCTION

"Doctor, I'm a 40-year-old man with several episodes of depression. My grandfather made and lost several millions of dollars before his suicide. My father had periods of gambling, womanizing, rage, drinking excessively, and depression. My mother had chronic depression until she finally got onto a selective serotonin re-uptake inhibitor (SSRI). In my cocaine and alcohol-abusing days, I had a

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couple of seizures and acquired hepatitis C, but I'm clean and sober for 2 years now. I have migraines at least 2-3 times a month. I'm recovering from a divorce and just starting to date again. Please treat my depression with something that won't put weight on me, kill my sex life, harm my liver, or give me more headaches."

Someone like this patient will show up in our office at least a couple of times a month. In the senior author's 18 years as a clinical professor and 13 years of private outpatient practice, such patients have presented for treatment when the primary care physician or other psychiatrist felt overwhelmed by the difficult differential diagnosis and comorbidity. Does this man have bipolar depression, depression due to his medical condition, substance-induced mood disorder, or a brain tumor? Where does a thoughtful clinician turn for advice on treating such a patient? This patient would certainly never get into a drug study! He would never be addressed in treatment guidelines. Yet, as more primary care physicians become comfortable treating simple patients, increasingly complex and treatment-refractory patients present to psychopharmacologists for expert treatment.

This literature review will provide evidence-based guidelines for the clinician facing the daunting task of selecting which antidepressant to prescribe for a patient presenting with depression. We will review drug types and knowledge derived from studies, clinician issues, and patient issues impacting this process. Our goal is to provide useful and clinically relevant information for treatment of complex or comorbid depressed patients.

There is an unfortunate lack of placebo (PBO)-controlled studies addressing highly complex, real-world patients, and the application of available data on drug efficacy to clinical practice is limited. It is our assertion, however, that adequate data does exist to say that no single drug is "first line" for every patient. Drug selection factors include those rationally based on the clinician and treatment setting, the drug itself, the illness and subtype, psychiatric and medical comorbidity, life stage, past responses and side effects, and patient requests. Some factors may be less rationally based: the patient's statement that he has seen an advertisement or heard of a friend doing well on a particular drug, for example.

Although future promise of brain imaging and genetic prediction of drug response is considerable, current state-of-the-art requires careful evaluation of the many factors outlined here.

MULTIPLE ANTIDEPRESSANTS ARE AVAILABLE BUT REAL WORLD DATA ARE LIMITED

There are many antidepressant drugs from which to choose, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors

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(MAOIs), SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and the atypical drugs including nefazodone, bupropion, and mirtazapine. Often polypharmacy or augmentation strategies become necessary, which may employ off-label agents from any of several classes, including antipsychotics, lithium, anticonvulsants, stimulants, thyroid replacement, and dopamine agonists.

The quality of data on antidepressant response available to clinicians is highly variable. The most scientifically rigorous data consists of PBO-controlled randomized double-blind multicenter phase III investigational new drug (IND) studies intended for submission to the U.S. Food and Drug Administration (FDA) for marketing approval. Although these studies essentially define the highest standard of efficacy, their relevance to the clinician is limited. The patient population enrolled is dissimilar to that of a community practice, adherence to monotherapy often at fixed dosages is required, and there is disparity between the goals of treatment in a study and those in community practice. Statistical significance on a depression rating scale may not translate into real-world effectiveness in a clinical population. Less scientifically rigorous, but perhaps more relevant to the clinician, are case report series, which often involve add-on rather than monotherapy. Case reports are often biased by initial enthusiasm for new drugs in open treatment settings where PBO effect and psychosocial factors are uncontrolled.

Patients presenting for clinical treatment of depression are not the same as those who are included in Phase III IND studies.

In a study that carefully evaluated patients seeking treatment for depression at a university hospital faculty private practice clinic, common inclusion/exclusion criteria used in efficacy studies of antidepressants were applied to determine how many patients would have qualified for a drug study. Zimmerman and Posternak[1] found that criteria excluding bipolarity, psychosis, comorbidity with anxiety or substance use disorders, mild severity, suicidality, and long or brief duration of episode would eliminate approximately 86% of clinically depressed, treatment-seeking patients from phase III drug studies.[1] Such criteria may not be necessary to demonstrate drug/PBO differences.[2] We have recently performed a review of our private outpatient practice database and found a similarly low percentage of treatment-seeking depressed patients who would qualify for a randomized controlled trial (manuscript in preparation).

As information extrapolated from even the most rigorous data on "pure" research patients is of limited practical value to clinicians caring for complex patients, treatment decisions require a step beyond statistics into the realm of expert opinion. Expert consensus guidelines are available from the American Psychiatric Association (APA), the Texas Implementation of Medical Algorithms, and The Expert Consensus

TABLE 1

FACTORS IN ANTIDEPRESSANT SELECTION

Key Elements of History Taking

Psychiatric history
  Symptom profile
    Symptoms most problematic now
    Symptoms persisting during past treatment
    Severity
    Exacerbating/relieving factors
    Suicidal ideas or attempts
  Psychiatric comorbidity
  Personality traits and temperament
  Substance use
  Illness related impairments
  Medication history
    Helpful & problematic medications (patient & close relatives)
    Reason for stopping medications
  Support system: family, therapy, support groups
  Treatment setting (hospital or outpatient)

Depression subtype
  Unipolar single episode or recurrent
  Bipolar
  Atypical
  Melancholic
  Psychotic
  Dysthymia
  Adjustment disorder with depressed mood
  Seasonal
  Premenstrual exacerbations
  Postpartum
  Childhood or geriatric

Medical history
  Medications & chronic illnesses
  Screening labs: metabolic, cbc, thyroid
  Habits

Personal preference
  Medication +/- psychotherapy
  Side effects desired or to be avoided
  What would the "ideal medication" do for you?

Family history
  Diagnosis & best treatment responses of blood relatives

Drug factors
  Effectiveness for comorbid symtpoms/illnesses
  Tolerability
  Interactions
  Medical contraindications
  Cost

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Guidelines series.[3-10] The APA guidelines follow the old formulation of indicating approximately equal efficacy among all antidepressants, with choices being made largely based on side effects, tolerability, and cost, although some consideration is given to depressive subtype and medical comorbidity. We believe that the concepts of comorbidity and coeffectiveness of drugs to treat other symptoms besides depression are under-emphasized in current treatment guidelines, yet very important in clinical practice. For example, the senior author has often seen migraines dissipate when divalproex was used to treat bipolar affective disorder, premenstrual dysphoric disorder disappear when SSRI antidepressants were used to treat depression, and irritable bowel syndrome improve when TCAs were widely used for the treatment of depression. For the patient who desires an antidepressant that is both sex and weight neutral, bupropion may be a wise choice, especially if he or she also presents with attention-deficit/hyperactivity disorder (ADHD) or a desire to stop smoking. Nefazodone may be more appropriate if he has trouble sleeping or has anxiety comorbidity. Such extra benefits of treatment are often apparent to the astute clinician long before the pharmaceutical company performs controlled studies seeking a new drug indication: unintended and surprising coeffectiveness lead to the discoveries of bupropion as an aid for smoking cessation and sildenafil as a treatment for erectile dysfunction.

Antidepressant efficacy in a randomized controlled trial (RCT) involves time to response and percentage of patients responding at a given time, based on a criterion such as 50% reduction on a widely accepted and validated rating scale of depression severity, such as the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Åsberg Depression Rating Scale (MADRS). Generally, response rates at 6 to 8 weeks are approximately 50-65% among all antidepressants, with very few differences among drugs. Unfortunately, a patient could be a rating scale "responder," yet still have enough residual symptoms and functional disability to qualify to enter a depression treatment study.

Further limitations of applying Phase III clinical trial data to community practice are described by Thase. As he has pointed out, meta-analysis suffers from the "file drawer effect" of unpublished negative studies and author bias in selection of which studies are to be included in an analysis. He emphasized the importance of remission, defined as a score of ≤ 7 on the 17-item HAM-D, over-response (HAM-D decrease of 50% or more) in assessing efficacy of antidepressant treatment. Remission implies return to normal functioning and a lower risk of relapse or recurrence than in response. A significant difference emerged in the Thase pooled analysis which, using raw data from all available studies of venlafaxine versus SSRIs versus PBO, showed 8-week remission rates of 45% vs. 35% vs. 25%,

respectively.[11] The "good news" is venlafaxine's higher remission rate, but the "bad news" is that more than half of research qualified (noncomorbid, medically healthy) patients treated on the most effective antidepressant available do not get well by 2 months. Pharmaceutical manufacturers seldom fund studies of patients who fail to remit on their drugs, so the clinician is left with very little hard data on what to do with the half of their patients who are still ill after 2 months of treatment.

In real-world clinical practice, effectiveness is defined by long-term remission, with criteria taking into account the subtlety of an individual patient's symptoms, overall functioning in major life areas compared to baseline, quality of life, and side effect tolerability. Multiple drug trials, drug augmentation, dose flexibility, and treatment with both drugs and psychotherapy are common clinical practice. These very different treatment approaches and evaluations of response illustrate the disparity between drug studies and clinical practice.

CLINICIAN PERCEPTIONS

Clinician beliefs about drugs are influenced by many factors, including advertising, pharmaceutical representatives, experiences with the drugs when taken by similar patients in the past, formulary limitations, literature review, and the influence of colleagues who are considered "thought leaders." Drug choices may reflect popular, well-marketed "favorites" rather than thoughtful analysis of published research data. University grand rounds, continuing medical education meetings, and dinner presentations are increasingly used by pharmaceutical companies to bring information to clinicians' attention. Despite attempts to present fair and balanced information, speakers may present mostly positive information about the sponsor's drug, and are forbidden by the FDA to present interesting off-label information at promotional activities.

A survey of Hawaiian psychiatrists found that fluoxetine was the drug of choice for nonpsychotic unipolar depression with weight and appetite gain, hypersomnia, and psychomotor retardation, while mirtazapine was preferred for symptoms of weight and appetite loss, trazodone for insomnia, and nefazodone for psychomotor agitation.[12]

A survey of physicians attending the Massachusetts General Hospital Psychopharmacology Review Course showed that most clinicians would give a severely ill patient with new-onset unipolar major depression the combination of an antidepressant and psychotherapy together. If the patient failed to respond to 3 antidepressants, they would next choose venlafaxine over combinations or augmentation strategies for refractory depression.[13] Another survey of these clinicians demonstrated that 48% believed the SSRIs were the most effective antidepressants, while 25% favored venlafaxine.[14] Ninety-three percent used an SSRI as first-line

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treatment, 56% considered mirtazapine most likely to be related to weight increase, 57% considered fluoxetine most closely associated with sexual dysfunction, 48% linked paroxetine with discontinuation syndrome, and 52% connected fluoxetine with agitation.[14] Anxious, atypical, and melancholic subtypes were most likely to be treated with SSRIs, while insomniac depressed patients would presumably be offered mirtazapine or nefazodone.[14] The authors noted discrepancies between clinicians' perceptions and empirical evidence.

DRUG FACTORS

As succinctly outlined by Mendlewicz, antidepressant selection factors may include tolerability, safety, efficacy, real-world effectiveness, and cost.[15]

Tolerability clearly favors the SSRIs over the TCAs; more patients complete acute studies when randomized to the SSRI arm of a trial. In clinical studies, the discontinuation rate of TCAs such as imipramine can be 3 times higher than that of SSRIs.[16]

Safety factors favor the new generation of SSRI, SNRI, and atypical antidepressants over the TCAs. TCAs are often lethal in overdoses corresponding to a 1-4 week supply of a typical antidepressant dose, while SSRI and atypical antidepressants, taken alone, are almost never lethal at such doses. Transdermal selegiline represents a major step forward in MAOI therapy, with substantially less risk of a hypertensive "cheese reaction" (tyramine sensitivity) than in phenelzine and tranylcypromine.

Safety is also influenced by the risk of displacing other drugs from protein binding sites, thereby blocking their metabolism. Fluoxetine, paroxetine, and sertraline are over 95% protein bound, while protein binding of citalopram/escitalopram is 50% and of fluvoxamine is 77%.[16] Venlafaxine is only 27% protein bound. Low protein binding is an advantage in decreasing the risk of interactions with digoxin, warfarin, and other highly protein-bound drugs. SSRIs are weakly bound, however, primarily to the α1-acid glycoprotein. Perhaps, for this reason, even the highly protein-bound antidepressants have not been found to increase the free fraction of concomitantly administered drugs that are highly protein-bound.[16]

Cytochrome P450 (CYP) enzymes are not inhibited by the TCAs and are only minimally inhibited by citalopram, escitalopram, sertraline, and venlafaxine, while fluoxetine, paroxetine, fluvoxamine, bupropion, and nefazodone all significantly block some of the P450 enzymes. Extreme examples of the blocking of CYP2D6 include ineffectiveness of codeine analgesia, development of psychotic symptoms with dextromethorphan, and death with standard doses of TCAs.

Some anticonvulsants, such as carbamazepine, induce CYP isoenzymes, thus increasing clearance of other agents and of itself. Divalproex

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may have enzyme-inhibitory action and may displace other protein-bound drugs. Although lithium is not metabolized, caution should be used if it is given with nonsteroidal antiinflammatory drugs, ACE inhibitors, and calcium channel blockers, as these raise serum lithium levels. Caffeine may increase clearance of lithium.[17,18] Such drug interactions may be ignored in the patient taking no additional medications, but can become complex and potentially lethal in a patient taking many agents concomitantly.

Historically, efficacy was a simple issue: meta-analyses of published double-blind, PBO-controlled studies indicated that each SSRI or TCA produced approximately a 60% overall response rate, and a 30% higher response rate than parallel, PBO control.[19] If any drug could be considered equally efficacious, then selection could be based on side effect profile. Data suggest, however, that the dual-mechanism TCAs and SNRIs are favored in some cases over the single mechanism SSRIs. Long before the Thase venlafaxine study cited above, the Danish University Antidepressant Group depression studies demonstrated that the dual-action TCA clomipramine was more effective than either citalopram (in inpatients)[20] or paroxetine.[21] Among patients with chronic depression, premenopausal women preferentially respond to sertraline, while post-menopausal women respond equally well to sertraline or imipramine; men preferentially respond to imipramine than to sertraline.[22] The dual-mechanism drug versus SSRI battle will probably continue in the arena of severe, inpatient, melancholic depression.

The reverse of efficacy is the potential of antidepressants to worsen the course of depression, as discussed by Fava. Tolerance, bipolar switching, cycle acceleration, resistance to rechallenge of a previously beneficial drug, withdrawal symptoms, loss of long-term efficacy, and relapse on drug discontinuation are unintended consequences, the understanding of which may be beneficial for optimizing antidepressant treatment.[23]

An "adequate trial" (dosage and length of treatment), time to response, and retention in treatment are all crucial in determination of efficacy. Leon's team at Cornell followed 285 patients with major depressive disorder (MDD) for 20 years. Despite having more severe depression, patients who receive higher levels of somatic antidepressant treatment are more likely to recover from recurrent affective episodes than are those with lesser severity. In contrast, those receiving lower levels were no more likely to recover than those who were untreated. These findings indicate that clinicians should treat depression aggressively. It is of interest that such results as these extend the generalizability of reports from randomized clinical trials of antidepressants to a wider, more representative group of major depressive patients.[23] Our own experience is that, early in the course of a mood disorder, patients are seldom willing to

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accept lifelong maintenance pharmacotherapy; after several episodes, however, their desire for prophylactic treatment grows. Controlled data demonstrating benefit of antidepressants beyond approximately 2 years is lacking for drugs other than imipramine, so that lifetime maintenance is often the standard of care but is seldom tested.

The majority of current research suggests that the newer antidepressants should provide some benefit, although not full remission, by 4 to 6 weeks, after which time the nonresponding patient should have their dose increased until either benefit or side effects occur (to accommodate the occasional rapid drug metabolizer), be switched to another medication, or receive augmentation therapy. A trial with fluoxetine cautioned, however, that treatment should be continued beyond 6 weeks for depressed patients who show minimal improvement. Quitkin et al[24] found that patients who showed no response at week 6 still had a 31-41% chance of attaining remission by week 12. Patients should be informed that it may take 8-10 weeks to determine how helpful fluoxetine will be. Similarly, the recent STAR*D trial indicated that many patients who ultimately achieve remission do not do so until after 8 weeks of citalopram treatment.[25]

In another trial, early improvement with antidepressant treatment appeared to predict later stable response with high sensitivity: within the first 2 weeks, 68% of subjects (n = 275) randomly assigned to mirtazapine or paroxetine showed improvement, as defined by a 20% or greater reduction in HAM-D scores. Moreover, based on a 50% or greater reduction in HAM-D score at weeks 4 and 6, 61% were considered to be stable responders. Importantly, the researchers note that improvement after 2 weeks predicted later stable response with an average sensitivity of 94%.[26] Another study demonstrated that improvement by 2 to 4 weeks predicted an 80-90% chance of remaining well.[27]

Clinicians should evaluate a patient's depressive symptoms on a weekly basis, allowing changes to treatment strategies to be made earlier if no improvement is observed or if side effects are intolerable.[26]

More primary care patients with depression could achieve long-term remission and improved emotional and physical functioning if they were to receive ongoing intervention over 2 years rather than only 6 months. In a study of depression treatment in primary care, ngoing intervention was associated with significantly increased patient use of antidepressant drugs over 2 years, and both symptoms and functioning were significantly improved at 24 months. In total, 74% of patients receiving enhanced care met criteria for remission.[28]

Finally, drug availability and cost are important issues for many patients. Many managed care formularies restrict the availability of brand-name drugs and favor less costly generics. Some California HMOs allow only generic drugs to be used. Self-funded patients may

find the new generation medications beyond their economic means. Preferred drug lists and fail-first procedures often force physicians and consumers to choose medications that they would otherwise not use; in the long run, such policies actually increase costs in hospitalization as well as in emergency and primary care visits. Many pharmaceutical companies offer patient assistance programs to help unfunded patients to receive free medicine if the physician and patient are willing to submit the necessary paperwork; the patient must be without insurance and financially qualified.

DEPRESSION SUBTYPE

Several subtypes of major depressive episodes (MDE) are recognized in the *DSM-IV*. Patients may present with atypical features, melancholic features, psychosis, or catatonia. Dysthymia, bipolar, seasonal, and treatment-refractory depression may also require special treatment approaches, and maintenance therapy for patients with recurrent or chronic depression across all subtypes deserves attention.

Atypical Depression

Atypical features are present in 1/4 of depressed outpatients;[29] in the STAR*D trials, 18% of depressed patients met criteria for atypical depression.[30] Features include vegetative symptoms of reversed polarity (i.e. increased, rather than decreased, sleep, appetite, and weight), marked mood reactivity, sensitivity to emotional rejection, phobic symptoms, and a sense of severe fatigue that creates a sensation of "leaden paralysis" or extreme heaviness of the arms or legs.[10] This clinical picture is associated with anxiety disorders[29,31] and with Axis II[31] comorbidity; some consider it to be a variant of bipolar II disorder or a bridge between unipolar and bipolar II.[32] Atypical depression has a significantly worse prognosis than does major depression alone,[33] although when patients were followed up 24 months after completion of a trial on fluoxetine or phenelzine, they reported a high frequency of symptom recurrence, but generally little symptomatic or social impairment between episodes. Overall, outcome was rated as moderate or good in the majority of subjects. These results suggest that atypical depression presents with some similarities to other subtypes of depression, with high rates of symptomatic recurrence and lasting response to chronic antidepressant treatment. Conversely, social functioning and overall outcome appear more favorable in atypical depression.[34] Although MAOIs are more effective than imipramine[33,35,36] or other TCAs,[37] clinicians consistently choose SSRIs due to their relative tolerability and safety.[38,39]

The traditional use of MAO inhibitors has been in cases of atypical and treatment-resistant major depression, in dysthymia, and in panic

disorder, social phobia, and bulimia.[40] Because of their diet and drug interactions, many clinicians have avoided MAOIs in favor of other, safer drugs. Selegiline is a selective MAO-B inhibitor that has been used orally at low dose as a treatment for Parkinson's disease, with benefit in delaying progression of the illness.[41] It may offer benefit in negative symptoms of schizophrenia when added to an antipsychotic,[42] and has shown potential as a treatment for childhood attention deficit hyperactivity disorder,[43,44] for apathy associated with traumatic brain injury,[45] and as an adjunct to transdermal nicotine for smoking cessation.[46] Selegiline has been developed as a transdermal patch for the treatment of major depression at a dose that is nonselective for MAO-B.[47] By delivering the drug transdermally, the first-pass effect and blockade of intestinal MAO are minimized, so that risk of tyramine-induced hypertensive crisis is significantly diminished.[48] Results of tests for tyramine sensitivity factor suggest a wide tyramine safety margin for the selegiline transdermal system and provide evidence that the 6-mg/24-h selegiline transdermal system can be administered safely without dietary tyramine restrictions.[49] At 9 and 12 mg/day there is an FDA mandated recommendation of low-tyramine diet, although this was not required in 6 of 7 studies during drug development, in which no hypertensive crises were observed.[50,51] Unfortunately, we will probably never know if transdermal selegiline will be especially beneficial for the diagnostic groups mentioned above because its patent life is too short to encourage industry sponsorship of further studies; its only approved indication is for major depressive disorder.

Melancholic Depression

Melancholic patients are often severely ill (HAM-D over 25); they may also be inpatients. They often present with diurnal variability, early morning wakening, psychomotor disturbances, appetite/weight loss, sustained anxiety, dread of the future, and excessive or inappropriate guilt.

Potential complications of untreated severe depression include suicide, self-mutilation, refusal to eat, and treatment-resistance.[52] This group may respond better to dual mechanism drugs (TCA or SNRI) than to SSRIs, with favorable response to venlafaxine.[53-55] Age and gender appear to be critical variables in understanding differential responses to TCAs and SSRIs: in a 113 patient study of patients with melancholic depression, those 40 years or older, especially men, had a markedly superior response to nortriptyline compared with fluoxetine. Conversely, patients age 18-24 years, especially women, had a markedly superior response to fluoxetine.[56] The use of an SSRI-TCA combination, while controversial, may rapidly reduce depressive symptoms in some patients with severe depression.[52] In a pooled analysis of PBO-controlled trials of duloxetine,

both melancholic and nonmelancholic patients improved significantly, with no difference in effect between men and women.[57] Atypical antipsychotics have recently shown some utility in the management of severe and resistant depression.[52] In a trial with olanzapine augmentation, most rapid impact was evident for insomnia, compared to a slower and linear improvement in depressed mood.[58]

Psychotic Depression

Psychotic major depression (involving hallucinations or delusions) may respond best to the combination of an antipsychotic and an antidepressant. The amitriptyline-perphenazine combination is perhaps better replaced by the safer fluoxetine-olanzapine combination,[59] although some recent case reports indicate that imipramine with serum level control[60] or an SSRI alone[61] may be beneficial for such patients. Clozapine was found safe and efficacious for treatment-resistant patients with bipolar disorder with psychotic features,[62] and quetiapine[63] and risperidone[63,64] have both been tried successfully; risperidone is currently in phase III trials for this indication. For the majority of patients using an antidepressant and antipsychotic concurrently, the antipsychotic can be tapered after 4 months of combined treatment without relapse on antidepressant monotherapy.[65] A fascinating 5-case series indicated that the glucocorticoid receptor antagonist mifepristone might be rapidly effective for psychotic depression, bringing about substantial improvements in both depression and psychosis in as few as 4 days with a 600-mg dose.[66] Mifepristone continues to show promise in this area,[63,64] and 6 phase III trials are underway for this agent in psychotic depression.

Electroconvulsive therapy (ECT) may be indicated in severe psychotic depression,[52,67] and research into the most efficacious and tolerable methods is ongoing: high-dose right unilateral ECT offers comparable efficacy to bilateral (bitemporal) ECT, with less memory impairment; investigation of bifrontal electrode placement has revealed differential therapeutic, cognitive, and neurophysiologic aspects of electrode placement, with even fewer cognitive side effects and similar efficacy.[68,69]

Catatonic Depression

Catatonic depression is best treated by lorazepam[10,70] or ECT.[10,71,72] After the catatonic manifestations are relieved, treatment may be continued with antidepressant medications, lithium, antipsychotics, or a combination of these agents, as determined by the patient's condition.[10]

Bipolar Depression

The long-term course of bipolar affective disorder involves far more time in a depressive than in a manic phase. More recent treatment outcome

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reports of the Stanley Foundation Bipolar Network have shown that, despite comprehensive expert pharmacologic treatment, mean time for the average patient spent symptomatic in a given year is 33.2% in depression and 10.8% in a manic or hypomanic episode, with 26.4% of patients being ill for more than 3/4 of the year.[73] According to a 12.8-year longitudinal study, bipolar I patients spend approximately 50% of the time sympto-matic; depressive symptoms were more than 3 times as common as (hypo)manic symptoms, and cycling or mixed symptoms occurred during ~6% of all follow-up weeks.[74] Bipolar II patients are more likely than bipo-lar I patients to have chronicity and a more depressive course of illness;[75] they are depressed 50.3% of the time, hypomanic 1.3%, and cycling/mixed 2.3% of the time.[76] In both bipolar I and II patients, minor depressive, hypomanic, and subsyndromal symptoms are nearly 3 times more frequent than syndromal-level symptoms.[74,76]

Bipolar depression often presents with anergic features and is usually best treated with a mood stabilizer such as lamotrigine, lithium, or valproate,[9] or a combination of these.[9]

Lamotrigine is the only anticonvulsant showing substantial efficacy both in acute treatment and in prophylaxis of bipolar depression,[77,78] demonstrating response rates of 60%[79] in clinical trials. Lamotrigine may be particularly effective in rapid cycling,[80-85] treatment-refractory[86-88] and bipolar II patients.[84,87,89-91] Lamotrigine, lithium, olanzapine, and aripipra-zole are all FDA approved for bipolar maintenance treatment, but current data indicate that lamotrigine may have the most robust effect among these drugs in prevention of depression,[92] with lithium[92] and the antipsy-chotics having better antimanic than antidepressive prophylactic effects.

Lithium, the "gold standard" in treatment of bipolar disorders, is rec-ommended as a first-line treatment of bipolar depression in the APA Practice Guideline.[9] Rigorous studies over the past 50 years involving hundreds of patients have repeatedly shown the efficacy of lithium therapy, with approximately 80% of subjects responding favorably.[93] It is the only medication proven to decrease risk of suicide, due in part to its reduction of anger and impulsivity: results from 33 studies yielded 13-fold lower rates of suicide and reported attempts during long-term lithium treatment than without it or after it was discontinued.[94] A sec-ond analysis of 28 studies reported 8.6-fold lower rates of suicidal acts on versus off lithium treatment.[95] Lithium is also the drug proven best for prophylaxis,[96,97] although more so in cases of "classic" bipolar disorder than in atypical and comorbid cases,[96,98] and especially for bipolar II subtype.[89-91] It is also an effective augmentation strategy for those who partially respond to anticonvulsants.[99] Lithium's value in potentiation of antidepressants for unipolar depression is also well known, although caution should be used as cases of serotonin syndrome have rarely been

reported.[100-102] Recent studies demonstrate lithium's protective effects on neuronal plasticity.[98,103] Long-term treatment promotes expression of brain derived neurotrophic factor (BDNF),[104] suppresses p53 and Bax expression, and increases Bcl-2 expression, protecting against excitotoxicity.[105] This is important, as neuronal apoptosis is implicated in the worsening longitudinal course of bipolar illness. Lithium also demonstrates effects on hippocampal neurogenesis, as do valproate and antidepressants;[106-108] recent brain imaging studies reveal a marked increase in gray matter volume with lithium.[109] Regrettably, the dropout rate in bipolar patients receiving lithium long-term is high, and complete suppression of recurrences is relatively rare.[96] Social support and stressful life events appear to modulate lithium's effectiveness.[97,110]

Antidepressants are used sparingly in bipolar depression by some due to risk of switching into mania and/or of inducing rapid cycling.[3,111] Current treatment guidelines recommend discontinuation of an antidepressant within 3 to 6 months after remission of depression;[112] however, research tends to indicate that a longer term of treatment (6 months or more) may aid in the prevention of relapse.[113] In an examination of data from the Stanley Foundation Bipolar Network, 71% of those who discontinued their antidepressants before 6 months had a relapse into depression after 12 months, compared to 57% who maintained their regimen between 6 and 12 months, and to 29% who, at follow-up, stayed on their drugs for more than a year. Equally significant, the 18% who switched into mania were equally divided among the 3 groups, suggesting that antidepressants played little or no role in increasing the risk of switching.[112] By the 1-year follow-up evaluation in a study by Altshuler et al,[114] 15 (18%) of the 84 subjects had experienced a manic relapse; only 6 of these subjects were taking an antidepressant at the time of manic relapse. In other trials, the continuation of antidepressants was associated with no increase in the rate of switching into mania compared with those who discontinued therapy.[115] In over 80 patients taking antidepressant therapy, acute switch rates were not significantly different between those receiving antidepressants and those not taking these medications (15.2 vs. 17.6%, respectively),[116] and in an analysis of 73 continuation phase antidepressant trials, 16.4 and 19.2% were similarly associated with hypomanic to manic and hypomanic switches, respectively.[117] Many antidepressant studies either find little incidence of cycling or find that manic switches are due to other factors: the NIMH Collaborative depression study of 345 bipolar I and II patients demonstrated that 25.8% had rapid cycling at some point in their illness. Early age of onset, and not use of the antidepressant medication, was implicated as the risk factor for rapid cycling.[115] Retrospective assessment of 53 bipolar patients yielded an estimate of 39.6% who had a lifetime history of antidepressant-induced mania or hypomania; risk

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factors were more antidepressant trials per year and substance abuse or dependence.[118] Finally, during the 2 years following a first hospitalization for major depression with psychotic features, 13% of 157 patients developed a manic or hypomanic episode. Patients treated with an antidepressant were 4 times less likely to develop a (hypo)mania, compared to those who were not similarly treated, suggesting a possible protective effect in this population.[119]

The addition of an antidepressant in bipolar depressed patients may not shorten the episode length,[120] although it may lessen suicidal tendencies[121] and symptom severity. Moller[122] has suggested that treatment guidelines have gone too far in the restriction of antidepressants in bipolar depression, and points out that the risk of suicidal acts and ineffective treatment with mood stabilizers possibly leading to chronicity are major reasons for liberalizing their use, as is the high incidence of comorbidity with anxiety disorders.

A large retrospective study showed that depressed bipolar I and unipolar major depressive inpatients had comparable response rates when treated with antidepressants.[123] Bipolar II and unipolar women showed similar antidepressant efficacy in open 6-week treatment with venlafaxine.[124] Moclobemide (a reversible MAO-A inhibitor) and imipramine were comparably effective for treatment of bipolar depression, with moclobemide being less likely to precipitate mania.[125] Paroxetine and imipramine were comparably effective and better than PBO in bipolar depression treatment among patients with lithium level ≤.8 mEq/L, but these agents were no better than PBO in patients receiving lithium and maintaining levels of over .8 mEq/L. Paroxetine induced mania less often than did imipramine.[126] Bupropion is regarded by some to be both the most effective antidepressant for augmenting mood stabilizers and the least likely to precipitate switching or rapid cycling.[5,127] TCAs are of greatest risk for switch to mania,[128,129] and should be avoided.

Olanzapine-fluoxetine combination (Symbyax) is FDA-indicated for acute treatment of bipolar depression. Quetiapine has shown promise in monotherapy for bipolar depression;[130] 3 phase III monotherapy trials are currently underway. Aripiprazole has been used successfully as an adjunct in treatment-resistant bipolar depression,[131] and is currently in phase III monotherapy trials. Atypical antipsychotics share the interesting property of relieving acute bipolar depression without increasing the risk of switching into mania above PBO rates.[132]

Other agents currently showing promise for bipolar depression include the glutamate-modulating agent riluzole[133] and the D2/D3 agonist ropinirole,[134] both of which are currently in phase III trials. Left prefrontal rTMS is also currently being studied, building on the success of past trials.[135,136]

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Regardless of drug choice, low free thyroxine index (FTI) and high thyroid stimulating hormone (TSH) levels are associated with slower response to algorithm-guided treatment of bipolar I depression. Cole[137] recommended that FTI should be above the median and TSH below the median values to obtain optimal response. Hypothyroidism is associated with subsequent risk of developing depression or bipolar disorder,[138] and there is a recent report of supraphysiologic doses of levothyroxine benefiting bipolar patients,[139] perhaps by altering regional cerebral metabolism.

Seasonal Affective Disorder

Seasonal affective disorder (SAD) most frequently involves fall or winter depressions with spring or summer euthymia or hypomania.[10] During depressions, classical "hibernation" features of overeating, carbohydrate craving, oversleeping, fatigue, and social withdrawal are often seen,[140] as well as a high incidence of premenstrual dysphoric disorder (PMDD) in women with SAD who are premenopausal.[141] These depressions may respond to the use of bright artificial light in the morning, or of dawn simulation as an alternative to antidepressant drugs.[142-144] In severe cases of SAD, bright light should be used to augment pharmacotherapy;[10] as depression improves, suicidal ideation tends to resolve.[145] Bright light is also associated with improvement in nondepressive symptoms, including poor vision and skin rash, itch, and irritation.[146] In one study, the hours of sunshine during the week before each assessment were associated with a positive clinical response.[142] Bright light therapy often benefits other types of depression as well, although it should be used with caution in bipolar patients who may develop manic symptoms;[147-149] being overactive/excited/elated may show greater emergence under morning light and greater remission under evening light.[146] Interestingly, bright light benefits both the bulimic and depressive symptoms in women with bulimia comorbid to SAD.[150] Metergoline single dose,[151] fluoxetine acutely,[152] and citalopram with bright light therapy in maintenance have all shown benefits in SAD.[153] Modafinil targets the cardinal SAD symptom of hypersomnia, and relieves depression as well when used adjunctively: response rates in trials were as high as 67% on 3 depression instruments; fatigue was reduced and wakefulness promoted.[154,155] Recently, bupropion has been given FDA approval for use in preventing seasonal depression.[156]

Our own experience is that many SAD patients seen in Southern California report a history of much worse mood cycling when living in northern climates with more extreme seasons, and that the combination of the shorter, milder California winters and maintenance antidepressants make winter depressions much milder. The prevalence of seasonal affective disorder has been found to be unexpectedly low among Icelanders,[157,158] where the mean anxiety and depression scores in winter

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are not higher than those in summer for either sex.[157] In a colorimetric analysis of the spectral composition of daylight in Iceland, the main finding was that blue hue dominates the color of the sky, without significant seasonal variations.[159] Although it is not known whether the observed chromaticity of daylight is connected to low prevalence of SAD, light boxes are available with blue light, and research in treatment of SAD with colored light is ongoing.

Dysthymia

Antidepressant medications are efficacious for the treatment of dysthymia. We believe that the introduction of the SSRIs 15 years ago has dramatically lowered the threshold for pharmacologic treatment of chronic, mild depression both in primary care and in psychiatric practice. Between 54 and 65% of dysthymic patients report improvements in depression and functional limitations with antidepressant medications acutely and prophylactically.[160]

SSRIs and TCAs are equally effective and more effective than PBO, with fluoxetine or sertraline being the first choice of therapy. Antidepressants should not be administered in isolation but should include discussion of adjustments in interpersonal, family, marital, and work interactions and responsibilities; psychotherapy may assist in the acquisition of social skills and coping strategies to enable better self-management of symptoms and problems. Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) are as effective as pharmacotherapy in some but not all studies of dysthymic patients. Combined pharmacotherapy and psychotherapy are more effective than PBO or either treatment alone for dysthymia.[160]

Treatment-Resistant Depression

Treatment-resistant (refractory) depression (TRD) is defined differently by various authors, but essentially requires that the patient have a diagnosis of a mood disorder, and an adequate dose of a drug for a reasonable duration of treatment (approximately 4 weeks), with failure to show adequate response, typically defined as less than 25% decrease on an accepted symptom rating scale.[161] Usually the patient has been tried on an antidepressant from each of 2 different classes.[162] If a patient has failed 3 medication trials, there will likely be only a 30% chance of response to a fourth;[2] in a 2-year prospective, multicenter, observational study, 12- and 24-month IDS-SR-30 response rates were 11.6 and 18.4%, with 5/13 12-month responders still doing well at 24 months.[163] Treatment resistance has been reported to be associated with bipolarity, substance abuse, and anxiety disorder comorbidities;[164] hence, as discussed previously, the exclusion of such patients from many phase III

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drug studies. One study reported no correlation of treatment-resistance to Axis II comorbidity,[165] although several others have, and data are highly variable as to which personality disorders, traits, or clusters may impact response to pharmacotherapy or long-term outcome.[27]

The pharmacologic approach to treatment-resistant patients usually involves switching to another class of antidepressants if there has been no response or if there have been intolerable side effects. Augmentation with a drug that has a different mechanism of action is preferred in cases of partial response.[161] Most often, switching means changing from an SSRI to an SNRI, atypical, TCA, or MAOI. The best-studied augmentation strategies include the addition of lithium[166-169] or thyroxine[170] to an antidepressant, or the addition of bupropion, desipramine,[166,171] or stimulants[172,173] to an SSRI. There is evidence that thyroid hormone T3 increases serotonergic neurotransmission, and studies have shown accelerated response when adding triiodothyronine (T3) to TCAs in patients that have failed SSRI therapy,[174,175] with women benefiting more than men;[175] 25-50 µg/day adjuvant therapy in SSRI-resistant MDD, particularly in atypical subtype, is promising.[176] Research involving depressed hypogonadal men suggests that depressed men, particularly those older than 50 years of age, may benefit from testosterone augmentation;[177] 1% testosterone gel is a convenient and effective formulation.[178] In PBO-controlled studies of modafinil augmentation for residual symptoms[179] and for depression and fatigue in patients with partial response to antidepressants,[180] excessive sleepiness, fatigue, and mood were significantly improved. Augmentation with lamotrigine was superior to PBO in 23 patients receiving fluoxetine for refractory depression, suggesting its role as an augmentation agent in depression;[181] pindolol is also a useful adjuvant.[182,183] The combination of olanzapine with fluoxetine appears promising in resistant depression.[184] Quetiapine,[185,186] risperidone,[116,185] aripiprazole,[187] and ziprasidone[185] have all been tried successfully as augmentation agents;[185] quetiapine and aripiprazole are currently in phase III trials for use as monotherapy in TRD, and risperidone, quetiapine, and aripiprazole are pursuing indications as adjuvant therapies. Pramipexole plus TCA or SSRI was shown efficacious for TRD in an extended 16-week trial;[188] current controlled trials include an NIMH study of pramipexole plus escitalopram versus either drug alone in TRD, and a second of pramipexole in monotherapy for TRD. Amantadine (AMN), an agent traditionally used in the treatment and prophylaxis of influenza, is now known to exhibit prominent effects at the level of dopaminergic, monoamine oxidase, and N-methyl-D-aspartate systems. In a 4-week study, AMN appeared to demonstrate efficacy as an augmenting agent in treatment-resistant depression.[189] Corticotropin-releasing factor receptor antagonists may represent a novel class of antidepressants and/or anxiolytics,[190,191] and several phase III trials

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are currently underway for the agent mifepristone. On the basis of literature review and clinical experience regarding patients with partial response or nonresponse to antidepressants, Hirschfeld et al[161] recommend simultaneous targeting of both the noradrenergic and serotonergic systems as one of the most effective augmentation strategies. Venlafaxine is FDA approved for the treatment of major depression, generalized anxiety disorder, and social phobia, and may have a special place in the treatment of refractory depression; it showed response rates greater than those of paroxetine when tried in multidrug nonresponsive patients in a controlled study.[192,193] Doses of 450-600 mg/day have been shown safe in a small group of treatment-resistant depression patients.[194] A combination of duloxetine and bupropion was helpful for patients who had not attained full remission on either drug alone,[195] and 2 meta-analyses of controlled trials of venlafaxine and duloxetine bore out a favorable trend in response and remission rates for venlafaxine, with no difference in dropout rates and adverse events.[196,197] We suspect that transdermal selegiline will be widely used for treatment-resistant patients whose treating clinicians have been reluctant to use conventional MAO inhibitors.

Repetitive transcranial magnetic stimulation (rTMS) is currently under FDA review for treatment of depression. Highly discrepant reports concerning its efficacy may relate to many technical factors in appropriate stimulus parameter selection.[198-200]

Vagus nerve stimulation (VNS) is the most recently approved treatment modality for treatment-resistant depression. Like many treatments developed originally for epilepsy control, it was noted to have beneficial mood effects. Eighty percent of the vagus nerve fibers are ascending, projecting to mood-affecting areas of the brain, including the nucleus tractus solitarius, locus coeruleus, and dorsal raphe nuclei. The original acute controlled study of VNS failed to show separation of active from sham treatment at 10 weeks, but long-term, nonrandomized follow-up studies have demonstrated substantial 1- and 2-year responses compared to treatment as usual. Although response is achieved slowly (often at 3-6 months), it is usually persistent and well tolerated, with very few patients requesting that the stimulator be turned off or removed.[201-203] The greatest problem facing clinicians wishing to utilize VNS for severely ill patients is the reluctance of insurance companies to pay the approximate cost of $25,000 for the device plus implantation. Cost of providing VNS devices to clients may perhaps be offset by a decrease in inpatient and outpatient use of psychiatric services, less expenditure related to medical comorbidities exacerbated by depression, and fewer suicide attempts.

A sometimes neglected augmentation strategy is the addition of depression-specific psychotherapy (cognitive-behavioral or interpersonal therapy) to pharmacotherapy. Several systematic reviews conclude these

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therapy models are beneficial in all forms of depression[204-207] and may enhance prophylaxis and improve long-term outcome;[208] another concludes the paucity of evidence—particularly of studies with well-controlled designs—in TRD specifically is a significant problem.[209] Childhood emotional abuse and comorbid anxiety disorders are more often present in treatment-resistant than treatment-responsive depressed patients,[210] and psychotherapy may be quite valuable in addressing these issues.[211,212] Similarly, identifying and addressing family issues via family therapy and substance abuse via 12-step programs may significantly complement pharmacotherapy.[213] Psychoeducation may decrease depressive symptoms and improve life functioning,[214-216] as well as reduce recurrence in pharmacologically treated patients with bipolar I and II disorder.[108]

A fascinating long-term trend in the authors' experience is the change from "either-or" to "both-and" thinking in the treatment of depression with pharmacotherapy and psychotherapy. Formerly, many psychiatrists would only medicate patients they were personally seeing for psychotherapy, and there were conflicts as to whether a specific patient was most appropriate for treatment with drugs (by a psychiatrist) or psychotherapy (by a psychologist). This decision used to be a function of which professional the patient contacted first, the severity of illness, and patient preference. Now there is general acceptance of a dual-treatment model in which psychotherapist and psychopharmacologist share in the patient's care and hopefully communicate and collaborate about the patient.

Chronic Depression

Maintenance treatment to prevent recurrences is recommended for chronic or recurrent depression of any subtype; indeed, approximately 8 of 10 people experiencing a MDE will have at least one more episode during their lifetime;[217] once a patient has suffered 3 episodes of depression, the likelihood that they will have another episode within the next 2 years is more than 90%, and approximately 20% of individuals with depression experience episodes lasting 2 years or longer.[218] In the STAR*D study, about 21.2% subjects were in current, chronic MDEs.[219] Few studies have examined maintenance efficacy of antidepressants in these patients, especially for 24 months or longer. The following agents have shown efficacy in 24-month studies: fluvoxamine and sertraline,[220] mirtazapine,[221] and fluoxetine, imipramine, or desipramine.[222] Paroxetine[223] and citalopram[224] did well in 28-month studies, and fluoxetine and amitriptyline in a 36-month trial.[225] A 5-year trial with imipramine is the longest study undertaken in the maintenance and prevention of recurrent depression.[226] The aim of long-term antidepressant pharmacotherapy is to reduce morbidity, restore productive and optimal functioning, and enhance the quality of life, and the attainment of

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previous levels of function is the gauge of success. There are alternate approaches to lifelong pharmacotherapy in striving to reach this goal. Both pharmacologic tachyphylaxis and the resistance of some patients to remain adherent to chronic drug therapy are significant problems. Use of intermittent pharmacotherapy with follow-up visits is an alternate therapeutic option, although the problems of resistance and of discontinuation syndromes are substantial disadvantages. In recent years, several RCTs have suggested that sequential use of pharmacotherapy in acute depression, and psychotherapy in its residual phase (and for prophylaxis) may improve long-term outcome.[217] Cognitive therapy (CT), effective in long-term prevention of relapse and recurrence,[227] may prevent relapse by training patients to change the way they process depression-related material rather than by changing beliefs in depressive thought content,[228] resulting in reduction of stress generation and/or disruption of kindling effects in some patients.[229] CT may be effective in sequential use after withdrawal from pharmacotherapy, as it was in a 6-year study of focused psychotherapy.[227] Interestingly, in a trial with mindfulness-based cognitive therapy, patients with 3 or more previous episodes of depression (77% of the sample), enjoyed significantly reduced risk of relapse/recurrence. For patients with only 2 previous episodes, relapse/recurrence was not reduced.[230] Although some patients may deny the need for psychotherapy, continued support and a life review may help them to acquire insights and adjust to changes. A patient can sustain progress by keeping active, pursuing interests, and socializing.

Premenstrual Dysphoric Disorder

PMDD is more responsive to serotonergic than to noradrenergic antidepressants (desipramine, maprotiline, or bupropion),[231-233] and SSRIs appear to be the treatment of choice.[231-235] Half-cycle (intermittent) treatment is often effective.[236-239] Interestingly, bright artificial light may be helpful,[240] as may calcium carbonate 1200 mg/day,[241-243] although this is recommended with caution in bipolar patients due to correlation between serum calcium ion shifts and mania.[244] CBT[245,246] and venlafaxine are also effective for PMDD,[247] nefazodone is not, and buspirone is only modestly helpful for associated irritability.[248] In 2 well-controlled trials, drospirenone 3 mg and ethinyl estradiol (EE) 20 μg (Yasmin), administered 24 days in a 28-day cycle (rather than usual 21-day active treatment) produced 61.7%[249] and 48% response rates;[250] a combination levonorgestrel and EE transdermal preparation is currently in phase III trials.

Postpartum Depression: Prevention and Treatment

Untreated depression can lead to potentially negative effects for the fetus and infant, in addition to serious morbidity for the mother.

Approximately 10 to 18% of women experience a MDE after childbirth, many with comorbid anxiety disorders.[251,252] The first 3 to 4 postpartum months represent a high-risk period for postpartum depression (PPD); approximately 12% of women in the community with PPD receive psychotherapy and fewer receive pharmacotherapy at this point in time.[253]

SSRIs have shown efficacy in prevention of recurrence of PPD in non-depressed women with ≥1 previous episode of PPD. In a PBO-controlled trial, sertraline was efficacious in preventing recurrence; in women who became depressed, time to recurrence was significantly longer in patients randomized to sertraline.[254] No difference was found in the rate of recurrence in women treated with nortriptyline compared with PBO; rates of recurrence were 25%.[255] The duration of preventive pharmacotherapy should be extended to about 6 months.[256] These 2 trials alone met criteria for a systematic review from the Cochrane Collaboration, which commented that intention to treat analyses were not carried out in either of these small trials; taken together with potential unknown harm to the fetus, they do not recommend antidepressants for prophylaxis of PPD.[257]

In reduction of depression and anxiety symptoms of women with PPD, paroxetine was equally efficacious in monotherapy and in combined treatment with CBT.[251] In a small open-label pilot study, bupropion SR was helpful.[258] Sertraline and nortriptyline were similarly efficacious in response rates, time to response, and remission. Breast-fed infant serum levels were near or below the level of quantifiability for both agents.[259]

Of the more frequently studied antidepressant drugs in breastfeeding women, paroxetine, sertraline, and nortriptyline have not, in selected trials, been found to have adverse effects on infants.[260] Other trials express reasonable doubt as to possible long-term side effects of SSRIs[261] in breast-fed infants, including their documented influence on children's growth rates.[262,263] Infants exposed to maternal depression lasting 2 months or more, however, appear to experience significantly lower weight gain.[264] SSRIs and their metabolites are variably detectable in infant serum; even when levels are low or undetectable, side effects may occur.[265] Until more is known, reticence of the FDA to approve SSRIs for use during lactation should be considered,[335] but so should depression's impact on maternal caregiving and bonding. In studies of children exposed in utero to SSRI antidepressants, gestational age, birth weight, and Apgar scores[266] are adversely affected, and the likelihood of a child being born at or before 36 weeks is 200% of normal, equal to that of the risk of smoking during pregnancy. TCA exposure did not affect perinatal outcome, and neither drug class was significantly associated with congenital malformations or developmental delay.[266]

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Fluoxetine specifically is linked to reducing growth and/or eliciting preterm delivery, and may interfere with normal fetal neurodevelopment.[267] Despite this evidence, a review published in a reputable journal, as recently as 2001, still "confirmed" the suitability of long-term fluoxetine treatment in pregnancy.[268] Despite the weight and gravity of this evidence, one must consider that untreated depression itself may harm the developing child: IQ, language development, and behavior of the child exposed in utero to a TCA or to fluoxetine are not adversely effected, but the mothers' depression itself adversely effects cognitive and language achievement.[269] The clinician is advised to review the literature thoroughly before recommending antidepressants to pregnant or breastfeeding women with depression.

Functional docosahexanoic acid (DHA) status of women is reduced during pregnancy, with maternal stores being depleted by the rapidly developing fetal brain; increased risk of PPD is associated with slower normalization of DHA levels postpartum.[270] Multinational studies indicate an inverse correlation between incidence of PPD and consumption of omega-3 fatty acids, particularly DHA.[271] Omega-3 fatty acid supplementation is an attractive alternative to antidepressants with associated health benefits: in a trial for prevention of PPD, Marangell[272] found 2,960 mg eicosapentanoic acid (EPA) and DHA daily in a 1.4:1 ratio to be an effective preventive therapy in a pilot study of 7 women with ≥1 previous episode of PPD. In treatment of current PPD, an open-label dose-finding trial of 0.5 g/day, 1.4 g/day, or 2.8 g/day omega-3 fatty acids produced a 48.8% decrease in HAM-D scores, with no between-group differences; ratio of EPA to DHA was 1.5:1.[273] In breastfeeding women taking 200 mg/day of DHA, phospholipid levels were 8% higher at 4 months, compared with 31% lower levels in those randomized to PBO. There was, however, no between-group difference in either self-rating or diagnostic measures of depression;[274] a low dose of DHA and uncontrolled fish consumption are limitations of this study. In a larger study, neither prenatal fish consumption nor postnatal omega-3 status was associated with PPD.[275]

Evidence suggests that women with a history of postpartum depression are differentially sensitive to the potential mood-destabilizing effects of gonadal steroids.[276] Estrogen deficiency has been implicated in etiology of PPD; 17-beta-estradiol sublingual was significantly helpful in a small preliminary study,[277] and is currently in phase III trials in a transdermal preparation.

At 10 weeks, but not at 5 weeks, therapy with bright artificial light versus sham therapy produced a clear treatment effect in antepartum depression similar in magnitude to that seen in antidepressant drug trials.[278] In an uncontrolled trial of antepartum depression, mean depression ratings

improved by 49% after 3 weeks of treatment, and persisted to endpoint at 5 weeks.[279] Successful treatment of antepartum depression with bright light was associated with phase advances of the melatonin rhythm.[278]

Finally, a critical review of nonbiologic interventions of interpersonal psychotherapy, CBT, peer and partner support, nondirective counseling, relaxation/massage therapy, infant sleep interventions, infant-mother relationship therapy, and maternal exercise suggested that methodologic limitations render their efficacy equivocal for PPD. Well-controlled trials comparing different treatments in women with diverse risk factors and/or clinical presentations of PPD are needed.[280]

PSYCHIATRIC COMORBIDITY

Psychiatric comorbidity also plays a role in drug selection. Comorbid anxiety and substance abuse disorders specifically worsen pharmacotherapy response and are associated with greater illness severity, lower functioning, and poorer prognosis.[27] The treatment goal for a patient suffering from 2 or more disorders is to use coeffectiveness to treat both the mood disorder and the other condition(s) with 1 drug whenever possible.

Anxiety Disorder Comorbidity

Anxiety disorder comorbidity is higher in unipolar and bipolar II disorders than in bipolar I disorder.[281] The spectrum of action of the SSRI antidepressants has evolved over the last decade, resulting in FDA approval of many members of this family for the treatment of panic disorder (with or without agoraphobia), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), social phobia, and post-traumatic stress disorder (PTSD).

Obsessive-Compulsive Disorder. OCD responds preferentially to SSRIs or to clomipramine, but patients stabilized on an SSRI and showing worsening depression may benefit from the addition of a noradrenergic antidepressant such as desipramine.[282] Venlafaxine in monotherapy has shown excellent response in recent trials.[283-285] A further augmentation strategy is to add olanzapine to an SSRI or SNRI.[286,287] Serotonergic antidepressants are the only pharmacologic treatment currently available for OCD, presenting a dilemma to clinicians treating patients with comorbid bipolar disorder. Mania and hypomania have been known to be induced by antidepressants in OCD patients without a previous diagnosis of bipolar disorder,[288,289] and the risk of this occurring in a patient with known bipolar disorder is of real concern.

Panic Disorder. Comorbidity of panic disorder with major depression is associated with greater severity, chronicity, and disability than is the presence of a single disorder.[290] SSRIs are recommended as first-line treatment for both social anxiety disorder and panic disorder.[291,292] Paroxetine has a

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TABLE 2

AUTHORS' SUGGESTIONS: ANTIDEPRESSANTS TO CONSIDER AND TO AVOID IN PATIENTS WITH PSYCHIATRIC OR MEDICAL COMORBIDITY

Depression Subtype or Comorbidity	Consider	Avoid/Less Effective
Depression subtype		
Atypical features	MAOI or SSRI	TCA
Melancholic	VLF or TCA, atypical antipsychotic (augmentation)	
Psychotic	SSRI + atypical antipsychotic (especially OFC), ECT	TCA alone
Catatonic	Lorazepam, ECT	
Bipolar	LTG, lithium (≥ 0.8 mEq/L), DVPX, OFC, QTP, aripiprazole, bupropion, SSRI, moclobemide	TCA
Suicidal	Lithium	TCA
Seasonal (Fall-Winter)	Bright light, bupropion (preventive), fluoxetine (treatment), modafinil (augmentation; for hypersomnia, anergia, depression)	
Dysthymia or chronic MDD	SSRI, nefazodone, imipramine	
Treatment resistance (refractory)	VLF, augmentation (lithium, thyroid , 2nd antidepressant with different mechanism, atypical antipsychotic, stimulant, modafinil, pramipexole), VNS, rTMS, ECT	NRIs (less efficacious)
PMDD	SSRI (luteal phase or continuous), VLF, serotonergic > noradrenergic, bright light	
Postpartum (prevention and treatment)	SSRI, TCA, omega 3 fatty acids 1.4 – 2.8 g/day	Paroxetine (pregnancy), fluoxetine (pregnancy and lactation)
Menopause/ perimenopause	Citalopram, VLF, HRT plus fluoxetine	
Childhood	Fluoxetine	TCA (ineffective)
Geriatric	SSRI, SNRI, VLF	TCA 2nd/3rd line

DVPX=divalproex sodium; ECT=electroconvulsive therapy; HRT=hormone replacement therapy;
LTG=lamotrigine; MAOI=monoamine oxidase inhibitor; MDD=major depressive disorder;
NRI=norepinephrine reuptake inhibitor; OFC=olanzapine fluoxetine combination;
PMDD=premenstrual dysphoric disorder; QTP=quetiapine; VLF=venlafaxine;
rTMS=repetitive transcranial magnetic stimulation; SAD=seasonal affective disorder;
SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor;
TCA=tricyclic antidepressant; VNS=vagus nerve stimulation

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TABLE 2 (continued)

AUTHORS' SUGGESTIONS: ANTIDEPRESSANTS TO CONSIDER AND TO AVOID IN PATIENTS WITH PSYCHIATRIC OR MEDICAL COMORBIDITY

Comorbidity	Consider	Avoid/Less Effective
Psychiatric comorbidity		
Insomnia	Trazodone, nefazodone, mirtazapine, amitriptyline, doxepin, OLZ, QTP	Bupropion, SSRI (without sleep medication)
Anxiety: panic, OCD, GAD, SAD, PTSD	SSRI, VLF	
Bulimia	Fluoxetine (high dose), imipramine, milnacipran	Bupropion
ADHD	Atomoxetine, bupropion, imipramine, VLF	
Borderline personality	SSRI, SNRIs (depression, intensity, volatility, fluoxetine (impulsivity)), MAOI (atypical depression), RIS, OLZ, QTP, aripiprazole (anxiety, compulsivity, suicidality, cognitive dyscontrol, acute anxiety), clonidine (acute anxiety), Lithium (anger/irritability, suicidality), CBZ, LTG, DVPX (anger/ irritability, behavioral dyscontrol, e.g. bingeing, promiscuity, impulsive suicide attempts, self-harm), mood stabilizers for impulsivity and suicidality > mood	Benzodiazepines
Smoking cessation	Bupropion, nortriptyline	
Medical comorbidity		
Migraine	DVPX, TCA, VLF, GBP, TPM, mirtazapine (low-dose), MAOI	
Epilepsy	Citalopram, reboxetine, mirtazapine, LTG, DVPX, CBZ, ECT	bupropion, maprotiline, amoxapine, TCA
Post-stroke depression	Sertraline (prevention), nortriptyline, SSRI, light therapy, mirtazapine, milnacipran, reboxetine	
Parkinson's disease	Pramipexole, SSRI, reboxetine, bromocriptine	
Dementia	SSRI, milnacipran	TCA, benzodiazepines
MI or angina	Sertraline, omega 3 fatty acids (depression, cholesterol, anti-inflammatory)	TCA, trazodone (arrhythmia risk)

(continued on next page)

CBZ=carbamazepine; GAD=generalized anxiety disorder; GBP=gabapentin; MI=myocardial infarction
OCD=obsessive-compulsive disorder; OLZ=olanzapine; PTSD=posttraumatic stress disorder;
RIS=risperidone; SAD=social anxiety disorder; TPM=topiramate

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TABLE 2

AUTHORS' SUGGESTIONS: ANTIDEPRESSANTS TO CONSIDER AND TO AVOID IN PATIENTS WITH PSYCHIATRIC OR MEDICAL COMORBIDITY

Comorbidity	Consider	Avoid/Less Effective
Medical comorbidity *(continued)*		
GI disorders	Mirtazapine (for nausea, anorexia)	SSRI (risk of bleeding)
Interferon treatment (MS or hepatitis C)	Citalopram, sertraline	nefazodone, VPA, DVPX in liver disease
Diabetes	SSRI (for depression), duloxetine (for depression and neuropathy)	Mirtazapine, doxepin, amitriptyline (weight gain)
Neuropathic pain and/or depression associated with psychogenic pain	Duloxetine, VLF, TCA, LTG, GBP, CBZ/OCBZ	
Fibromyalgia	Duloxetine, amitriptyline, milnacipran, mirtazapine (for pain, fatigue and sleep disturbances), reboxetine	
Cancer pain	TCA, SNRI, mirtazapine (for nausea, anorexia, insomnia), trazodone, anticonvulsants	
HIV/AIDS	SSRI, imipramine, stimulants, modafinil (vigilance , euthymia)	CBZ, TCA, and multiple interactions between protease inhibitors and psychiatric medications
Obesity	Bupropion, fluoxetine	Mirtazapine, doxepin, amitriptyline
SSRI-related sexual dysfunction	Bupropion, nefazodone, mirtazapine	SSRI, SNRI
Premature ejaculation	SSRI, clomipramine	
Overdose risk	Lithobid/Eskalith CR, SSRI, SNRI	Lithium carbonate (immediate release), TCA (overdose toxicity)

GI=gastrointestinal; MS=multiple sclerosis; OCBZ=oxcarbazepine

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prominent anxiolytic and antiphobic action, is well tolerated, and is effective in panic disorder.[293] Citalopram was found equally efficacious for panic.[294] Two studies achieved significant results using paroxetine as an adjunctive to cognitive therapy.[295,296] Although evidence is not as strong, nefazodone may be an effective alternative to the SSRIs, with an attractive side effect profile.[297,298]

Posttraumatic Stress Disorder. PTSD appears to be associated with neurobiologic changes in noradrenergic and serotonergic functioning, the hypothalamic-pituitary axis, and the endogenous opioid system.[299,300] Both SSRI treatment for at least 12 months and exposure therapy for 6 months are recommended as most appropriate therapies for PTSD.[301] In a controlled study with fluoxetine, 85% of patients at an outpatient clinic had minimal to no symptoms at 12 weeks; a "much improved" rating on the clinical global impressions improvement scale (CGI) was achieved by week 2. Disability, stress, and vulnerability measures showed improvement. Many patients responded to PBO, reinforcing the idea that improvement may be due to inadvertent exposure therapy or other psychologic benefits of frequent attention from clinicians. Some form of psychologic therapy remains central in the treatment of PTSD.[302] Another 12-week trial found a lack of efficacy for fluoxetine in highly comorbid combat veterans with PTSD.[303] Two studies with sertraline showed improvement; response was only modestly better than PBO, which seems to be the standard for drug treatments for PTSD.[304,305] Fewer patients in the sertraline group experienced a relapse of symptoms versus PBO, however, which supports the use of sertraline for relapse prevention.[306] Paroxetine was shown to be better than PBO on many PTSD scales in 2 controlled trials with improvement on all PTSD symptom clusters also superior to PBO.[307,308] Nefazodone treatment may significantly decrease PTSD and depressive symptoms, improveme global subjective sleep quality, and a reduce nightmares.[309]

In a controlled trial of rTMS in PTSD patients, 10 daily sessions of right dorsolateral prefrontal rTMS at a frequency of 10 Hz have greater therapeutic effects than slow-frequency or sham stimulation.[310] With left frontal cortical rTMS, comparable improvements were seen in depression, anxiety, hostility, and insomnia, but only minimal improvement was in PTSD symptoms was evident; there may be a dissociation between treating mood and treating core PTSD symptoms.[311]

Generalized Anxiety Disorder. GAD may be a discrete diagnosis—distinct from anxiety as a component of depressive symptomatology—if the anxiety symptoms are present during periods of euthymia. GAD is the most common anxiety disorder seen in primary care and is highly debilitating.[312] SSRIs (particularly paroxetine),[313] SNRIs (venlafaxine; duloxetine), and nonsedating TCAs are generally the most appropriate

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first-line pharmacotherapy for GAD, because they are also effective against comorbid psychiatric disorders (most commonly major depression and panic) and are suitable for long-term use. Buspirone is FDA approved for the treatment of generalized anxiety disorder, but has little antidepressant or antipanic effect and a delayed onset of action. Mirtazapine has both antidepressant and anxiolytic properties and is indicated in acute depression with anxiety.[314] Benzodiazepines have long been used to treat anxiety, and are particularly appropriate in short-term treatment situations; they have an adverse side-effect profile, however, and lack antidepressant action.[313]

CBT monotherapy is the preferred form of psychotherapy for GAD, though when depression symptomatology is comorbid, pharmacotherapy is indicated.[312] CBT may benefit the long-term course of GAD.[315]

Social Anxiety Disorder. Social anxiety disorder, or social phobia (SP) is an underdiagnosed, common, and disabling disorder. There are 2 distinct subtypes: generalized (pervasive), and discrete (e.g., stage fright). The incidence of SP was estimated at 5-13.3% of the population.[316-321] According to a large survey, over a 12-month period, only 0.5% of subjects had been accurately diagnosed, yet 44.1% had a mental health specialty visit or had been prescribed an antidepressant, and psychiatric comorbidity was found in 43.6%.[318] Another study showed comorbidity of 70-80%.[321] SP often is complicated by comorbid depression, panic disorder, substance abuse, and personality disorders.[319] In our experience, the patient with social phobia is often misdiagnosed with panic disorder, the difference being the presence of spontaneous attacks in panic disorder and attacks triggered only in social situations in SP. Our typical patient has discovered the rapid onset and easy titration of alcohol as a self-prescribed anxiolytic. SP often first presents at a young age, and aggressive treatment may prevent development of comorbid disorders and can substantially improve patients' quality of life.[316]

Individual or group CBT, with or without specific antidepressant therapy, is an evidence-based treatment of choice for many patients with SP, and may prevent relapse.[316,317,320,322] Of pharmacologic treatments, the SSRIs have emerged as first-line agents for the generalized subtype of SP.[316,317,323,324] Citalopram has shown promising results in patients with SP,[325] as has sertraline.[326] The RUPP Anxiety Study demonstrated efficacy for fluvoxamine in socially phobic youth.[323] Paroxetine, sertraline, and venlafaxine are FDA approved for treatment of social phobia. Among the benzodiazepines, clonazepam is the best studied.[327] Although their efficacy has been established,[322,323,328] benzodiazepines may cause cognitive impairments and dependence,[324,328] and are ineffective against comorbid depression.[274] Gabapentin[323,327,329] and pregabalin[323,327] have been shown to be more effective than PBO in double-blind studies, with gabapentin

having been the most extensively studied.[329] Controlled studies with paroxetine and fluvoxamine demonstrate highly significant differences from PBO.[328,330] Paroxetine is the SSRI most extensively studied in SP, with positive therapeutic results.[324,328] There is evidence supporting the efficacy of the atypical agents venlafaxine,[323,326] nefazodone,[323] and bupropion.[323] There is considerable evidence suggesting that MAOIs are effective in reducing both social anxiety and social avoidance in generalized social phobia.[331,332] Controlled studies have shown substantial efficacy for the MAOI phenelzine[324,326,328,333] and for the reversible inhibitors of monoamine oxidase (RIMA) moclobemide[326,328,333,334] and brofaromine.[326,328,335-337] In one study, good response was seen at 8 weeks, and 82% of patients randomized to moclobemide and 91% of the phenelzine-treated patients were almost asymptomatic at week 16.[333] Moclobemide was much better tolerated than was phenelzine.[333] One report noted that maladaptive personality traits characteristic of SP are at least as responsive to brofaromine as are the more circumscribed social anxiety responses.[338] The use of beta-blockers as needed has been found to be helpful in the treatment of circumscribed social and performance phobias.[321,322] In a review of 19 double-blind PBO-controlled studies, the reduction in the mean total score on the Liebowitz Social Anxiety Scale with MAOIs, SSRIs, and RIMAs was less than 50%, probably because the chronic nature of the disorder is not amenable to drastic changes in short-term trials.[328] Clinicians should anticipate long-term treatment, and allow 12-16 weeks for a trial before switching to another drug if the patient is tolerating the current medication well.

Perhaps because anxiety symptoms often occur as a part of major depression and are slow to respond to antidepressants, the combined use of a benzodiazepine with an antidepressant in the treatment of major depression provides an advantage over antidepressant only treatment in terms of dropouts and improvement in the first 4 weeks of treatment, but not at 6-8 weeks of treatment[339] This analysis of controlled study data fits with common clinical practice of providing short-term anxiolytic or hypnotic therapy while awaiting the delayed onset of antidepressant effects. A small open augmentation study reported that clonazepam 3 mg/day for 4 weeks in protracted depression may be more effective for unipolar than for bipolar depression.[340] Mirtazapine is helpful for acute anxiety and insomnia in depression[341,342] as well as for symptoms of weight loss.

Eating Disorders

Depression worsens the course and prognosis of eating disorders.[27] Fluoxetine is the only SSRI that is FDA approved for the treatment of bulimia. Treatment retention may be significantly better with fluoxetine

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than with PBO, and worse with TCAs than with PBO, indicating the greater tolerability of fluoxetine in bulimia treatment.[343] In a double-blind study, however, imipramine was associated with a significantly reduced frequency of binge eating and with improvement on several other measures of eating behavior. On 1- to 8-month follow-up, 90% of treated subjects had responded to imipramine or a subsequent antidepressant.[344] Of 10 patients who completed the 8-week observation period on 100 mg of milnacipran (a specific SNRI), an intent-to-treat analysis exhibited a significant reduction in weekly binge eating and vomiting frequency from baseline to the end of treatment. Three patients stopped binge eating and purging completely during the last week of treatment. Furthermore, there was a concomitant decrease of depression ratings (HAM-D, Beck Depression Inventory).[345] Antidepressants do not reduce core symptoms of anorexia nervosa, although they may be of benefit in prophylaxis of anorexia as well as of comorbid depression.[346] Fluoxetine may help by improving eating behavior and/or reducing obsessionality, depression, and anxiety. Seventy-one percent of patients with anorexia or bulimia had lifetime comorbidity of at least 1 anxiety disorder.[347] In an open trial of fluoxetine, anorexics who had restored their weight were followed up at 11 ± 6 months. Twenty-nine of the 31 patients had maintained their weight at or above 85% average body weight.[348] In comparison of antidepressant therapy with psychotherapy, psychotherapy appeared to be more acceptable to subjects.[349] Combined treatments with antidepressants and psychotherapy showed efficacy superior to single approaches, although with addition of an antidepressant, the acceptability of psychologic approaches was significantly reduced.[349,350] Bupropion is contraindicated in patients with anorexia or bulimia due to seizure risk.

Substance Abuse Comorbidity

Patients with substance abuse comorbidity are particularly difficult to treat unless abstinence is achieved. Cocaine abusers generally do not gain substantial benefit from antidepressants according to a major review,[351] although another review suggests desipramine may facilitate initiation of cocaine abstinence,[352] and lamotrigine treatment was associated with statistically significant improvement in mood and drug cravings but not drug use in an open-label study with dual-diagnosis bipolar patients.[353] Comorbid alcohol, cannabis, and/or cocaine abuse and/or dependence do not appear to directly affect the spectrum of efficacy of lithium and divalproex or response rates to these agents in compliant bipolar patients.[84] Nefazodone therapy was associated with improvement in mood/anxiety and alcohol use in a 12-week study,[354] and the SSRIs show some efficacy in treatment of depression with

comorbidity of alcoholism,[352,355,356] as does desipramine.[357] Three studies found the TCAs useful in treatment of depression with opioid dependence,[2] and nefazodone has been shown to decrease certain marijuana withdrawal symptoms, including muscle pain and anxiety.[358] Benzodiazepines are abusable, making them contraindicated in cases of substance abuse. Bupropion, especially if combined with transdermal nicotine, is helpful in smoking cessation;[359] anxiolytics are not.[360] Bupropion is contraindicated in those undergoing detoxification from alcohol, sedatives, or hypnotics, however, due to the risk of seizures in such individuals. Although sympathomimetics are generally contraindicated with MAO-inhibiting antidepressants, a small trial demonstrated that intravenous methamphetamine was well-tolerated by stimulant abusers receiving treatment with oral selegiline.[361] Surprisingly, pretreatment with transdermal selegiline attenuated the physiologic and subjective effects of intravenous cocaine in cocaine abusers.[362]

The review above represents just a smattering of the available evidence on antidepressants for substance use disorders, in areas including, but not limited to, alcoholism, nicotine dependence, benzodiazepine dependence, marijuana dependence, opiate abuse, methamphetamine abuse, and dependence on cocaine with or without comorbid opiate dependence. Several excellent systematic reviews and meta-analyses have been written in this area. A systematic review from the Cochrane Collaboration concludes "there is no current evidence supporting the clinical use of CBZ, antidepressants, dopamine agonists, disulfiram, mazindol, phenytoin, nimodipine, lithium, and NeuRecover-SA in the treatment of cocaine dependence." They recommend the addition of psychotherapeutic services aimed at improving retention of cocaine-dependent patients in treatment.[363] A second review from the same group remarked that, of 18 studies, no significant results were obtained regardless of the type of antidepressant. Compared to other drugs, desipramine performed better but showed just a nonsignificant trend.[351] A systematic review and meta-analysis by Torrens et al[364] concluded the prescription of antidepressants for drug abuse seems only clear for nicotine dependence with or without previous comorbid depression (bupropion and nortryptiline). In alcohol dependence without comorbid depression, the use of any antidepressant seems not justified, while in cocaine dependence this must be clarified. The use of antidepressants in alcohol, cocaine, or opioid dependence with comorbid depression needs further study in well-defined samples, with adequate dosing and duration of treatment; SSRIs do not seem to offer significant advantages compared with tricyclic drugs. For those desiring a very thorough review on the topic of antidepressants for treatment of substance use disorders, the Torrens review is recommended.[364]

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Personality Disorders

The most challenging patients for the psychopharmacologist are those with personality disorders, and debate exists as to whether personality disorders are cause, effect, or discrete comorbid illnesses occurring alongside chronic unipolar or bipolar mood disorders. Personality disorder comorbidity is not consistently considered to affect response to medication; Bagby[27] notes that studies of depression in which personality disorders have been specifically recorded do not statistically show a link; personality traits, or specific dimensions of personality, appear to be more important predictors of response and of outcome. Paykel's study on personality disorder comorbidity noted that patients with residual symptoms had much higher rates of personality abnormalities than did patients in remission.[365] Short-term response rates to somatic therapy have ranged from 9 to 52% among patients with Axis II comorbidity; no consistent pattern of nonresponse exists among clusters A, B, or C.[2] Although the literature fails to concur on the predictive value of many personality traits, with cluster B, schizoid, and passive-dependent traits being seen alternately as predictors of either good or poor response in various studies, low self-esteem, introversion, quietness, and neuroticism consistently have shown a negative effect on response and prognosis.[27] Many Axis II traits appear also as symptoms of Axis I conditions, and studies fail to demonstrate a causal relationship between predictor and outcome variables.[27] Fava presented the fascinating finding that many individuals with major depression and a comorbid personality disorder (diagnosed on structured interview) may demonstrate such a reduction in personality disorder traits that, after 8 weeks of treatment with fluoxetine, they no longer meet the criteria for the disorder if theirdepression improves.[366] Medication and psychotherapy may ameliorate the negative impact neuroticism has on outcome.[2]

Borderline Personality Disorder

Perugi et al[367] argue that mood lability, interpersonal sensitivity, and cyclothymic mood swings are underlying features of not only atypical and bipolar II depression, but also of borderline personality. The Cornell-Westchester group found that 44% of their borderline personality disorder (BPD) patients met criteria for bipolar I or II disorder; adding hypomanic switches during antidepressant pharmacotherapy, the rate of bipolarity in borderline personality reached 69%.[368] These patients exhibited 1-2 day hypomanic periods, considered by Perugi and Akiskal[369] to be expanded criteria of bipolar II disorder. Most responded negatively to antidepressants (demonstrating hostility and agitation), and positively to mood stabilizers.[368] The use of antidepressant or mood-stabilizing medications may substantially improve the

course of borderline personality disorder patients by limiting affective instability, depression, anger, and impulsivity. For example, a controlled study of divalproex sodium in borderline personality disorder patients demonstrated improvement in global symptomatology, functioning, aggression, and depression.[370] Another controlled study demonstrated that women with borderline personality randomized to divalproex treatment showed improvement in interpersonal sensitivity, anger/ hostility, and overall aggression.[371] A case report series also showed improvements in irritability and impulsive aggression in patients with a variety of personality disorders,[372] while another case report series demonstrated benefit of lamotrigine in borderline personality disorder patients without concurrent mood disorders, showing benefit in some patients in impulsive sexual, drug-taking, and suicidal behaviors to the point where they no longer met the criteria of the disorder.[373] Lithium also mitigates similar borderline symptomatology.[374,375] A study of depressed patients with BPD showed favorable outcomes, after 6 months of fluoxetine treatment, in depressive symptoms, social adjust-ment, and even in improvement of the character measure of self-direct-edness.[376] A double-blind study involving a novel approach using 1 g/day of the ethyl-ester form of the omega-3 fatty acid EPA (E-EPA) demonstrated decreased aggression and depressive symptoms in a group of women with borderline personality disorder.[377] The same author found olanzapine beneficial for symptoms other than depression in this population.[378]

Attention Deficit Hyperactivity Disorder

ADHD may be comorbid with depression and responds well to imipramine,[379,380] bupropion,[381-383] atomoxetine (FDA indicated for ADHD), and venlafaxine (especially in adults).[384-387] One study suggested that venlafaxine monotherapy may have similar efficacy to a treatment with stimulant plus antidepressant therapy, and superior to stimulant therapy alone.[384] For maximum impact, pharmacotherapy should be accompanied by behavioral, educational, and psychosocial intervention.[379]

MEDICAL COMORBIDITY

The major goals of pharmacotherapy of depression in the medically ill patient include diagnosing accurately (differentiating medical from mood disorder or drug induced symptoms), avoiding harm in the form of drug interactions or drug-induced confusion or sedation, decreasing pain, and assisting the patient to be an active participant in his or her rehabilitation.

More than 1 in 7 adults visit the ER each year, and the vast majority of those who visit for any reason present with clinical depression.

Diagnostically, depression accompanied by a major medical illness may be classified as either a mood disorder due to a general medical condition or as a primary mood disorder (such as recurrent major depression), depending on the historic order of occurrence. If the mood disorder was present before the medical problem, it would be considered as major depression, while the same symptoms presenting only after the onset of the medical disorder, and probably in response to the pathophysiology of the medical problem, would be considered a mood disorder due to a general medical condition. Cytokines may mediate the causal connection between major medical illnesses and depression,[388] and addressing medical issues often ameliorates depressive symptoms.[2] If the depression followed the medical treatment of a physical disorder, then substance-induced mood disorder enters the differential diagnosis, and consideration of discontinuing or changing medications is relevant.

Nervous System Comorbidity

Neurologic comorbidity may include stroke, migraine, or degenerative diseases.

Stroke. Stroke often precipitates depression, which, in turn, worsens rehabilitation potential and long-term prognosis.[389,390] Over a 1-year period, the rate of major and minor depression in a comparative study was 37.8% in stroke patients, compared with 25% for those status-post myocardial infarction.[391] Poststroke depression (PSD) responds to both nortriptyline and SSRI antidepressants, with suggestion that both sertraline[392] and citalopram[392,393] are drugs of choice based on their tolerability and minimal drug interactions. The effect of a combination of light therapy and citalopram in depressed stroke victims may be greater than citalopram alone,[394] and sertraline is helpful and well tolerated in patients with PSD.[395,396] This medication has utility in prophylaxis as well, with 10% of a sertraline-treated sample versus 30% of patients on PBO developing depression.[397] A controlled PSD study showed a greater response rate for nortriptyline than for fluoxetine; significant weight loss was associated with fluoxetine treatment.[398] A detailed review of fluoxetine studies for treatment of depression in medically ill individuals documented controlled studies demonstrating efficacy in poststroke individuals.[399] Mirtazapine is efficacious in prevention of PSD:[400,401] 40% of nontreated patients and only 5.7% of those treated with mirtazapine developed PSD. Of those who developed PSD, 94% remitted after initiation of treatment with mirtazapine.[400] The SNRI milnacipran may improve cognitive impairment, but not depression,[402] though 58.3% of the ITT population and 70% of completers in a second study attained remission status.[403] Reboxetine also shows good efficacy, safety, and tolerability.[393,404]

Parkinson's Disease. Forty to 50% of patients with Parkinson's Disease (PD) suffer from depression,[405] which is is associated with faster progression of physical symptoms, greater decline in cognitive skills, and greater decline in the ability to care for oneself. In patients without motor complications of PD (which may be a confounding factor in assessment of depression treatment), 60.6% versus 27.3% responded to pramipexole and sertraline, respectively.[406] In a trial with sertraline and low-dose amitriptyline, response rates were 83.3% and 72.7% respectively. Benefit in quality of life was derived from sertraline, but not amitriptyline.[407] Treatment of depression with citalopram in patients with PD may lead to improvements in both anxiety and functional capacity,[408] and reboxetine, too, appears to be acutely effective and well-tolerated in PD patients.[409] It seems to be effective in progressively improving depressive symptoms over the first 4 months of treatment leading to complete remission. Reboxetine does not seem to increase PD symptoms, whereas patients' quality of life improves.[410] With or without depression, PD involves dopamine neuron degeneration; therapeutic attempts to increase dopamine levels in the brain are helpful, and bupropion is modestly effective for this purpose.[411] High doses of bromocriptine demonstrate significant mean improvement of both depressive and Parkinsonian symptomatologies.[412]

Alzheimer's Disease. Major depression affects about 25% of patients living with Alzheimer's disease and has serious adverse consequences for patients and caregivers.[413] There is only weak support for the use of antidepressants in depression associated with dementia,[414] although in a double-blind RCT comparing fluoxetine and amitriptyline, both were equally effective, with fluoxetine being better tolerated.[415,416] Sertraline provides modest improvement in depression and activities of daily living, but not cognitive function. Milnacipran is a promising medicine for depressive state in AD patients,[417] as are citalopram and escitalopram.[418] An analysis of controlled studies involving patients with comorbid depression and dementia suggested that TCAs were no better than PBO.[419] The risks of anticholinergic toxicity and postural hypotension would appear to make TCAs undesirable drugs in dementia.

Epilepsy. Depressive disorders are the most common psychiatric comorbidity in patients with epilepsy, with occurrence of symptoms or of syndromal depression in 30% of patients.[420] Depression is more likely to occur in patients with partial seizure disorders of temporal and frontal lobe origin, and is more frequent among patients with poorly controlled seizures.[421] Prognosis for depression in epilepsy is generally considered poor.[2] Four months of citalopram treatment (20 mg/day) was associated with an improvement in depressive symptoms and reduction in seizure frequency.[422] In a trial with mirtazapine, citalopram, and reboxetine,

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reboxetine showed a trend to be more efficacious than citalopram, but not mirtazapine, at week 4; dropout rate at endpoint for mirtazapine was significantly higher than that for reboxetine or citalopram, and there was no increase in frequency or severity of seizures on any drug.[423] Lamotrigine is promising for depression in epileptics.[424] In the first report of ECT for the simultaneous treatment of seizures and depression, the authors discuss the use of ECT as an alternative to anticonvulsants and antidepressants. ECT has numerous anticonvulsant effects, including elevated seizure threshold and decreased seizure duration, which make it useful as adjunctive therapy or as monotherapy in epilepsy.[425] Bupropion, maprotiline, and amoxapine are contraindicated in epilepsy as they lower seizure threshold, and TCAs appear to be epileptogenic as well.[426]

Migraine. Migraine headaches occurring more than 3 times monthly justify prophylaxis: drugs found helpful for this include divalproex (FDA indicated), which is especially effective in children,[427-429] topiramate (FDA approved), gabapentin,[429] TCAs (especially amitriptyline[430-432] or nortriptyline[433]), venlafaxine,[434,435] fluvoxamine,[436] low-dose mirtazapine,[437] MAO inhibitors alone[438-440] or in combination with beta-blockers,[440] calcium channel blockers,[441,442] beta-blockers,[443,444] or beta-blockers with riboflavin.[445] Preferential response has been shown to calcium channel blockers compared to beta-blockers.[446]

Central Neuropathic Pain. Central neuropathic pain following CNS lesions may respond to lamotrigine, gabapentin, or carbamazepine/oxcarbazepine, which are as effective as amitriptyline.[447] TCAs are the best-documented treatment for neuropathic pain, although their pronounced interindividual pharmacokinetic and concentration effect variability, and a narrow therapeutic index, make dose determination for efficacy and tolerability in an individual patient difficult[448] Venlafaxine and gabapentin are also potential treatments for neuropathic pain. TCAs and venlafaxine are quite effective for both pain and co-occurring depression and anxiety,[449-452] while gabapentin is indicated more for anxiety than for depression.[453,454]

Chronic Low Back Pain

Antidepressant medications that have both noradrenergic and serotonergic effects appear to have greater efficacy than those with only serotonergic activity in patients with chronic low back pain.[455] Systematic review concluded that tricyclic and tetracyclic antidepressants appear to produce moderate symptom reduction for patients with chronic low back pain, independent of depression status. SSRIs are not helpful, and evidence conflicts as to whether antidepressants improve functional status of patients with chronic low back pain.[456] Bupropion has shown

efficacy in neuropathic pain, but not in chronic low back pain,[455] and reboxetine studies suggest that this noradrenergic antidepressant may have efficacy in the treatment of chronic pain in patients with depression.[457]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) with depression was treated with either amitriptyline or paroxetine in 191 patients; both drugs were comparably effective for depression, pain, and disability, with paroxetine showing better tolerability.[458] In a 32-week crossover trial of amitriptyline, desipramine, trazodone, and PBO in depressed and nondepressed patients with RA, all drug regimens produced significant changes on pain measures relative to baseline, but only amitriptyline exceeded PBO, and was associated with a significant reduction in the number of painful/tender joints.[459] At 6 and at 15 months of follow-up in an open-label trial, sertraline was found safe and efficacious for depression complicating RA.[460]

Cancer Pain

Cancer pain may require opiates, but sometimes responds to antidepressants. TCAs might be selected early for patients with continuous dysesthesia, and early treatment with an anticonvulsant might be used if the pain is predominantly lancinating or paroxysmal.[461] In a survey of clinicians, amitriptyline, imipramine, clomipramine, and trazodone were prescribed: good or fair results were reported in 51% of the patients. In another study, trazodone and amitriptyline showed equal benefit.[462] Phenytoin has mild-to-moderate pain-relieving properties of its own, and can significantly enhance buprenorphine analgesia while also lessening depressive and anxious symptoms.[463]

Antidepressants are also rapidly effective in ameliorating depressive symptomatology in cancer patients with or without pain. One week after the start of treatment with TCAs in an open trial, 5 of 6 patients showed a marked improvement in their mood and showed no further suicidal thoughts or requests for terminal sedation. The average reduction in HAM-D score was 23.4 points.[464] Two other trials demonstrated response to paroxetine equal to that of the TCAs.[465,466] Because of its 5-HT3 receptor blockade, mirtazapine has antiemetic properties that may benefit medically ill patients,[467-469] produces better sleep quality than do benzodiazepines,[468] and is helpful in cases of weight loss or anorexia related to cancer.[469]

Depression in the Presence of Neuropathic and Psychogenic Pain

Over 2/3 of people suffering from depression complain of pain with or without reporting psychologic symptoms.[470] It is possible that

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depression and pain are linked via chronic stress-induced HPA axis dysfunction.[471] Antidepressants have an antinociceptive effect independent of their effect on depression—especially for neuropathic pain, but also for psychogenic or somatoform pain—with serotonergic-noradrenergic drugs demonstrating a more consistent pain-relieving effect than SSRIs.[472] Duloxetine, 60 mg once or twice daily, is the first psychotropic drug FDA approved for the treatment of painful peripheral diabetic neuropathy, with no adverse effects on diabetic control.[473,474] Duloxetine is also useful for painful physical symptoms in the context of major depression, with improvement in pain partially independent of depression improvement.[475,476] The antidepressant response to duloxetine is comparable in men and women, and in African Americans and Caucasians, but the pain response among depressed women is greater than that of depressed men.[477,478] Like most SSRI antidepressants (except fluoxetine), abrupt discontinuation of duloxetine may cause transient dizziness, nausea, headache, paresthesia, vomiting, irritability, and nightmares, and so the drug is best discontinued gradually.[479] Treatment-emergent hypomania and mania were rare (0.2%) in the pooled acute nonbipolar depression studies.[480] Sexual dysfunction, assessed with a standardized rating scale (ASEX) was comparable to PBO in men and greater than PBO—but less than that experienced with paroxetine—in women being treated for depression in 4 controlled studies.[481]

Fibromyalgia

Chronic pain is a hallmark of fibromyalgia (FM), for which rheumatologists often recommend low-dose amitriptyline to improve sleep;[482-484] alpha NREM sleep anomaly may have value in predicting response to amitriptyline.[482] In a RCT, the combination of MAOIs with 5-HTP significantly improved fibromyalgia syndrome, and was found more efficacious than MAO-A or MAO-B inhibitors alone or amitriptyline.[438] With the SNRI milnacipran, pain, global well being, and fatigue were significantly improved; effect sizes were equal to those previously found with TCAs.[485] In another trial, 75% of milnacipran-treated patients reported overall improvement in pain intensity, with 37% of those on twice-daily milnacipran enjoying 50% reduction in pain scores.[486] Milnacipran is currently in phase III investigation for treatment of fibromyalgia. Depression is the most frequent psychiatric concomitant of FM:[487] duloxetine 60-120 mg/day appears effective in alleviating the pain of fibromyalgia in women with or without major depression; the pain effect appears independent of mood effect. The drug has not been beneficial for the very few men studied.[488,489] In depressed patients with FM, reduction of pain, fatigue, and sleep disturbances after 6 weeks of mirtazapine treatment was significant, and this correlated with improvement

in depression for patients who were also depressed.[487,490] In treatment with reboxetine, subjects experienced significant relief of pain before any significant improvement in actual mood symptoms.[457]

Diabetes

In the context of diabetes, an increase of catecholamines appears to increase glucose while reducing both insulin release and sensitivity to available insulin. In contrast, increases in serotonergic function seems to increase sensitivity to insulin and reduce plasma glucose.[491] Depressive symptoms present in diabetes respond well to fluoxetine[399] and to sertraline,[491,492] which has potential to improve dietary compliance.[492] Diabetic neuropathy responds to TCA antidepressants such as imipramine and nortriptyline, but these may worsen glucose control;[493] alternatives include citalopram or venlafaxine.[491] CBT is an effective nonpharmacologic treatment of depression in diabetes; it is also associated with improved glycemic control.[494]

Cardiovascular Comorbidity

Angina, myocardial infarction (MI), and congestive heart failure carry worse prognosis if accompanied by depression. Post-MI depression predicts increased 1-year mortality.[495] Moderately to severely depressed patients with coronary artery disease have decreased heart rate variability in comparison to nondepressed individuals with similar coronary disease, and this may indicate altered autonomic modulation and be a factor in increased mortality.[496] Although the TCAs do not generally worsen ejection fraction, they are Type IA antiarrhythmics and thus may increase mortality in post-MI patients.[497-504] Additionally, the use of TCAs, but not of SSRIs, is associated with a substantially increased risk of having an MI, after correction for other risk factors.[505] Although both paroxetine and nortriptyline are effective treatments for depressed patients with ischemic heart disease, nortriptyline treatment has been associated with a significantly higher rate of serious adverse cardiac events compared with paroxetine.[500] A large case-control study comparing smokers age 30 to 65 years old, status-post first MI, to community control individuals, showed that the odds ratio among current SSRI users for having an MI is 0.35 relative to that among non-SSRI users (confidence interval .18-.68, $P < .01$), implying that SSRIs are protective against a first MI, perhaps due to platelet activation effects or other factors.[506] The SSRI sertraline has been shown safe in post-MI patients and appears to improve survival compared to PBO, perhaps as a result of inhibition of platelet aggregation. Sertraline also appeared safe and tolerable in geriatric patients with hypertension or other cardiovascular illness with no excess of adverse events or discontinuations in those with

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5 or more concomitant medications versus those with none or 1 concomitant medication.[507]

Interferon Therapy

Interferon, a cytokine, is associated with depressed mood early in treatment; severity of symptoms appears to be dose dependent.[508] Interferon treatment of hepatitis C and of multiple sclerosis (MS) involves risk of depression, and the SSRIs citalopram[509-511] and sertraline[510,511] have been shown to be effective treatments. Nefazodone is contraindicated in the presence of liver disease as it would be difficult to determine if worsening liver function tests were due to underlying hepatitis or to the drug, which carries a black box hepatotoxicity warning. Divalproex and valproic acid also carry hepatotoxicity warnings. Another treatment for depression in context of MS is desipramine: HAM-D scores of patients with serious depression who were assigned to desipramine were significantly lower than those of controls in 1 controlled study. Side effects limited desipramine dosage in half of the treated patients. Although modest beneficial effect was achieved, side effects may be a limiting factor for these patients.[512] In another trial comparing CBT, supportive-expressive group therapy (SEG), and sertraline, CBT and sertraline were more effective than SEG at reducing depression.[513]

Gastrointestinal Disorders

Gastrointestinal (GI) disorders often co-occur with depression and/or anxiety. In a study of 9 patients with diffuse esophageal spasm (DES), 8 of the 9 patients' medical symptoms improved with antidepressants.[514] In a meta-analysis of 12 RCTs of antidepressant treatment (several TCAs and mianserin) for functional gastrointestinal disorders (FGD), treatment with antidepressants was found to be efficacious. Whether this improvement is independent of antidepressant effect needs further evaluation.[515] Mianserin may be an effective and well-tolerated short-term pharmacologic treatment for FGD.[516] In the same patients, assessment of the personality traits negativism, irritability, aggression, and neuroticism may predict response to drug treatment of FGD even when serotonergic sensitivity is controlled for.[517] Because there have been reports of GI bleeding with SSRIs, these drugs should be used with caution in patients with GI disorders.[518,519]

Female Stress Urinary Incontinence

Although not FDA approved for treatment of female stress urinary incontinence, duloxetine has demonstrated efficacy in several large controlled studies and may be used in combination with pelvic floor muscle training.[520-524] In a pooled safety analysis, adverse effects were mildtomoderate, transient, and resulted in 20.5% dropouts versus 3.9% on

PBO.[525] Duloxetine appears to act via central modulation of 5-HT and NE on the pudendal somatic motor nucleus.[526]

HIV/AIDS

The lifetime prevalence of depression in patients infected with HIV has been estimated at 22-45%,[527] occurring in about 1 in 10 individuals at any one time. Subjects who completed 6 weeks of SSRI treatment experienced significant reductions in both affective and somatic symptoms, many of the latter having been attributed to HIV rather than depression. These results suggest that, even in later stages of HIV illness, the contribution of depression to perceived somatic symptoms may be significant, and that these symptoms may improve with antidepressant treatment.[528] Common painful symptoms that may require attention include headaches, herpetic lesions, peripheral neuropathy, back pain, throat pain, arthralgias, and muscle and abdominal pain. AIDS patients may also present with delirium or dementia, or with sexual dysfunction. In an antidepressant study with 45 HIV-positive men, imipramine and fluoxetine earned favorable efficacy ratings while ratings on measures of side effect burden were minimal.[529] Psychostimulants are particularly useful in promoting both vigilance and euthymia in patients with AIDS: dextroamphetamine offers the potential for rapid onset of antidepressant effect and of its activation properties, both of which are important to persons with late stage HIV illness.[530] In a case study, use of dextroamphetamine and methyl-phenidate brought a prompt remission of depressive and cognitive dysfunctions without adverse side effects.[531] The dopaminergic effects of methylphenidate are thought to be responsible for its antidepressant properties. Anxiolytics should be used with caution because many benzodiazepines demonstrate increased levels in the presence of protease inhibitors, particularly of ritonavir. Of special concern in this population are cytochrome drug interactions; those with AIDS may be taking many medications concomitantly. It is important to focus on drug side effect profiles to avoid unnecessary adverse effects (e.g., anticholinergic effects from tricyclic antidepressants, leukopenia from carbamazepine). Changes in immune status are also of concern. Psychotherapeutic approaches to situational anxiety can help patients work through intense affect and adjustments to their circumstances.[532]

LIFE STAGES AND DEPRESSION

Childhood and Adolescent Depression

At any one time, approximately 1 in 20 children and adolescents suffer from MDD.[533,534] The rate of MDD rises dramatically in adolescence, with the rate in girls exceeding that in boys by about 2 to 1 at age 14

years.[533] Many if not most adolescents with MDD suffer from psychiatric comorbidity, more commonly disruptive behaviors in boys and anxiety in girls.[535] Unlike the episodic course of illness in adults, depression in youth frequently is a chronic waxing and waning disorder that predicts long-term depression and associated psychosocial impairment in adulthood.[536] Even when remission of MDD occurs, relapse rates are relatively high.[534]

One meta-analysis indicates that several different psychosocial interventions for child and adolescent depression produce moderate to large treatment gains that were clinically meaningful.[537,538] CBT has obtained strong empirical support for close to 2 decades as a treatment for MDD in youth.[539,540] Given that response rates for both CBT and medication hover around 60% and that up to half of patients who respond relapse during the first year off treatment, expert clinicians often recommend combined treatment for MDD in the pediatric population.[541,542]

Although the vast majority of pharmacologic interventions have not been shown effective in treating depressed children and adolescents, there is recent evidence that selective SSRIs such as fluoxetine are efficacious.[538,543] Citalopram showed good results in depression and anxiety in a retrospective chart review,[544,545] paroxetine is effective and well tolerated in adolescent depression,[546] and 3 open trials with sertraline were successful.[547-549] Fluoxetine is the only antidepressant that has demonstrated efficacy in 2 PBO-controlled RCTs of pediatric depression, however.[71,550] Melancholic features are relatively rare in adolescence, while "reactive" depression and comorbidity with anxiety, personality disorders, and substance abuse are common. Anxious or irritable patients may respond well to SSRIs.[551] TCAs have not been demonstrated to be effective in prepubertal children with depression;[552,553] desipramine-associated sudden deaths in children make this drug inappropriate for treatment of childhood ADHD.[554,555] An FDA letter has indicated caution when using antidepressants as these might worsen suicidal ideation in youth. After the black box warning was added to labels of antidepressants, we learned that the studies lacked uniformity regarding which age groups constituted children and which behavior was considered suicidal.[556] In an FDA study of PBO-controlled trials of antidepressant efficacy in children, although none of the 4,487 children completed suicide, 1.7% exhibited suicidality; a Bayesian meta-analysis found association only in SSRIs in children with a diagnosis of MDD.[557] Several recent, large, nonindustry studies have indicated that rates of suicide and suicidal behavior are actually reduced in children who used antidepressants. Suicidal behavior—if it does occur—most likely does so in the acute phase of antidepressant use; clinicians must be vigilant in educating patients and families about warning signs and must monitor children often and closely.[556]

Menopause and Perimenopause

Treatment of major depression in menopausal women is controversial. Estrogen replacement therapy treats mild depression but may not treat more severe depression.[558] Short-term, low-dose estrogen augmentation of antidepressant medication has been significantly associated with improved mood, but not memory, in perimenopausal women with MDD in partial remission;[559] transdermal 17-beta-estradiol replacement has been effective in monotherapy for treatment of depression.[560] Hormone replacement therapy (HRT) (14 days of estrogen therapy and 14 days of estrogen plus progesterone) plus fluoxetine therapy may be effective in the treatment of menopausal depression.[561] Venlafaxine treatment improved overall well-being, depressive symptoms, and decreased vasomotor symptoms in 16 depressed perimenopausal women.[562] The effect of fluoxetine plus HRT on menopausal depression is significantly superior than that of HRT only, and the difference becomes more obvious with treatment time.[563] Citalopram alone is an efficacious treatment for perimenopausal and postmenopausal women with depression and anxiety, and also as an adjunct for subjects who remain symptomatic after treatment with estrogen.[564,565] Mirtazapine is effective for major depression in perimenopausal and postmenopausal women whose depression precedes HRT use and does not respond to HRT, or whose depression develops after HRT is initiated.[558]

Geriatric Depression

The numerous disadvantages of the TCAs in terms of anticholinergic effects (confusion, constipation, urinary hesitancy, visual disturbances), postural hypotension, and cardiac risk clearly make them second or third line drugs for older patients, with SSRIs such as sertraline being favorable and demonstrably effective in the presence of vascular morbidity, diabetes mellitus, and arthritis, and showing less cognitive impairment than TCAs such as nortriptyline.[566] In a single-blind study, remission rate to nortriptyline was higher than that to citalopram, especially those with endogenous or psychotic features. On the other hand, citalopram was much better tolerated.[567] A single-blind trial showed equal efficacy of nortriptyline and venlafaxine in the treatment of moderate to severe unipolar depression in patients with an average age of 71 years. Venlafaxine presents a slightly better side-effect profile, even when doses as high as 225-300 mg/day are prescribed.[568] At least 6 weeks of antidepressant treatment is recommended to achieve optimal antidepressant effect in the elderly,[569] and dosage should be titrated slowly. As many older patients take several medications concomitantly, drugs like citalopram/escitalopram, sertraline, and venlafaxine, with their low risk for cytochrome P450 and protein binding interactions, offer a safety advantage over other SSRIs or TCAs.

Bright light treatment may be effective for depression among institutionalized older adults; the length of institutionalization may play an important role in determining the efficacy of bright light treatment, as this reflects lack of exposure to sunlight.[570] In treatment with white light in noninstitutionalized patients, both treatment and PBO groups experienced a clinically significant overall improvement of 16%.[571] Although it is theorized that green light could decrease the intensity duration of exposure if light therapy needed, bright green light was not shown to have an antidepressant effect in a small trial with patients age 59-80.[572]

PATIENT FACTORS

Patient factors in antidepressant selection include past responses, family history, and side effects.

If a patient reports that a particular antidepressant worked very well in the past for him or for a close blood relative, then it would be intuitively reasonable (though perhaps not evidence-based) to assume that this medication would be a good first-choice treatment for the present mood episode.

A patient with a prior adverse experience may demand a drug that does not cause a particular side effect. In the case of SSRI-induced anorgasmia, switching to a different SSRI may be futile, as this appears to be a class effect, and a trial on nefazodone, bupropion, or mirtazapine may be helpful. Reboxetine (if it becomes available in the United States) may be of particular benefit for patients at risk for sexual dysfunction with SSRIs.[573] A patient who has experienced significant weight gain while taking doxepin, amitriptyline, or mirtazapine may refuse to take a drug associated with substantial weight gain, and may do well on nefazodone (if an anxiolytic effect is desired), or on bupropion (if an energizing effect is desired). Mirtazapine's 5-HT3 receptor blockade provides an antiemetic effect that may be attractive to those who have experienced severe nausea while taking other antidepressants.

Nefazodone has sleep normalizing and rapid anxiolytic effects, and lacks sexual and weight gain side effects, but has recently been taken off of the European market due to an incidence of severe hepatic reactions estimated at about one case in 250,000 patient years. The FDA has given it a black box warning, and some authors recommend monitoring liver functions during the first 6 months of treatment with this drug.[574]

Nefazodone, mirtazapine, amitriptyline, doxepin, and trazodone should be avoided if somnolence/daytime drowsiness is problematic. Better choices would be bupropion, desipramine, or sertraline.

It should be noted that several side effects of SSRIs including anorexia, nervousness/agitation/anxiety, fatigue, and sexual dysfunction may be dose dependent.[16]

CONCLUSIONS

Unfortunately, there is usually a 2- to 8-week lag time between initiation of antidepressant therapy and substantial response. Most antidepressant drug studies show that 50-65% of patients will have a decrease in their depression severity of at least 50% by 4-8 weeks.[19] Many attempts have been made to predict which patient will respond to which drug, including analysis of cerebrospinal 5-HIAAA and urinary MHPG, computerized cordance analysis of EEG,[575,576] and, most recently, genetic analysis of serotonin-related genes.[577-581] EEG biomarkers are still under active investigation, and the GENPOD project hopes to identify links between preferential response to SSRIs or to noradrenergic reuptake inhibitors, zygosity for serotonin transporter polymorphism, and behavior. The Emory CIDAR project seeks to identify behavioral factors predictive of treatment response, and its sister project aims to characterize imaging-based brain subtypes (using positron emission tomography) that distinguish groups of depressed patients who later remit or not to SSRI pharmacotherapy or CBT. Hopefully, brain imaging or gene chips will eventually provide us with a means of obtaining profiles of responders to various drugs. Until that time comes, careful diagnostic history taking and the clinical factors outlined above must suffice for making difficult treatment decisions. ✤

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DISCLOSURE

This work was unfunded. The senior author, Dr. Zetin, has served on the Speaker Bureaus of GlaxoSmithKline, Eli Lilly, Wyeth-Ayerst, Bristol Myers Squibb, Forest, Pfizer, Sanofi-Aventis, Ciba-Geigy, and Cephalon.

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