Safety and Tolerability of Antidepressants: Weighing the Impact on Treatment Decisions

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Major depressive disorders affect an estimated 23 million U.S. adults per year. While antidepressants are effective in improving the symptoms of depression, side effects are an undesirable outcome of treatment and can have an impact on patient adherence to treatment. Compared with older drugs, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other antidepressants have more benign side effect profiles. Research continues to elucidate new agents that may combine efficacy with a minimum of side effects, as well as new methods of predicting individual response to particular antidepressants.

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Major depressive disorder (MDD) affects an estimated 23 million adult Americans each year and is associated with significant morbidity and mortality, impaired social and physical functioning, and increased risk for suicide.[1] Although a range of effective treatments is available, a substantial proportion of patients do not respond adequately to treatment. Some patients do not tolerate specific drug effects. The decisions about which treatments to use, whether to use them alone or in combination, and in what sequence are not well defined. There is thus an on going need to educate clinicians about all the possible components of an effective treatment strategy, such as drug selection, titration schedules, and managing side effects.

Major depressive disorder can be very disabling and costly. The Medical Outcomes Study showed that patients who meet criteria for MDD are more limited than other primary care outpatients in physical, occupational, and social activities.[2] A recent World Health Organization report ranked depression as the fourth most disabling medical condition worldwide based on disability-adjusted life-years and predicted that depression would be the second most disabling condition worldwide by 2020.[3] In 2006, Stein et al.[4] reported that the presence of comorbid MDD was associated with approximately 2 times the likelihood of health care utilization, as well as significantly increased functional disability and work absence, compared to having a chronic physical illness and no comorbid MDD. Coupling the cost of treatment and lost productivity,[4] MDD also carries an impressive economic burden. In the United States, direct and indirect costs (inpatient/outpatient care, lost productivity) are estimated to be over $40 billion per year.[5]

Today, MDD remains relatively underdiagnosed and undertreated for various reasons, even though we now have safe and effective treatments.[6] The selective serotonin reuptake inhibitors (SSRIs) that have been released in the United States over the past 2 decades have significant safety advantages over first-generation agents, i.e., the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Thus, the SSRIs are now first-line medications for the treatment of MDD.[7] In this article, I review findings on side effects of antidepressant agents.

CLINICAL PHARMACOLOGY

The mechanism of action of antidepressants remains uncertain. After norepinephrine (NE) and serotonin (5-hydroxytryptamine; 5-HT) are released into the synapse, their action is terminated largely by reuptake into presynaptic neurons. Free NE and 5-HT in the neuronal cytoplasm are degraded by monoamine oxidase. MAOIs (isocarboxazid, phenelzine, tranylcypromine, selegiline, selegiline transdermal) augment the action of norepinephrine and serotonin by blocking their intracellular catabolism. The SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram) selectively block reuptake of 5-HT, or serotonin, while TCAs (imipramine, amitriptyline, and others) and the serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine) preferentially inhibit the reuptake of NE, 5-HT, or both, thus increasing synaptic concentrations of both neurotransmitters. Bupropion appears to have no direct effect on 5-HT; instead, it may act as both a dopamine (DA) reuptake inhibitor and an NE reuptake inhibitor, although its exact mechanism of action is still

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Table 1. Possible Therapeutic and Adverse Effects of Transporter and Receptor Blocking Effects of Antidepressant Drugs[a]

Blockade Effect of Antidepressant	Therapeutic Effects	Adverse Effects
Norepinephrine reuptake blockade	Antidepressant	Tremors, tachycardia Blockade of hypertensive effects of guanethidine and guanadrel Augmentation of pressor effects of sympathomimetic amines
Serotonin reuptake blockade	Antidepressant	Gastrointestinal disturbances Increase or decrease in anxiety (dose dependent) Sexual dysfunction Extrapyramidal side effects Interactions with tryptophan, monoamine oxidase inhibitors, and fenfluramine
Dopamine reuptake blockade	Antidepressant Antiparkinsonian	Psychomotor activation Precipitation/aggravation of psychosis
α_1-adrenoceptor antagonism	Antihypertensive	Potentiation of antihypertensive effect of prazosin, terazosin, doxazosin, labetalol Postural hypotension and dizziness Reflex tachycardia
Dopamine D_2 receptor antagonism	Amelioration of signs/ symptoms of psychosis	Extrapyramidal movement disorders Endocrine effects (prolactin elevation, galactorrhea, gynecomastia, menstrual changes, sexual dysfunction)
Histamine H_1 receptor antagonism	Sedation	Sedation, drowsiness, weight gain, potentiation of central depressant drugs
Muscarinic receptor antagonism	Antidepressant	Blurred vision, exacerbation of narrow-angle glaucoma, dry mouth, sinus tachycardia, constipation, urinary retention, memory dysfunction
5-HT_{2A} receptor antagonism	Antidepressant Anxiety reduction Promotion of deep sleep Migraine prophylaxis Antipsychotic	Sedation Weight gain

[a]Adapted with permission from Richelson.[10]

unclear. Nefazodone is a potent inhibitor of 5-HT_{1A} and 5-HT_2 receptors and a mild inhibitor of both 5-HT and NE uptake.[8] Mirtazapine has the most complicated mechanism of action of any antidepressant, increasing the transmission of serotonin and norepinephrine by its α_2-receptor blocking effects, while also blocking postsynaptic 5-HT_2 and 5-HT_3 receptors.[9] Pharmacologic benefits and side effects associated with specific pharmacologic effects are summarized in Table 1.

Adverse Effects

Despite the much improved side effect profile of the newer antidepressants, all of them are still associated with side effects that vary widely. Short-term and long-term side effect profiles vary across all classes of antidepressants and within each class. It is important to recognize that intolerance to a specific antidepressant does not necessarily predict intolerance to another.[11] Failure to address these side effects prevents clinicians from recognizing and managing them appropriately, which compromises adherence and increases the risk of premature medication discontinuation.[12]

In general, medication side effects are related to a number of different factors, including pharmacokinetics, pharmacodynamics, dosing strategies (e.g., dose escalation, sudden cessation), pharmacogenetics, and psychological reactions to taking medications. The side effects produced by many of the tricyclic antidepressant drugs arise from their ability to block muscarinic cholinergic receptors, H_1 histamine receptors, and α_1-adrenergic receptors, as well as blockade of transport of certain transmitters—NE, 5-HT, and DA—back into the nerve ending. The affinity (K_i) of a drug for a specific receptor is defined as the concentration of drug needed to occupy 50% of the available receptors; the lower the K_i value, the more potently the receptor is blocked. Many antidepressants block muscarinic cholinergic receptors, causing side effects such as dry mouth, blurred vision, constipation, and urinary retention. The TCAs as a class block these receptors more potently than other types of antidepressant, and they are all associated with these side effects. The complaint of dry mouth has also been noted with paroxetine, an SSRI, which has a mild to moderate affinity for these receptors.[13] Postural hypotension is associated with blockade of α_1-adrenoceptor, and this side effect is often seen with TCAs due to their relatively high affinity for this receptor; this same property may also be responsible for the potentiation of several antihypertensive drugs that block α_1-receptors.[14] Histamine (H_1) receptor blockade causes sedation and drowsiness. Given the high affinity of mirtazapine for H_1 receptors, it is not surprising that many patients taking this medication report drowsiness and sedation. These side effects are not frequently observed with selective 5-HT reuptake transporters, reboxetine, or venlafaxine due to their low affinity for H_1 receptors. Blockade of neurotransmitter reuptake or transport most likely relates to certain adverse events of antidepressant drugs and to some potential drug interactions as well. For example, serotonin reuptake blockade underlies the nausea, diarrhea, and sexual adverse effects, including decreased libido.[10] Serotonin reuptake contributes to the serotonin syn-

Table 2. SSRI Inhibitors of Selected Isoenzymes, Cytochrome P450 (CYP) System[a]

CYP Isoenzyme	Substrates	SSRI Inhibitors
1A2	Clozapine, haloperidol, theophylline, caffeine, diazepam, thiothixene, trifluoperazine, cyclobenzaprine; propranolol, fluvoxamine, fluoxetine	Citalopram (+) Fluoxetine (+) Fluvoxamine (+++) Paroxetine (+) Sertraline (+)
2C19	Carisoprodol, diazepam, phenobarbital, phenytoin, propranolol	Citalopram (+) Fluoxetine (++) Fluvoxamine (++) Paroxetine (+) Sertraline (+)
2D6	Aripiprazole, carvedilol, chlorpromazine, codeine, dextromethorphan, flecainide, fluphenazine, haloperidol, labetalol, lidocaine, metoprolol, mexiletine, oxycodone, perphenazine, procainamide, propranolol, risperidone, thioridazine, warfarin	Citalopram (+) Fluoxetine (+++) Fluvoxamine (+/++) Paroxetine (+++) Sertraline (+)
3A4	Alprazolam, amlodipine, aripiprazole, atorvastatin, bisoprolol, buspirone, carbamazepine, chlordiazepoxide, clarithromycin, clonazepam, clorazepate, cyclosporine, diazepam, diltiazem, disopyramide, erythromycin, felodipine, fentanyl, flurazepam, haloperidol, itraconazole, ketoconazole, lidocaine, lovastatin, methadone, nifedipine, phenytoin, quetiapine, quinidine, rifampin, sildenafil, simvastatin, theophylline, triazolam, verapamil, zolpidem	Fluoxetine (+) Fluvoxamine (++/+++) Paroxetine (+/++) Sertraline (+/++)

[a]Adapted with permission from reference 16.
Abbreviation: SSRI = selective serotonin reuptake inhibitor. Symbols: + = weak inhibition of isoenzyme, ++ = moderate inhibition of isoenzyme, +++ = strong inhibition of isoenzyme.

drome seen when an MAOI is combined with an antidepressant that blocks the transport of serotonin.[15]

Drug-drug interactions are another factor in side effects. Most of the antidepressants are metabolized in the liver by isoenzymes of the cytochrome P450 (CYP) system (Table 2). In the clinical setting, CYP2D6, CYP3A3/4, and 2C19 are responsible for many potential drug interactions. Common substrates for 2D6 include TCAs, paroxetine, haloperidol, and propranolol; for 3A4, alprazolam, diazepam, estradiol, and some TCAs; for 2C9, amitriptyline, warfarin, and tolbutamine; and for 2C19, some TCAs, diazepam, and ibuprofen. Inhibition of an isoenzyme by an agent can result in increased levels of agents metabolized by the enzyme. Fluvoxamine, fluoxetine, and nefazodone have been thought to carry a greater risk for interactions since they inhibit multiple isoenzymes.[17]

OVERVIEW OF THE MEDICATION CLASSES AND THEIR POSSIBLE SIDE EFFECTS

Monoamine Oxidase Inhibitors

Monoamine oxidase, a common enzyme found in presynaptic nerve endings, is responsible for the breakdown of all 3 neurotransmitters associated with the etiology of depression—5-HT, NE, and DA. Monoamine oxidase A (MAO-A), found in the brain, gut, and liver, preferentially deaminates NE, 5-HT, and tyramine and is thought to be the most directly linked with the antidepressant effect; MAO-B, found primarily in the brain, breaks down DA. Tyramine is potentially a potent vasopressor and can be responsible for surges in blood pressure and headaches. The nonselective MAOIs currently available in the United States include phenelzine, isocarboxazid, and tranylcypromine. These agents are all irreversible inhibitors of both MAO-A and MAO-B. Selegiline is a selective MAO-B inhibitor that is approved at low oral doses (up to 10 mg/day) for the treatment of Parkinson's disease. Doses of 20 to 60 mg/day exhibit antidepressant activity; however, these higher doses result in MAO-A inhibition in the intestinal mucosa and liver and can result in the tyramine reactions noted above.

Irreversible MAOIs are characterized by a unique set of food-drug and drug-drug interactions, due in part to the inhibition of tyramine in the intestinal mucosa. The combination of foods rich in tyramine consumed in conjunction with an MAOI that inhibits tyramine deamination can lead to an accumulation of tyramine, which is a potent vasopressor. To avoid a possible hypertensive crisis, patients taking irreversible MAOIs must be counseled to restrict their intake of food having a documented high tyramine content, such as aged cheeses, cured meats, and tap beer.

Selegiline transdermal system is approved for the treatment of MDD in adults. Animal studies suggest that transdermal delivery of selegiline may avoid the inhibition of MAO activity in the intestine and thus avoid inhibiting degradation of tyramine.[18,19] In fact, both MAO-A and -B inhibition in brain is produced when selegiline is delivered transdermally to rodents.

Another potential, but rare, complication of MAOI therapy is the development of serotonin syndrome. The serotonin syndrome is characterized by a constellation of at least 3 symptoms that occur after the recent addition or increase in dosage of a serotonergic agent: changes in mental status, agitation, myoclonus, hyperreflexia, fever, shivering, diaphoresis, ataxia, and diarrhea.[20,21] MAOIs should not be used in combination with dextromethorphan or with central nervous system (CNS) depressants. Meperidine given to a patient on treatment with MAOIs may induce tachycardia, hyperactivity, hypertension, hyperpyretic crisis, and severe

Table 3. Neurotransmitters Responsible for the Side Effects of Irreversible Monoamine Oxidase Inhibitors[a]

Action, Neurotransmitter	Side Effects
Increase in serotonin	Sexual dysfunction Serotonin syndrome
Increase in norepinephrine	Hypotension Sweating
Increase in dopamine	Insomnia Racing sensation
Marked increase in norepinephrine and serotonin	Hypertensive crises Serotonin syndrome

[a]Data from Holschneider and Shih.[22]

seizures. Over-the-counter cold and weight-loss products should also be avoided.[22]

Table 3 categorizes the neurotransmitters responsible for the more common side effects of irreversible MAOIs. Side effects include stimulation and insomnia (tranylcypromine and selegiline transdermal in particular), sedation (isocarboxazid and phenelzine), hypotension, urinary hesitance, and sexual dysfunction.

Tricyclic Antidepressants

Tricyclic and the related quadracyclic antidepressants represented first-line pharmacologic treatment for major depression from the 1960s through the 1980s.[23,24] Although TCAs have generally been replaced by SSRIs, at least 1 meta-analysis suggests equivalent efficacy of the tricyclics and newer antidepressants in short-term treatment, with a generally superior side effect profile for the latter.[25] The tricyclic antidepressants are now used most commonly as a second- or third-line pharmacotherapy in the event of insufficient response and in patients who are severely depressed.[26] There is some evidence that for hospitalized patients with severe depression, TCAs may be more effective than SSRIs[7,27]; however, SSRIs and other newer agents appear to be better tolerated than TCAs, specifically lacking adverse anticholinergic and cardiovascular effects that may limit the use of TCAs.[28]

Tricyclic and related antidepressants are typically started at relatively low dosage to minimize side effects. Side effects of TCAs can be categorized generally by the blockade of certain receptors—anticholinergic side effects (muscarinic-1 or M_1) include dry mouth, constipation, urinary hesitance, blurred vision, tachycardia, problems with memory, and confusion. Antiadrenergic effects due to α_1 blockade include dizziness, postural hypotension, and reflex tachycardia. Blockade of the H_1 receptor may cause weight gain and sedation. Blockade of 5-HT reuptake may also cause sexual dysfunction.

TCAs (particularly the tertiary compounds such as amitriptyline) are well known for causing weight gain over both the short and long term, and thus this effect may be seen as early as 5 weeks after the start of treatment.[29] A study by Fernstrom et al.[30] corroborates the effect of TCAs on weight gain with data showing that 15% of patients treated with imipramine had a weight gain equal to or greater than 10 lb after 16 weeks of treatment. To date, there are no definitive studies as to why TCAs promote weight gain, although various theories have been proposed, ranging from an increased preference for sweets[31] and excessive appetite caused by blockade of the histamine H_1 receptors,[32] to changes in the regulation of body fat stores,[33] changes in energy efficiency,[34] or even clinical improvement in depression.[35,36]

Tricyclic antidepressants have effects on cardiac action potentials typical of class IA antiarrhythmics, which include drugs such as quinidine and procainamide.[11] Class I antiarrhythmics have been implicated as a factor in increased mortality after myocardial infarction, leading to some concern about the use of TCAs in patients with cardiovascular disease.[37] An overdose of a tricyclic medication is serious and potentially lethal and requires immediate medical attention. Symptoms of an overdose usually develop within an hour of ingestion and may start with rapid heartbeat, dilated pupils, flushed face, and agitation and progress to confusion, loss of consciousness, seizures, irregular heart rate, cardiorespiratory collapse, and death.[38]

SSRIs

SSRIs have replaced TCAs as the drugs of choice in the treatment of depressive disorders, mainly because of their improved tolerability and safety if taken in overdose. SSRIs block the reuptake of serotonin into the presynaptic nerve terminal, which presumably results in their antidepressant effects.[39] Although this is the predominant mechanism of action of this class of drugs, each of the 6 SSRIs approved by the U.S. Food and Drug Administration (FDA) has a slightly different pharmacologic profile that leads to mild differences in clinical activity, side effects, and risk for drug interactions.[40] For example, paroxetine has in comparison to the other SSRIs a relatively high affinity for muscarinic receptors, which may explain the common complaints of dry mouth and constipation reported in some clinical trials with paroxetine.[41] Common side effects of all the SSRIs include transient nausea, diarrhea, insomnia, anxiety or agitation, somnolence, dizziness, weight gain, and long-term orgasmic dysfunction. SSRIs have a low affinity for histamine, DA, γ-aminobutyric acid, and α-adrenergic receptors, which reduces their potential to produce certain side effects such as dry mouth, constipation, and cardiotoxicity.[42]

SSRIs were initially viewed by clinicians and researchers as weight neutral or, in some cases, associated with weight loss. Studies suggest that when SSRIs are prescribed over the short term, weight gain is not likely to occur; if it does, the rates appear to be similar to placebo.[43,44] The literature on the effects of SSRIs over the long term is less clear. Michelson et al.[43] report that after 26 weeks of treatment with fluoxetine 20 mg/day, 4.8% of the patients had a ≥ 7% increase in body weight. However, this rate was not significantly different from the rate of weight gain seen with placebo (6.3%). Mackle and Kocsis[44] reported that after 6 months on citalopram, the difference in weight gain between

citalopram and placebo was not significant (3.9% vs. 2.8%, respectively). Fava et al.[45] tracked the weight status of 284 patients with major depressive disorder randomly assigned to double-blind treatment with fluoxetine, sertraline, or paroxetine for a total of 26 to 32 weeks. Paroxetine-treated patients experienced a significant weight increase, fluoxetine-treated patients had a modest but nonsignificant weight decrease, and patients treated with sertraline had a modest but nonsignificant weight increase. The number of patients whose weight increased ≥ 7% from baseline was significantly greater for paroxetine-treated patients (25.5%) compared with either fluoxetine-treated patients (6.8%) or sertraline-treated patients (4.2%).[45] It is unclear whether the weight gain noted with paroxetine reflected a return of depressive symptoms (including overeating) or a true side effect of the medication. However, the weight gain potential for paroxetine was confirmed in a 24-week study of sertraline versus paroxetine.[46] Possible mechanisms for SSRI-induced weight gain include clinical improvement of depression, increase in appetite, or changes in serotonin 5-HT_{2C} receptor activity.[33]

Sexual dysfunction is also a common side effect of antidepressant treatment, particularly pharmacotherapy with SSRIs. Treatment-emergent SSRI-induced sexual dysfunction occurs in approximately 30% to 70% of patients treated for depression.[47] Sexual dysfunction often reverses within a few days after discontinuation of the SSRI and is likely to return when the SSRI is reintroduced. Recovery after withdrawal from fluoxetine may occur within 1 to 3 weeks.[47] In a multicenter, prospective study of 628 patients treated with a number of different SSRIs, patients were asked about the incidence of sexual dysfunction. Nefazodone (7%) and mirtazapine (29%) had the lowest rates of sexual dysfunction; there were no significant differences among fluoxetine, sertraline, fluvoxamine, paroxetine, and venlafaxine (68%).[48] In another study of 107 depressed men and women,[49] SSRI-induced sexual dysfunction occurred in approximately 30% to 70% of patients who were treated with sertraline or paroxetine. Lower, although not significant, rates were reported with venlafaxine. Uncontrolled case studies and case reports suggest that the addition of bupropion, nefazodone, or mirtazapine may decrease sexual side effects and that sildenafil may be useful if the patient has no history of angina and is not taking nitrates.[50] Drug "holidays" may be one method for addressing the sexual side effects of the SSRIs. At least 1 study has reported that for some patients taking sertraline and paroxetine who experience sexual dysfunction side effects, brief drug holidays may allow for significant improvement in sexual functioning without a significant return of depressive symptoms.[51]

As indicated above, SSRIs can inhibit cytochrome P450 isoenzymes, which are responsible for the metabolism of a number of common medications.[52] Depending on the degree of inhibition, serum levels of medications that act as substrates for these isoenzymes may be significantly elevated and require downward dosage adjustments to avoid toxicity (Table 2).[16] One such interaction is the inhibition of 1A2 by an SSRI, such as fluvoxamine, resulting in elevated levels of clozapine when the 2 are coadministered.

SNRIs

Venlafaxine and duloxetine are unique agents in that they block the reuptake of both serotonin and norepinephrine. The dual-acting antidepressants have tolerability profiles that are comparable to those of the SSRIs.[53] Venlafaxine is an activating antidepressant and is associated with anxiety, nervousness, and insomnia at approximately twice the rate of placebo. The most common side effects include nausea, dizziness, insomnia, somnolence, and dry mouth.[54] Venlafaxine in its original immediate release formulation was associated with an elevation in supine diastolic blood pressure in 3% to 13% of patients, requiring ongoing monitoring of blood pressure. The effect was dose related, with most clinically significant elevations occurring at doses of 300 mg/day or greater.[55] Today, the extended release form with a maximum recommended daily dose of 225 mg/day has largely eliminated the problem. SNRI antidepressants inhibit sexual libido, ejaculation, and orgasm, and several studies suggest that there are no significant differences between the SSRIs and the SNRIs relative to antidepressant-induced sexual dysfunction.[48,49]

Duloxetine appears to have a safety profile much like the SSRIs, with nausea, dry mouth, fatigue, insomnia, dizziness, and constipation ranging from 11% to 22% in a pooled database of 6 clinical trials using 40 to 120 mg/day.[56,57] However, in the 60-mg/day studies, higher rates (30%–40%) have been reported.[56] No evidence of hypertension has been noted; in 4 double-blind placebo- and paroxetine-controlled trials, the incidence of acute treatment-emergent sexual dysfunction was significantly lower among duloxetine-treated patients compared with those receiving paroxetine ($p = .015$), although both rates were significantly higher than placebo ($p = .007$ and $p < .001$ for duloxetine and paroxetine, respectively), as measured by the Arizona Sexual Experience Scale.[58] Further studies on sexual dysfunction with duloxetine are needed.

Bupropion

Bupropion is a unique antidepressant in that it has no direct effect on serotonin levels, instead blocking the reuptake of norepinephrine and dopamine. The magnitude of effects at these uptake sites in man is in some debate. Bupropion causes few cardiovascular effects, virtually no anticholinergic effects, little sedation, and no more sexual dysfunction than placebo. Short-term side effects include dry mouth, constipation, headache, nausea, excessive sweating, and tremor.[59] Bupropion has shown a favorable profile in terms of both weight gain and sexual dysfunction.[60] In marked contrast to some of the TCAs, it does not produce anticholinergic side effects in the elderly.[61]

5-HT_2 Antagonists

Trazodone primarily acts as a 5-HT_2 antagonist, and thus a key side effect is sedation. Orthostatic hypotension can be seen when a large dose is taken on an empty stomach because trazodone can also exert α_1 effects. This probably accounts for a risk of priapism in men. Efforts to improve the pharmacologic profile of trazodone led to the development of nefazodone, which combines mild reuptake inhibition of 5-HT and NE with potent blockade of the 5-HT_2 receptor.[62] The most common adverse events of nefazodone are somnolence, dry mouth, nausea, dizziness, and constipation. Unlike the SSRIs, nefazodone produces minimal, if any, sexual side effects.[63] Compared with trazodone, nefazodone has much less α_1-adrenergic blocking activity and therefore produces a much lower risk of priapism than that seen with trazodone. Nefazodone is a potent inhibitor of cytochrome P450 3A4 isoenzymes and is capable of elevating serum levels of benzodiazepines, alprazolam, triazolam, astemizole, and cisapride. In 2002, the FDA issued a "black box" warning that nefazodone can cause severe and possibly irreversible liver failure, leading to transplant or death.[64] There is no recommendation, however, for periodic testing of liver function since the rates are low, at approximately 1 in 250,000 cases. The original manufacturer no longer produces nefazodone, but it is available as a generic formulation.

Mirtazapine

Mirtazapine has perhaps the most complicated mechanism of action of all the recent antidepressants, increasing 5-HT and NE release, while blocking 5-HT_2 and 5-HT_3 receptors. Because of this unique pharmacologic profile, mirtazapine has a unique side effect profile.[60] The most frequently reported side effects are somnolence, which results largely from blockade of the 5-HT_{2C} as well as H_1 receptors, and weight gain, caused by its potent H_1 blockade. Of note is that in the premarketing trials conducted in the United States, patients seldom exceeded 45 mg/day; in the non-U.S. trials, patients were titrated up to 60 mg/day. The non-U.S. trials reported substantially lower incidences of somnolence, dizziness, increased appetite, and weight gain. This has led to some speculation that the higher incidence of side effects seen at lower doses may be due to unopposed histamine blockade that is counteracted by the increased release of NE at the higher doses.[65] However, a study[66] comparing 15 and 30 mg/day failed to demonstrate differences in sedation.

Mirtazapine has few, if any, cardiac effects and causes very little orthostatic hypotension. Unlike the SSRIs, mirtazapine is associated with a very low incidence of sexual dysfunction, so it may be a good choice for use in patients who have experienced this side effect with other antidepressants.[67] Mirtazapine is metabolized by multiple cytochrome P450 isoenzymes, but does not inhibit any of them to an appreciable degree; therefore, its drug interaction profile appears very positive. In the United States, the drug has become most commonly used in geriatric depression patients.

Reboxetine

Reboxetine is a selective inhibitor of norepinephrine reuptake that appears to be associated with autonomic side effects, but no cognitive impairment. It is not available in the United States, although it is on the market in Canada and South America. Reboxetine does not affect dopamine or serotonin reuptake, and it has low in vivo and in vitro affinity for adrenergic, cholinergic, histaminergic, dopaminergic, and serotonergic receptors.[68] It has minimal cardiovascular and anticholinergic effects and essentially lacks serotonergic effects such as gastrointestinal symptoms, insomnia, and sexual dysfunction.[69] It can produce urinary hesitance in men. Reboxetine does not appear to produce orthostatic hypotension or weight gain.[67]

TREATING SIDE EFFECTS

Selection of a particular antidepressant should be influenced by its side effect profile. Patients should be encouraged to follow up regularly and be informed about the possibility of the more common side effects. The anticholinergic side effects of the TCAs can often be managed by switching from tertiary compounds (e.g., amitriptyline) to secondary compounds (e.g., nortriptyline) that have lower M_1 affinities. Bethanechol is often helpful to counteract anticholinergic side effects. The hypotensive effects of MAOIs are managed by maintenance of adequate salt and fluid intake and use of support stockings. Fludrocortisone is an effective antidote. The insomnia effects of these agents can be treated by using hypnotics or low doses of trazodone.[70]

Patients should be weighed at the start of treatment to obtain a baseline measure. Clinicians should try to identify those patients likely to be at risk for weight gain based on medical history and lifestyle. These patients can be targeted for dietary intervention and an appropriate program of physical activity. Patients who gain more than 5–6 lb over the course of treatment may require more aggressive dietary treatment; if possible, switching to a medication less likely to cause weight gain may prove beneficial. The addition of bupropion, topiramate, or sibutramine may also be instituted.[9,61]

Data from various studies suggest that sexual dysfunction complaints particularly with the SSRIs and SNRIs can be managed with several options—reducing the dosage of the antidepressant, switching to an agent of another class, or adding another agent. Uncontrolled case studies and case reports suggest that the addition of bupropion, nefazodone, or mirtazapine may decrease sexual side effects, although there is a small failed bupropion trial.[71] Sildenafil may be useful if the patient has no history of angina and is not taking nitrates.[50] Drug "holidays" may be one method for addressing the sexual side effects of the SSRIs. At least 1 study has reported that for some patients taking sertraline and paroxetine who experience sexual dysfunction side effects, brief drug holidays may allow for significant improvement in

sexual functioning without a significant return of depressive symptoms.[51]

Sleep disturbances are common long-term side effects of antidepressants and can be managed by a change in dosing schedule or the use of adjunctive medications to reduce insomnia. For patients with hypersomnia, switching to less-sedating antidepressants such as bupropion may be a reasonable option.[59]

DISCONTINUATION SYNDROME

Abrupt termination of treatment with selective SSRIs can result in the SSRI discontinuation syndrome, characterized by the rapid onset of 1 or more symptoms that include anxiety, crying, dizziness, headache, increased dreaming, insomnia, irritability, and paresthesias, among others.[72] Similar symptoms have been noted with TCAs, MAOIs, and various other antidepressants, including venlafaxine and mirtazapine.[73] The incidence of discontinuation syndrome differs depending on the SSRI, with rates varying from almost 0% (fluoxetine) to as high as 17.2% to 78% for SSRIs with shorter half-lives.[72,74] In studies comparing fluoxetine, sertraline, paroxetine, and citalopram, discontinuation from paroxetine was shown to cause more severe symptoms that may occur more quickly, even after the second missed dose.[75] Placebo substitution for sertraline resulted in less pronounced changes, while interruption of fluoxetine was not associated with any significant increase in symptomatology.[75] The higher frequency of discontinuation effects with paroxetine may be attributed particularly to its high affinity for the 5-HT transporter and its shorter half-life than some of the other agents.[76] Venlafaxine has an even shorter half-life and can be associated with considerable discontinuation symptoms on rapid cessation.

Distinguishing features of the discontinuation syndrome include symptoms that are not attributable to other causes and that emerge following abrupt discontinuation of SSRIs, intermittent adherence, and on occasion, dose reduction. The symptoms are often mild, short-lived, and self-limiting; are rapidly reversed on reintroduction of the SSRIs; and are minimized by slow tapering or by adding a drug with a long half-life.[77] In addition, recent proposed guidelines recommend that patients be monitored carefully during the taper, that clinicians be available to patients by phone and/or e-mail during the tapering period, and that clinicians reassure their patients that the syndrome is generally manageable.[75]

REGULATORY ISSUES

In October 2004, the FDA issued a Public Health Advisory to warn the public about the increased risk of suicidal thoughts and behavior in children and adolescents being treated with antidepressant medications. The FDA directed the manufacturers of all antidepressant medications to add a "black box" warning that describes the increased risk of suicidality in children and adolescents given antidepressant medications and notes what uses the drugs have and have not been approved for in these patients. These labeling changes are applicable to the entire category of antidepressant medications because the currently available data are not adequate to exclude any single medication from the increased risk of suicidality. A black box warning is the most serious warning placed in the labeling of a prescription medication. The new warning language does not prohibit the use of antidepressants in children and adolescents. Rather, it warns of the risk of suicidality and encourages prescribers to balance this risk with clinical need. The FDA recognizes that depression and other psychiatric disorders in pediatric patients can have significant consequences if not appropriately treated. The new warning language recognizes this need but advises close monitoring of patients as a way of managing the risk of suicidality.[78] A similar review of the risk of suicidal thoughts in adults treated with SSRIs is currently under review.

FUTURE DIRECTIONS

Many 3-dimensional computational approaches have been used to predict, and thus help explain, the metabolism catalyzed by the enzymes of the cytochrome P450 system (P450s). P450s are responsible for > 90% of the metabolism of all drugs, so the genetic prediction of how a drug may be metabolized can help to design out potential drug-drug interactions in the early phases of the drug discovery process. Models derived for P450s have evolved from simple comparisons of known substrates to more elaborate experiments that require considerable computer power involving 3D overlaps and docking experiments. These models help explain and, more importantly, predict the involvement of P450s in the metabolism of specific compounds and guide the drug-design process.[79]

The development of radioligands suitable for studying the CNS norepinephrine transporter (NET) in vivo will provide important new tools for examining the pathophysiology and pharmacotherapy of a variety of neuropsychiatric disorders including major depression.[80] This may help assess the relative monoaminergic effects of specific agents and risk for related side effects.

There are currently efforts underway to develop effective compounds that potently block more than one transporter; specifically, some compounds under early stages of development include those that block all 3 transporters—NE, 5-HT, and DA—known as super neurotransmitter uptake blockers.[81] An alternative approach to developing new drugs may emphasize neurogenic properties or specific agents. For example, data from Santarelli et al.[82] suggest that the behavioral effects of chronic antidepressants may be mediated by the stimulation of neurogenesis in the hippocampus and that strategies aimed at stimulating hippocampal neurogenesis could provide novel avenues for the treatment of anxiety and depressive disorders.

Other research is investigating factors that affect an individual's response to antidepressant treatment. For example, our group[83] has identified a genetic marker that may explain why some people experience side effects to SSRIs and others do not. We reported that in a study of 246 elderly patients randomly assigned to either paroxetine or mirtazapine, discontinuations because of paroxetine-induced side effects were associated with the HTR2A 102 C/C genotype. The severity of side effects was also greatest in patients treated with paroxetine who had the C/C genotype. In contrast, the HTR2A 102 T/C genotype had no effect on mirtazapine side effects. Of note is that the CYP2D6 genotype, which has been postulated to underlie intolerance to antidepressants, did not predict treatment outcome for either medication. A subsequent study[84] found that among paroxetine-treated subjects, S-allele carriers for the 5-HT transporter promoter experienced more severe adverse events during the course of the study, achieved significantly lower final daily doses, and had more discontinuations throughout the course of the study. Among mirtazapine-treated subjects, S-allele carriers had fewer discontinuations due to adverse events, experienced less severe adverse events, and achieved higher final daily doses, indicating that the effect of this polymorphism on outcome may depend on the mechanism of antidepressant action.

SUMMARY

Antidepressant side effects present a challenge to both clinicians and patients. Unfortunately, there is a paucity of data as to how to prevent and manage side effects. Future research should focus on the development of new agents that maximize efficacy and minimize side effects, as well as elucidate those factors that predict individual response to any one medication.

Drug names: alprazolam (Xanax, Niravam, and others), amlodipine (Norvasc and others), aripiprazole (Abilify), atorvastatin (Lipitor), bethanechol (Urecholine, Duvoid, and others), bisoprolol (Zebeta and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), carisoprodol (Soma and others), carvedilol (Coreg), chlordiazepoxide (Librium and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clarithromycin (Biaxin and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), clozapine (FazaClo, Clozaril, and others), cyclobenzaprine (Flexeril and others), cyclosporine (Gengraf, Sandimmune, and others), diazepam (Diastat, Valium, and others), diltiazem (Cardizem, Dilacor, and others), disopyramide (Norpace and others), doxazosin (Cardura and others), duloxetine (Cymbalta), erythromycin (Ery-Tab, Eryderm, and others), escitalopram (Lexapro and others), estradiol (Estrace, Menostar, and others), felodipine (Plendil and others), fentanyl (Actiq, Fentora, and others), flecainide (Tambocor and others), fludrocortisone (Florinef and others), fluoxetine (Prozac and others), flurazepam (Dalmane and others), haloperidol (Haldol and others), imipramine (Tofranil and others), isocarboxazid (Marplan), itraconazole (Sporanox and others), ketoconazole (Nizoral, Ketozole, and others), labetalol (Trandate and others), lidocaine (Xylocaine, Lidopen, and others), lovastatin (Mevacor, Altoprev, and others), meperidine (Demerol and others), methadone (Dolophine, Methadose, and others), metoprolol (Toprol-XL, Lopressor, and others), mexiletine (Mexitil and others), mirtazapine (Remeron and others), nifedipine (Procardia, Adalat, and others), nortriptyline (Pamelor and others), oxycodone (OxyContin, Roxicodone, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), phenytoin (Dilantin, Phenytek, and others), prazosin (Minipress and others), procainamide (Pronestyl, Procanbid, and others), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel), rifampin (Rifadin, Rimactane, and others), risperidone (Risperdal), selegiline (Eldepryl and others), selegiline transdermal (EMSAM), sertraline (Zoloft and others), sibutramine (Meridia), sildenafil (Revatio and Viagra), simvastatin (Zocor and others), terazosin (Hytrin and others), theophylline (Theo-24, Elixophyllin, and others), thiothixene (Navane and others), topiramate (Topamax and others), tranylcypromine (Parnate and others), triazolam (Halcion and others), trifluoperazine (Stelazine and others), venlafaxine (Effexor and others), verapamil (Isoptin, Calan, and others), warfarin (Coumadin, Jantoven, and others), zolpidem (Ambien).

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