

Clinical Pharmacology of Antidepressants

Based on a presentation by Henry Cohen, MS, PharmD

Presentation Summary

The cyclic antidepressants category includes the older tricyclic antidepressants (TCAs) and a diverse group of second-generation agents, including the selective serotonin reuptake inhibitors (SSRIs). For the management of depression, the SSRIs have begun to replace the TCAs as first-line treatment. The adverse reactions that occur with the alpha-adrenergic blockage, anticholinergic, and antihistaminic effects of the TCAs are the predominant reason for the switch. Additionally, TCAs may cause cardiac conduction disturbances and seizures, especially in an overdose setting. The pharmacokinetic parameters of the TCAs—a large volume of distribution, long elimination half-life, and high myocardial concentrations—may contribute to their toxicity profile and the inefficiency of extracorporeal removal techniques in the overdose setting. SSRIs have a more favorable tolerability and safety profile compared

with the TCAs. In general, they have minimal antimuscarinic, antihistaminic, adrenergic, and dopaminergic effects. They lack a quinidine-like effect and are rarely seizuregenic. The SSRIs are also more effective than TCAs in improving adherence to treatment, an effect related to their more benign tolerability profile. However, the Syndrome of Inappropriate Antidiuretic Hormone secretion and the serotonin syndrome are 2 side effects that may occur after treatment with all cyclic antidepressants. In addition, various SSRIs inhibit hepatic cytochrome P450-2D6 and -3A4 isozymes, leading to potentially significant drug interactions.

Because it has a major impact on individuals and society in terms of absenteeism, lost productivity, and increased healthcare costs, treatment of depression is of primary importance. Selecting the antidepressant agents that are most effective and improve patient adherence to treatment plays an important role in reducing that impact.

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Acute phase treatment with medication is effective for the reduction and resolution of signs and symptoms of major depressive disorders. The cyclic antidepressants include the older tricyclic anti-

depressants (TCAs) and a diverse group of second-generation agents, including selective serotonin reuptake inhibitors (SSRIs). The pharmacology, adverse effects, significant drug interactions, and pharmacoeco-

nomics of these agents were discussed by Henry Cohen, MS, PharmD, Associate Professor of Pharmacy Practice at The Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, and Coordinator of Clinical Pharmacy Services, Kingsbrook Jewish Medical Center, Brooklyn, New York.

The precise mechanism of antidepressant action of the cyclic antidepressants is not well elucidated. The SSRIs block serotonin reuptake and cause serotonin to accumulate at the central presynaptic terminals. The TCAs block norepinephrine, serotonin, and dopamine to a varying extent and with a varying degree of selectivity.¹ In addition, when TCAs are used the reuptake blockade occurs rapidly, and within the synapse, concentrations of serotonin and/or norepinephrine increase in 6 to 8 hours, but the clinical antidepressant effects take 2 to 4 weeks to appear.

In the depressed patient, what appears to be happening centrally, explained Dr. Cohen, is that there is erratic firing from the presynaptic to the postsynaptic receptors, and the target receptors do not respond accordingly. The mechanism of

action of antidepressant drugs presents as somewhat complex and contradictory because both buspirone, which is a 5-HT_{1A} partial agonist, and pindolol, which has the opposite effect, can help patients with depression and are being used as options in refractory depression.

Tricyclic Antidepressants

Adverse Effects. TCAs have numerous adverse effects (Table 1), which have led to their replacement by SSRIs as first-line agents.² One of the adverse effects of TCAs that is particularly annoying to patients is constipation, which is a result of the TCAs' antimuscarinic properties and antiperistaltic action and may not be transient. Stool softeners, such as docusate, will not counteract TCA-induced constipation. Stimulant laxatives, such as PeriColace® (an over-the-counter agent that contains casanthranol), bisocodyl, and cascara, must be used for treatment. Another problem, especially in male geriatric patients with prostatic hypertrophy, is urinary retention, which can be exacerbated if narcotics or sedating antihistamines are administered concurrently.

Blockade of alpha-1 receptors by TCAs may cause orthostatic hypotension, which leads to an increase in syncope, falls, and hip fractures. Concomitant administration of other antihypertensives, especially alpha-1 antagonists, such as prazosin, doxazosin, or terazosin, and alpha-beta antagonists, such as labetalol and carvedilol, may dramatically increase the prevalence of orthostasis. The TCAs exhibit quinidine-like membrane effects on the myocardium and slow the influx of sodium during phase 0 of the action potential. TCAs may not be suitable for patients with heart disease because they can induce sinus tachycardia and exacerbate cardiac dysrhythmias or angina symptoms.³ Cardiac conduction disturbances become more pronounced, especially in the overdose setting;

Table 1. Adverse Effects of Tricyclic Antidepressants

<ul style="list-style-type: none"> ■ Antimuscarinic: xerostomia, blurred vision, constipation, urinary retention, anterograde amnesia, sinus tachycardia ■ Histamine-1 receptor blockade: sedation, drowsiness, weight gain ■ alpha-1 receptor antagonism: orthostatic hypotension and sedation ■ Myocardial sodium channel blockade (quinidine-like effect): prolongation of PR, QRS, QT intervals on ECG, ventricular dysrhythmias, torsades de pointes, supraventricular tachycardias ■ γ-Aminobutyric acid receptor inhibition: lowers seizure threshold; generalized tonic-clonic type seizures

ECG = Electrocardiogram.

therefore, caution must be exercised in the use of TCAs in patients with suicidal ideation.

TCAs are seizuregenic and must be used with care in depressed patients with epilepsy.⁴ A plausible mechanism is γ -aminobutyric acid receptor inhibition. The seizures, which are seen primarily in cases of overdose, are of the generalized tonic-clonic type, which are generally well controlled with lorazepam. Abrupt discontinuation of TCAs can also precipitate a seizure, so slow weaning is recommended, Dr. Cohen stated, adding that TCAs may lower the seizure threshold and cause breakthrough seizures in epileptic patients. In contrast, the SSRIs have a lower seizuregenic potential and do not cause seizures on abrupt withdrawal.

Pharmacokinetics. The TCAs undergo significant first-pass metabolism, are highly lipophilic, and are extensively bound to alpha-1 acid glycoproteins, resulting in a high volume of distribution (Vd, 10 to 50 L/kg). These pharmacokinetic properties help explain why TCAs pose a danger when overdosed. Therefore, as a result of a greater Vd, half-life ($t_{1/2}$) and extensive protein binding, extracorporeal removal techniques are not efficient. The inherent long $t_{1/2}$ of TCAs of 8 to 90 hours allows for once-daily dosing but prolongs toxicity. Furthermore, significant accumulation of TCAs in parenchymal tissues, such as the myocardium, may enhance cardiac toxicity.

Overdose. "The tricyclics continue to be a leading cause of drug morbidity from overdose in adults as well as children," Dr. Cohen said, explaining that half a million people overdose on these drugs annually.⁵ An overdose of these agents is extremely difficult to treat because of the constellation of anticholinergic, antimuscarinic, alpha-adrenergic blockade, seizuregenic, and cardiac membrane depres-

sive effects.⁶ TCA plasma levels are not a good predictor of toxicity. TCA levels higher than 1000 ng/mL are more likely to be associated with dysrhythmias and seizures, although lower levels may also be associated with toxicity. Furthermore, TCA plasma levels may fluctuate unpredictably, and assays often lack the sensitivity and specificity for toxic active metabolites. The ingested TCA dose also is not a reliable predictor of toxicity, with some patients surviving an ingested dose of 4000 mg, and in other instances fatalities occurring after ingestion of 500 mg.⁷

No antidotes are available for TCA poisoning. Syrup of ipecac, which is readily available in the home setting, is absolutely contraindicated for TCA overdose, Dr. Cohen stressed. In all cyclic antidepressant poisonings, the propensity for seizures, coma, hypotension, and cardiac dysrhythmias precludes the use of syrup of ipecac. Ipecac causes vomiting, and because TCAs are sedating and seizuregenic, a patient who is sedated or has a seizure during emesis may aspirate gastric contents, resulting in the potential for greater morbidity and mortality. Treatment of a TCA overdose includes supportive care, gastric decontamination with orogastric lavage, activated charcoal, and alkalization with sodium bicarbonate.

Selective Serotonin Reuptake Inhibitors

Side Effects. The SSRIs have several advantages over the TCAs (Table 2). Antimuscarinic, antihistaminic, adrenergic, and dopaminergic effects are generally not observed or observed minimally with SSRIs, which are safer than TCAs for patients with seizures. However, as experience with SSRIs increases, some adverse effects are emerging. Still, the advantageous pharmacologic profile of the SSRIs makes them more tolerable and safer than the TCAs and enhances compliance, Dr. Cohen noted.

Some of the more common adverse events observed with SSRIs are nausea, vomiting, diarrhea, headaches, and somnolence, all of which tend to be transient.¹ An exception is fluoxetine, which unlike the other SSRIs, exerts a stimulant effect and causes insomnia, nervousness, anxiety, and agitation and should not be administered after 2 P.M. Sexual dysfunction, in both men and women, is more prevalent with SSRIs than TCAs.

Pharmacokinetics. Four SSRIs are currently marketed for depression—fluoxetine, paroxetine, sertraline, and citalopram—and they are of equivalent efficacy in improving symptoms

of depression. However, the pharmacokinetics differ and are clinically significant (Table 3). SSRIs with a shorter half-life are preferred. Shorter acting agents achieve steady state faster and enable faster dosage titration. Additionally, they allow for faster and safer substitution of another antidepressant and minimize the risk of serotonin accumulation.

The half-life of fluoxetine is long—1 to 3 days after acute administration and 4 to 6 days after chronic administration—and its active metabolite, norfluoxetine, has a half-life of 4 to 16 days. SSRIs with a shorter half-life include paroxetine, which has a half-life of 20 hours and no active metabolites, sertraline, which has a half-life of 25 hours and a short-acting metabolite, and citalopram, which has a half-life of 35 hours with weak metabolites. Sertraline and citalopram exhibit linear elimination or dose-proportional increases or decreases in plasma levels; the other SSRIs possess nonlinear elimination or dose-disproportional increases or decreases in plasma levels.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

A major and somewhat underacknowledged adverse effect of the cyclic antidepressants (both TCAs and SSRIs) is the Syndrome of Inappropriate Antidiuretic Hormone

Table 2. Advantages of Selective Serotonin Reuptake Inhibitors

- Relatively devoid of antimuscarinic, antihistaminic, adrenergic, and dopaminergic effects
- Less cardiotoxic: no cardiac membrane depression; no torsades de pointes
- Less seizuregenic
- Improved tolerability
- Improved compliance
- Safer in suicidal ideation patients

Table 3. Comparative Pharmacokinetic Parameters of the Selective Serotonin Reuptake Inhibitors

	Fluoxetine	Paroxetine	Sertraline	Citalopram	Fluvoxamine
Percent protein bound	94	95	99	80	77
Peak plasma level (hour)	6	2-8	6-8	3-4	2-6
Parent t _{1/2} (hours)	24-72	20	25	35	16
Dose range (mg/day)	20-80	10-50	50-200	20-80	50-300
Linear pharmacokinetics	No	No	Yes	Yes	No

secretion (SIADH). A higher prevalence of SIADH may occur when a cyclic antidepressant is combined with carbamazepine. The typical clinical manifestations of SIADH are nausea, vomiting, weakness, confusion, and seizures. Paradoxically, depression may also be a symptom of SIADH, a connection that should be kept in mind if patients are not responding to antidepressants. The serum is hyponatremic and hypoosmolar, whereas the urine is hypernatremic and hyperosmolar. Management includes discontinuation of the causative agent, or fluid restriction and/or administration of demeclocycline.⁸ Other agents that cause SIADH are carbamazepine, neuroleptic agents, barbiturates, chlorpropamide, diuretics, vincristine, vasopressin, and desmopressin.

Serotonin Syndrome

The serotonin syndrome is a constellation of mental status changes—neurologic and neuromuscular symptoms that result from an excess of serotonin (Table 4).^{9,10} The syndrome often presents with mild transient symptomatology, but it can present or progress to life-threatening symptoms. This occurs most often when 2 serotonergic agents are combined or after an increase in the dosage of 1 agent—therapeutic or toxic levels of an SSRI can result in the serotonin syndrome. The onset of symptoms is rapid (within minutes to hours), with resolution being equally fast after the causative agent is discontinued and supportive care is administered. Activated charcoal may be administered, especially if one of the offending agents is a TCA (in combination with a serotonergic agent) because TCAs undergo significant enterohepatic recirculation. Therefore, even 24 hours after the TCA has been administered, activated charcoal will be effective because it enhances gastric elimination by interfering with enteroenteric circulation, interrupt-

ing enterohepatic circulation and/or minimizing desorption. Because the serotonin syndrome may present with respiratory failure, patients may need to be monitored in an intensive care unit with mechanical ventilation. There is a paucity of data regarding treatment with serotonin agonists, such as cyproheptadine, methysergide, and propranolol, however, both efficacy and failure have been reported.

The difficulty in diagnosing the serotonin syndrome stems from nonspecific symptoms that include cognitive and behavioral disturbances and autonomic dysfunction (Table 4). The symptom of muscle rigidity has been considered a distinguishing feature between the neuroleptic malignant syndrome and the serotonin

Table 4. The Serotonin Syndrome

Mechanism	
■	Augments serotonin synthesis
■	Increases serotonin release
■	Inhibits serotonin metabolism
■	Inhibits serotonin reuptake
■	Directly stimulates serotonin postsynaptic receptors
Occurrence	
■	Generally occurs with 2 serotonergic agents
■	Noted with therapeutic or toxic levels of serotonergic agents
Presentations	
■	Cognitive and behavioral: confusion, disorientation, anxiety, agitation, coma, hypomania, seizures, hallucinations
■	Autonomic dysfunction: hyperthermia, diaphoresis, sinus tachycardia, hypertension, hypotension, tachypnea
■	Neuromuscular dysfunction: myoclonus, hyperreflexia, muscle rigidity, tremor, hyperactivity, ataxia, chills
■	Onset is minutes to hours
■	Resolution within 12 to 24 hours
Treatment	
■	Discontinue serotonergic agent
■	Supportive care
■	Activated charcoal (1g/kg)
■	Cyproheptadine, methysergide, propranolol
■	Intensive care unit admission and ventilatory support if necessary

syndrome in patients receiving both agents. However, muscle rigidity is commonly reported with the serotonin syndrome.

Dr. Cohen cautioned that a wide array of drugs are serotonergic (Table 5), so the clinician must be alert to drug interactions and adverse effects. Several of these drugs are available over the counter and are widely used, such as L-tryptophan, St. John's Wort, and dextromethorphan (a component of many cough remedies). Buspirone and lithium are popular adjunctive medications for depression, but both are also serotonin agonists.

Cyclic Antidepressant Drug Interactions

Hepatic Cytochrome P450-2D6 System. Genetic polymorphism of the cytochrome (CY) P450-2D6 isozyme results in 5% to 10% of whites and 3% of Asians and blacks being poor metabolizers. Because they have lower concentrations of the 2D6 isoenzyme, the latter groups are at high risk for a significant drug interaction with 2D6 substrate drugs. Detection of high-risk patients is not possible in clinical practice until they

develop a drug interaction. Fluoxetine and paroxetine are equipotent inhibitors of CYP450-2D6; sertraline has a less pronounced inhibition, and fluvoxamine and citalopram are devoid of inhibitory properties.

Inhibition of the hepatic CYP450-2D6 system by SSRIs can have serious consequences when certain drug combinations are used, as several drugs are metabolized (substrates) through this system (Table 6). For example, when a TCA is combined with a drug such as fluoxetine, levels of the TCA increase 10- to 11-fold and can lead to an overdose scenario or the serotonin syndrome. Other interactions of significance occur with the antiarrhythmic drugs, such as metoprolol, timolol, and pindolol. The latter is also an adjunctive agent for depression and if used in patients who are already receiving a CYP450-2D6 inhibitor, it can lead to high pindolol serum concentrations. Codeine may be rendered ineffective for pain relief in patients who are also receiving an SSRI because codeine must be metabolized to morphine by the CYP450-2D6 enzyme to have an analgesic effect.

Hepatic Cytochrome P450-3A4 Isozyme System. Many drugs, including the cyclic antidepressants fluoxetine, fluvoxamine, and nefazodone, have inhibitory effects on the 3A4 isozyme system and cause significant drug interactions. For example, when combining cisapride, a prokinetic agent, and a cyclic antidepressant, cisapride levels can increase, leading to QT prolongation on an electrocardiogram and the life-threatening ventricular cardiac dysrhythmia torsades de pointes. Another interaction occurs with triazolam, a rapid and short-acting sedative hypnotic. CYP450-3A4-inhibiting drugs prolong triazolam's time to peak concentration, so it takes hours for triazolam to take effect and causes prolonged daytime sedation because the drug is not

Table 5. Serotonergic Agents

<ul style="list-style-type: none"> ■ Increased synthesis: L-tryptophan ■ Inhibits serotonin metabolism: monoamine oxidase inhibitors, selegiline, St. John's Wort ■ Serotonin reuptake inhibitors: TCAs, SSRIs, venlafaxine, trazodone, nefazodone, meperidine, dextromethorphan, cocaine, amphetamines, tramadol ■ Increases 5-HT release: amphetamines, fenfluramine, dexfenfluramine, phentermine, monoamine oxidase inhibitors, cocaine, "ecstasy," mirtazepine ■ Serotonin agonists: buspirone, LSD, lithium, mescaline, psilocybin, sumatriptan, rizatriptan, naratriptan, zolmitriptan
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LSD = Lysergic acid diethylamide; SSRI = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

metabolized quickly. Paroxetine and sertraline do not seem to be associated with CYP450-3A4 inhibition.

Societal Impact of Major Depression

Depression not only affects patients on a personal level through its impact on their social and physical functioning but also places a burden on society. The estimated annual cost of depression in 1990 was \$44 billion (Table 7).¹¹⁻¹³

The major costs were ascribed to days lost from work, decreased productivity, increased healthcare utilization because of more physical illness and increased mortality from suicide.^{11,12,14,15} Major depression annually accounts for about 6 workdays lost and 33 workdays cut back¹⁶; thus, it has considerable implications for profitability and productivity. Antidepressant therapy, therefore, becomes important because it improves outcomes. In 1990, the cost of pharmaceutical treatment was only 3% of the total US depression budget (\$1.2 billion). With the advent of the SSRIs after this 1990 data was collected, the current costs are likely to be higher.

In a report comparing the adequacy of pharmacotherapy with different antidepressants, the percentage of patients completing an adequate trial rose from only 27% with trazodone to 41% and 44% with TCAs, to 62% with an SSRI, suggesting that the favorable tolerability profile of the SSRIs greatly improves adherence to medication regimens.¹⁷ However, a recent observational study that examined the use of antidepressants in nursing homes was unable to show a difference in cost effectiveness between the TCAs and SSRIs.¹⁸ Furthermore, there was little difference in the rate of falls between those treated with a TCA and those treated with an SSRI. However, the observational nature of the study and the lack of randomization were serious limitations. Earlier

studies, Dr. Cohen noted, have shown better outcomes after SSRI treatment compared with TCAs because of the increase in hip fractures among patients treated with TCAs.

Dr. Cohen concluded his presentation with a note of caution about the similarity in the nomenclature of certain drugs, in particular, Celexa™ (citalopram hydrobromide; 20- and 40-mg tablets; indicated for major depression), Celebrex™ (celecoxib;

Table 6. Cytochrome P450-2D6 Substrates

Tricyclic antidepressants	Flecainide
Maprotiline	Mexiletine
Trazodone	Propafenone
Venlafaxine	Metoprolol
Dexfenfluramine	Timolol
Fenfluramine	Dextromethorphan
Neuroleptics	Codeine
Clozapine	Morphine
Risperidone	Meperidine
Donepezil	Methadone

Table 7. Financial Impact of Depression (1990 Data)

	Estimated Annual Cost (in \$ billions)	Percentage of Total Costs
Total costs	43.7	
Decreased productivity	12.1	27%
Absenteeism (lost workdays)	11.7	27%
Inpatient care	8.3	19%
Death from suicide	7.5	17%
Outpatient/partial care	2.9	7%
Pharmaceutical treatment	1.2	3%

Source: References 13-15.

100- and 200-mg capsules; indicated for osteoarthritis and rheumatoid arthritis), and Cerebyx® (fosphenytoin sodium injection; indicated for prevention and treatment of seizures). More than 50 cases of drug errors by physicians and pharmacists have been reported to the Food and Drug Administration because of the similar-sounding names. One of the errors involved an 80-year-old woman who mistakenly received the antidepressant Celexa instead of Celebrex twice a day for a month. A pharmacy staffer confused the drug names when pulling the drug from the shelf (personal data). Pharmacists should check a drug's name, indication, dosage form, and strength carefully to ensure accurate dispensing.

...DISCUSSION HIGHLIGHTS ...

Dr. Rabins: My clinical experience with seeing a lot of patients with SIADH is that the vast majority who present with it on any one drug also get it on another. For example, if you switch from a tricyclic to an SSRI, or vice versa, SIADH occurs in 90% of patients when you use a different drug. This shows that we really do need data on these kinds of questions.

Use of Ipecac

Dr. Rabins: The other issue is the use of ipecac. It's clear that ipecac is contraindicated in anyone who is sedated. For an acute overdose, I would like to see a consensus from toxicology experts that a poison center should not instruct a telephone caller to take ipecac if the caller or someone else has just overdosed on any of these drugs.

Dr. Cohen: Due to the unpredictable rapid deterioration during cyclic overdoses, including with SSRIs, and the risk of seizures, coma, cardiac dysrhythmias, and hypotension, syrup of ipecac is contraindicated.

This is a common consensus among all toxicologists and pharmacologists.¹⁹ We recommend gastric decontamination and/or activated charcoal.

Dr. Rabins: If I was relatively certain it was within a half hour after the overdose, I'd probably recommend ipecac if it's available.

Dr. Klinkman: It depends on whether it is somebody who is using the drug regularly or someone who doesn't have any level to begin with. That would probably change the pharmacology.

Dr. Cohen: It might plausibly minimize the risk of syrup of ipecac administration; nevertheless, ipecac is still contraindicated in this scenario. Numerous studies corroborate that the sooner syrup of ipecac is administered following an ingestion, the greater the amount of ingredient recovered. The other issue is that if someone takes syrup of ipecac, even within 5 minutes of ingestion, in studies looking at acetaminophen or ampicillin, we can only recover about 50% of these drugs. Additionally, syrup of ipecac will delay the administration of activated charcoal.

Dr. Treisman: Have you changed your opinion regarding the use of ipecac based on studies and data, or have you changed it based on an opinion?

Dr. Cohen: The recommendation not to use syrup of ipecac in cyclic antidepressant poisoning is based on studies that observed the lack of ingestant recovery, the lack of benefit for patients who have gastric emptying prior to activated charcoal compared with activated charcoal alone, and the increased risk of aspiration with the combined regimen.

Outcomes: TCAs Versus SSRIs

Dr. Treisman: Do you have data showing that the outcomes are affected by

hip fractures? There are actually anti-theoretical data, which show that patients receiving SSRIs have more hip fractures than patients receiving tricyclics. We have done a retrospective review of all the trials with SSRIs and tricyclics that were used to obtain SSRI approval. The dropout rate from the tricyclic group is identical to that from the SSRI groups in those trials. Some of these data are not turning out to be true, particularly the hip fracture data, which have just been rereviewed.

Dr. Wilson: The hip fracture data are interesting. However, one wonders if this is an issue of selection bias; that is, are the patients really comparable because it is possible they received an SSRI rather than a TCA because their doctors thought they were specifically at risk of falls?

Dr. Cohen: Absolutely. The results may be caused by a selection bias, because patients at greatest risk of orthostatic hypotension or dizziness are placed on an SSRI rather than a TCA. Based on the adverse-effect profiles of TCAs and SSRIs, TCAs should have a greater propensity to cause orthostatic hypotension, dizziness, and syncope. SSRIs are generally devoid of alpha-1 blocking effects and should be less likely to cause orthostasis-induced dizziness and syncope.

Dr. Katon: I agree more with your comment about the selection bias than about why patients received SSRIs, because most of the comparison studies are efficacy ones, in which patients are highly selected and intensively followed. When you do those, there is a bit of a difference but not much between adherence. But when you look at, for example, the Simon and associates study in which primary care patients were actually randomized, the rates of dropout because of side effects were 3 times as

great with the tricyclics compared with SSRIs in the first 12 months.²⁰

Ease of Use: TCAs Versus SSRIs

Dr. Rabins: An important issue we haven't touched on is: What's easier for the doctor to prescribe? This is a crucial element, and my own feeling is the SSRIs have been successful because they're much easier for doctors to use and for patients to take because they require once-a-day dosing and do not need titration, which makes adherence easier.

Dr. Cohen: The titration of an SSRI may be easier than with many TCAs; however, almost all the TCAs can be administered once daily, based on their inherently long half-life.

Dr. Wilson: There is considerably more ease of use with the SSRIs, but I'm puzzled by this mini boom for tricyclics that seems to have emerged in the past year or so. Based on almost every experience I've had in using SSRIs compared with tricyclics, SSRIs are much better appreciated by patients.

Dr. Treisman: That has not been my experience in 10 years of treating hundreds of patients. I have a lot of patients who have failed on many SSRIs but have become better on tricyclics. Tricyclics have all kinds of wonderful therapeutic advantages over SSRIs that we tend to forget. For instance, their constipating qualities can be very useful in patients with AIDS diarrhea. They cause profound weight gain, so in elderly patients with weight loss they can be very helpful.

Dr. Wilson: That's not exactly what I am trying to say. Tricyclics certainly are useful and relevant. However, at the population level, the vast majority of patients with depression respond to and tolerate newer antidepressants

better than the tricyclics. Psychiatrists may be seeing somewhat sicker patients than was the case 10 years ago as primary care physicians become more comfortable with SSRIs. Certainly, the side-effect profiles are different, and one can sometimes tailor these to different therapeutic ends.

Dr. Katon: I think it's also a specialist versus a primary care physician issue. Those of us in psychiatry have used tricyclics for years, are familiar with them, and have never really had a lot of problems with them. Primary care physicians were tending to undertreat patients, using 25 mg of amitriptyline or 25 mg of imipramine, and when they switched to 20 mg of fluoxetine they thought it was a miracle drug, because a lot of people hadn't actually been titrated well, and if patients had side effects, physicians weren't seeing them that frequently. There is no question that the ease of use of antidepressants in primary care is much greater because of the ease of use of SSRIs. You also don't have to worry about overdose.

Dr. Wilson: This specialty-primary care distinction is a useful one. Most of the patients are being treated in primary care, and psychiatrists are called in for the difficult cases.

Dr. Treisman: There is also the issue of the type of patients seen in a primary care practice. If you are in an office practice that sees a medical assistance, Medicaid population, who often have chronic illnesses, you are going to see very high rates of major depression because of comorbidity. You should be familiar with the use of tricyclics in that setting. On the other hand, if you're looking at a panel of essentially healthy patients, screening them for depression, and picking up depression in that panel, you're going to tend to be a very SSRI-driven treater.

A second issue is that as you recognize and treat depression, you run

into more and more refractory patients. A lot of primary care physicians in Baltimore are using tricyclics. They tend to treat sick populations and populations in which a high percentage of all patients have a mood disorder and in which a high percentage are on an antidepressant.

Dr. Rabins: Hopefully, now that primary care physicians are at the point where they are comfortable with 1 or 2 SSRIs, many may be willing to learn how to use a tricyclic, whereas 10 or 15 years ago it just seemed too overwhelming. At that time, they were not convinced that depression was that clinically significant an issue, and I think the beauty of the SSRIs was they convinced many primary care physicians that depression is both important and very treatable and that they need to become comfortable with the use of these agents.

The SSRIs have also helped expand the spectrum for an effective symptomology that we overlooked when we only had TCAs.

Dr. Choksi: The preference for SSRIs versus tricyclics depends on the managed care company. If you look at the APA [American Psychiatric Association] guidelines, they also start with the SSRIs and novel antidepressant medication compared with tricyclics, so you may have to defend your decision to use a tricyclic first in court. These new medicolegal issues will come up sooner or later. In that sense, it is easier for a psychiatrist to prescribe the newer antidepressant medications.

Dr. Cohen: In regard to prescribing TCA for patients with suicidal ideation, a practice that might be prudent is prescribing less than 1000 mg of a TCA at a time. This dose would be less likely to be toxic in a single ingestion compared with more than 1000 mg. Additionally, several novel antidepressants such as trazodone and nefa-

zodone may be preferred in patients with suicidal ideation.

Dr. Choksi: Most HMOs [health maintenance organizations] only cover 1 month; they don't want to give you only a 5-day prescription.

Dr. Treisman: There are issues related to what you write in the chart of a patient to whom you are going to give a tricyclic as a first drug; for example, why you did it and when you did it. In many cases, it goes beyond the purview of the primary care practitioner and a consult is needed. At the same time, I would teach primary care givers who are interested in being sophisticated treaters of depression some of the things that we have discussed; that tricyclics can be lethal, which should be a consideration in their use; that they have certain advantages over SSRIs, that is, the disadvantages related to SSRIs; and then I would describe some cases in which a primary care giver might use a tricyclic. These are the uncommon cases. Those of us in the AIDS clinic and in geriatrics still use SSRIs to a much greater extent than tricyclics, but we use a lot of tricyclics too.

The question then becomes for whom would you expect a primary care giver to think of prescribing a tricyclic? Some examples are patients with intractable diarrhea, weight loss, inability to sleep, and neuropathic pain.

Dr. Katon: Neuropathy may be the other edge tricyclics have over SSRIs; they also may have some advantages in patients with migraine.

Dr. Cohen: TCAs are considered second line to β -blockers for migraine prophylaxis; they may decrease the frequency and intensity of migraines.

Serotonin Depletion

Dr. Klinkman: I would like someone to address serotonin depletion and

neurotransmitter depletion in patients who are treated with SSRIs for short or moderate terms, which creates problems after withdrawal of medications.

Dr. Katon: There are some patients who are taking short-acting serotonergic agents who develop nausea, dizziness, and a flu-like syndrome when they stop SSRIs abruptly. Most patients have no problems, but I've had some very uncomfortable patients who forgot their short-acting drug for a 3- or 7-day vacation and who berated me afterwards for not telling them how bad withdrawal would be.

Dr. Klinkman: As a longer-term issue, I've heard that therapy becomes more difficult because patients are so profoundly depressed after coming off antidepressants for months at a time.

Dr. Treisman: The research that's been done does not distinguish that from relapsed major depression. If you go back to the original literature on tricyclics, and even on ECT [electroconvulsive therapy], those who get partially better but must have their treatment stopped and then relapse say that it's much worse when they relapse, even though their Hamilton or Beck scale may be the same.

Many symptoms that get blamed on the drugs may actually be caused by the disease.

Another interesting pharmacological entity that's involved with SSRIs is what is sometimes generically called "Prozac [fluoxetine] fade," which is an abatement of response on the SSRI dose that was effective for a prolonged period of time, sometimes as long as 6 months. Patients suddenly find that their drug is ineffective. Sometimes boosting the dose will reactivate the effect, and sometimes it won't. I'm interested in an update on the pharmacological knowledge base about that.

Dr. Cohen: I haven't seen anything recent with fluoxetine specifically,

but generally the SSRIs do have a flat dose-response and blood level response curve. In other words, more SSRI may not increase efficacy; however, it may increase toxicity. So after a certain dose we don't see any greater effect; but, there are several anecdotal case reports in which patients improved after the dose was increased. For example, it has been shown that in patients who fail to respond to 8 weeks of therapy with 20 mg fluoxetine, increasing the dose is effective in more than 80%. This may be because some patients are rapid hepatic metabolizers and require higher doses or simply because some patients require larger doses for efficacy. Nevertheless, it makes sense to increase the dose based on efficacy and tolerability.

Sexual Dysfunction

Dr. Klinkman: One of the issues that appears to come up more and more with SSRIs is sexual dysfunction, to the degree that some of us are now beginning to treat with slightly lower doses of SSRIs and balancing them with tricyclics to try to minimize that side effect. Especially for the more activating SSRIs, using trazodone as an adjunct is often a very good strategy to maintain compliance at the same time that you are minimizing some of the side effects. We have had as much patient-initiated cessation of SSRI therapy because of sexual dysfunction as we did with the TCAs for other reasons.

Dr. Rabins: This emphasizes the point that when you discover a lot more depression, you need a lot more treatment options. The tricyclics are still second or third on the line, but we're discovering the good aspects. There are so many more cases for which we need to fall back on these drugs.

Dr. Wilson: I've had a number of patients, particularly women, who are

just completely inorgasmic. In the past year or so a number of them have gone on little drug holidays once in a while when they wanted to be orgasmic. But it seems to me that it has disturbed their well-being, and I've had a harder time keeping them undepressed. It is just 3 or 4 days, once a month for a few months. Should we try to treat that side effect?

Dr. Treisman: The other thing is, if you get patients just subtherapeutic, so that they're not quite all the way well, they have a really bumpy road and are very hard to keep well. But if you get them well, even if they do not take their drugs for a week, they seem to do well and then go back on the drug.

I have many patients on whom I tried shorter-acting SSRIs, telling them to stop their drug over the weekend. Sometimes they'll have a restoration of orgasmic function. I've had orgasms restored in some people by prescribing bupropion combined with their SSRI. Trazodone added to their SSRI restored orgasm in 2 patients. I've tried cyproheptadine in almost everybody, and I haven't had anybody succeed with it yet, but several other physicians at Johns Hopkins have had cyproheptadine work. I had one nice success with buspirone, but I haven't had any others in terms of restoration of orgasm. I tried sildenafil in a woman who happened to be inorgasmic, but it didn't work.

Dr. Cohen: Sildenafil and to a lesser extent ginkgo biloba have been successful in males with cyclic antidepressant-induced erectile dysfunction.

Atypical Antidepressants

Dr. Treisman: The issue of inorgasmia might bring up the third group of antidepressants, which we didn't really talk about—the atypical agents. If you

can't give patients a tricyclic, what about nefazodone, mirtazapine, and bupropion?

Dr. Katon: I've had really good success with mirtazapine for patients who didn't respond to any other combinations.

Dr. Treisman: I tend to use nefazodone and mirtazapine in those to whom I would like to give a tricyclic, but who have reservations about it. I've used a lot of bupropion in high-functioning people. It's now my rule of thumb that if the patient is a doctor, lawyer, or financier I tend to use bupropion. There is very little of the frontal apathy you get with the SSRIs and very little of the sedation that you get with tricyclics.

Inappropriate Use

Dr. Jack: There is a downside to the use of SSRI antidepressants. One of the issues about the management of depression is the appropriate use of antidepressants, and the SSRIs have opened up a Pandora's box. I sometimes think when a patient comes into the primary care physician's office asking for a prescription for an SSRI, they may get it, whether they need it in the first place. Given their low-risk profile, the threshold for use of SSRIs is much lower.

Dr. Rabins: This is an important point. Ten or 20 years ago, under-recognition and undertreatment were serious problems. They still are, but today the other side of that is the question of inappropriate use. As Dr. Katon said, we have as yet no good data in minor depression to show the efficacy of these drugs. Now we are starting to ask questions such as, When does it not work? When is it not needed?

Dr. Nichol: I think about that whole population of noncompleters and

wonder whether we don't have a group of people who really aren't depressed to begin with. I don't think we've done a very good job pursuing this, but we may have a situation where the noncompleters represent some proportion of those who really aren't sick. Such patients use the drug on an as-needed basis, but it doesn't make much difference one way or the other so there is no reason for them to renew their prescription, in contrast to those who really have a major depressive disorder or a minor depressive disorder that can be helped by the pharmacologic intervention.

Dr. Treisman: One of the questions that needs to be answered about minor depression is whether it is sub-syndromal major depression or a variant of grief or demoralization. How can we make distinctions in the minor depressive population, where symptomology is inadequate to really provide the differential? There, you have to make a decision about the risk and benefit of treatment.

With regard to primary care patients who demand an antidepressant, it becomes a risk-benefit issue. I'm reluctant to give just anybody a drug that might turn off their sex life, make them apathetic, give them the serotonin syndrome, give them SIADH, or make them fall asleep at the wheel.

On the other hand, by the time a patient sees a psychiatrist, he or she is almost always sick compared with the primary care patient. So the issue of risk and benefit changes, depending on which doctor is seen and the level the patient is at.

Dr. Klinkman: It takes time to weed out the benefits and costs. It took years and a lot of good data, but we still have cardiologists prescribing quinidine. So from a managed health-care perspective, it's going to be tough to set policies about what and for

whom we should or should not allow clinicians to prescribe until we know a little bit more about what happens to the patients.

There is information that suggests a lot of folks may not need treatment. We are still trying to figure out exactly who they are, but we know that's an issue now, which is a step forward. We just don't know how it plays out in decisions about supplementing benefits or restricting access to formulary.

Dr. Jack: We clearly know what to do for somebody who has major depression, so we should allow the treatment for it. We need to be working on a system to identify patients who definitely have major depression and get them the appropriate treatment.

The issue of treating minor depression remains pertinent, but it is still investigational. We can identify the group that has minor depression or the subsyndromal depression through the screening process for major depression. Then, in those with minor depression, we can hopefully do some more effectiveness studies and figure out what we are supposed to do with that group. That is how I perceive we should proceed with patients who have minor depression.

But first, let's work with an identified group. I agree that the DSM-IV [*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*] is limited in terms of its usefulness in some ways, but it is what we have right now, and it is the standard of care, so let's be sure to use the guidelines that are clear.

Dr. Rabins: One of the things that treatment guidelines and evidence-based medicine has shown is that studies and data allow us to answer some questions. That is the best evidence we can have. However, we are never going to be in a situation where every question can be answered by data because people are too variable. So we have a hierarchy of evidence,

ranging from controlled trials at the top to expert opinion to anecdotal reports on which guidelines and recommendations are made. What level of evidence does managed care pay for or encourage to treat? What are we going to require? Answers to these questions depend partly on a number of things, such as how much morbidity comes from the condition, how prevalent it is, and so on. It's a very complicated issue but a really important one.

Dr. Katon: In the history of medication, whenever a dramatic advance occurs, it gets tried for various conditions. We are in an era where we're still expanding, but there will be a contraction as we get more evidence about what things work. Such an expansion is appropriate because we are always looking for new treatments.

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