

# THE JOURNAL OF CLINICAL PSYCHIATRY

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SUPPLEMENT 15

SUPPLEMENT



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Optimizing Clinical Use of SSRIs:  
Theory and Practice

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## Introduction

# Optimizing Clinical Use of SSRIs: Theory and Practice

Alexander H. Glassman, M.D.

Selective serotonin reuptake inhibitors (SSRIs) have been available for almost a decade, and in that period they have had a tremendous impact on pharmacotherapy. A number of SSRIs currently are available in the United States, including fluoxetine, paroxetine, and sertraline, and new ones, such as citalopram, soon will be added to the clinician's armamentarium. SSRIs have demonstrated a broad range of clinical applications. In addition to their usefulness in depression, SSRIs also have been shown to be of therapeutic benefit in the treatment of obsessive-compulsive disorder, panic disorder, bulimia nervosa, social phobia, and premenstrual dysphoric disorder. They also have been noted to decrease anger and rage attacks, as well as to have potential roles in autism and anorexia nervosa. SSRIs generally have established better safety and tolerability profiles compared with tricyclic antidepressants. However, optimal clinical use of these agents requires understanding of both the similarities and differences among the SSRIs, as well as the clinical dilemmas that often face clinicians in the selection of an appropriate therapeutic intervention. This supplement to *The Journal of Clinical Psychiatry*, based on papers presented at a roundtable symposium, explores some of the issues surrounding the use of the SSRIs, with the goal of providing the clinician a useful review of the data to help better understand and utilize the SSRIs in practice.

After years of study and clinical use, SSRIs are considered first-line agents for the treatment of depression. In clinical trials, patients treated with SSRIs suffer fewer adverse events, especially events that are cognitive or cardiovascular in nature, than do patients treated with tricyclic antidepressants. Particularly in overdose, the SSRIs have demonstrated improved safety compared with tricyclic antidepressants; few SSRI-only deaths have been recorded.

Despite what we have learned about SSRIs, a number of issues remain unresolved. We still are uncertain how inhibition of neuronal serotonin reuptake works to relieve signs and symptoms of disease. It also is unclear why patients may respond preferentially to one SSRI compared with another. When faced with a patient who is refractory to treatment, it is arguable whether augmentation or switch to another agent is a preferred strategy.

As a group, the SSRIs have been studied and used extensively around the world, but additional research is re-

quired to understand the breadth as well as the limitations of their usefulness. For example, further study to establish the safety and effectiveness of SSRIs in the treatment of patients with comorbid medical disorders—such as post-infarction—is needed. In addition, there are marked differences among the SSRIs in their effects on P450 isoenzymes (which are involved in the metabolism of many drugs) and thus the potential for causing clinically significant drug interactions. Since suicidal thoughts and acts are symptoms of major depression, a concern with the prescription of any medication is its margin of safety in overdose. Although the SSRIs are far safer than TCAs in overdose, clinicians need to appreciate the signs and symptoms of SSRI overdose, as well as the potential for toxicity when SSRIs are ingested with other drugs or alcohol.

This supplement contains 6 papers, each discussing a different aspect of SSRI use in the clinical setting. First, Dennis L. Murphy, M.D., and his colleagues review and update what is known about the mechanisms of serotonergic neurotransmission. Recognizing that depression and cardiovascular disease frequently co-occur, and that they may be pathologically related, my paper discusses the cardiovascular effects of antidepressant drugs. Next, David J. Greenblatt, M.D., and associates review the effects of SSRI antidepressants on the human cytochromes P450. Laurel E. S. Mayer, M.D., and B. Timothy Walsh, M.D., discuss the potential role SSRIs play in the treatment of patients with eating disorders. J. Craig Nelson, M.D., reviews the evidence supporting whether augmentation or switch to an alternative antidepressant medication is a preferred strategy among partial or nonresponders to an adequate course of SSRI therapy. Finally, Jean T. Barbey, M.D., and Steven P. Roose, M.D., describe the signs, symptoms, and risk of mortality associated with SSRI overdose.

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*The closed roundtable symposium "Optimizing Clinical Use of SSRIs: Theory and Practice," was held December 6, 1997, in San Francisco, Calif., and was supported by an unrestricted educational grant from Forest Laboratories.*

# Brain Serotonin Neurotransmission: An Overview and Update With an Emphasis on Serotonin Subsystem Heterogeneity, Multiple Receptors, Interactions With Other Neurotransmitter Systems, and Consequent Implications for Understanding the Actions of Serotonergic Drugs

Dennis L. Murphy, M.D.; Anne M. Andrews, Ph.D.; Christine H. Wichems, Ph.D.;  
Qian Li, Ph.D.; Michihisa Tohda, Ph.D.; and Benjamin Greenberg, M.D., Ph.D.

Knowledge about serotonergic neurotransmission has been expanding rapidly. Recent research has delineated 15 molecularly different serotonin receptors and multiple, discrete neuronal and nonneuronal (including endocrine) pathways and mechanisms that mediate the many functions of serotonin. Nonetheless, gaps remain regarding aspects of the anatomy and physiology of serotonin in its roles as a neurotransmitter, a neuromodulator, and a hormone. Few serotonin receptor-selective drugs are available for clinical use. A group of selective serotonin reuptake inhibitors (SSRIs) remain the agents with greatest therapeutic utility, although the mechanisms underlying their delayed efficacy, which clearly result from adaptive consequences following repeated administration rather than early uptake inhibition of serotonin by itself, are incompletely understood and appear to involve changes in signal transduction and gene expression in serotonergic and other neurotransmitter systems.

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A wealth of evidence strongly implicates the involvement of serotonin (5-HT) in many centrally and peripherally mediated physiological functions (Table 1; for review see reference 1). In some phylogenetically ancient organisms with relatively simple nervous systems, there is direct evidence for a specific role for serotonergic transmission in behaviors such as sexual, feeding, and aggressive behavior. In more complex organisms, experimental techniques such as electrophysiologic recording, microdialysis, and other neurochemical assessments have provided evidence implicating serotonin in centrally mediated functions. These techniques are especially valuable when used together with pharmacologic agents that selectively alter serotonin synthesis, release, metabolism, or uptake, or agents that have direct effects on specific serotonin receptors or their signal transduction mechanisms.

Additional evidence has been elicited by using lesions produced by surgical or other physical procedures that tar-

get the different 5-HT-synthesizing mesencephalic raphe nuclei, or the different 5-HT brain pathways or by using selective serotonin neurotoxins like 5,7-dihydroxytryptamine or 2'-NH<sub>2</sub>-MPTP, which target specific 5-HT projection fields.<sup>2,3</sup> More recently, transgenic methodology has led to the "knockout" or "knockdown" of individual molecular components of the serotonergic system, including different serotonin receptors, the serotonin transporter, and the 2 serotonin metabolizing enzymes, monoamine oxidase type A (MAO-A) and type B (MAO-B).

In some neuropsychiatric disorders, an etiologic role for altered 5-HT function has been suggested. Evidence for this hypothesized serotonergic neurotransmission dysfunction comes mainly from quantified observations rather than controlled experiments. Some evidence has been obtained from clinical trials of agents whose primary or only known direct mechanism of action is on serotonin neurotransmission, e.g., the demonstrated efficacy of selective serotonin reuptake inhibitors (SSRIs) in many major neuropsychiatric disorders (Table 2). This evidence, however, indicates only that therapeutic benefit results from an intervention in serotonergic neurotransmission; it cannot be used as primary evidence for serotonergic dysfunction in the pathophysiology of these disorders.

The primary objective of this overview is to highlight the heterogeneous and complex nature of serotonin neurotransmission in terms of both structure and function. This heterogeneity is implicitly recognized by the loose design-

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**Table 1. Physiologic Functions Influenced by Serotonin**

Aggression/impulse control
Anxiety/affect
Appetite/satiety
Cardiovascular functions
Circadian rhythms/sleep
Cognitive functions
Endocrine regulation
Gastrointestinal functions
Motor activity
Pain
Reproductive functions
Sensory functions

**Table 2. The Widening Spectrum of Therapeutic Efficacy for the Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants**

Demonstrated Efficacy	Suggested Efficacy
Depression (acute/continuation and maintenance treatment)	Autistic disorder
Obsessive-compulsive disorder	Anorexia nervosa
Panic disorder/agoraphobia	Ethanol consumption
Social phobia	Trichotillomania
Bulimia/binges (acute treatment and relapse prevention)	Onychophagia
Obesity (acute treatment, not maintenance or relapse prevention)	Migraine
Generalized anxiety disorder	
Premenstrual syndrome	
Chronic pain syndrome	

**Table 3. Characteristics of CNS Serotonin Subsystems**

15 different molecularly-identified 5-HT receptors with different pharmacologic properties identified for most receptors
Different projection pathways for 5-HT cell bodies in dorsal, medial, and caudal raphe nuclei
Different cellular location of 5-HT terminals with different effects on cellular function in some well-studied areas (e.g., hippocampus, cortex, basal ganglia, cerebellum)
Different cotransmitters or comodulator neuropeptides in some 5-HT terminals, particularly in the caudal raphe nuclei
Different actions of 5-HT as a classic neurotransmitter via synaptic connections, or as a neuromodulator or neurohormone, often with longer-lasting effects

**Table 4. Examples of Serotonin Receptor-Mediated Interactions With Other Neurotransmitter Systems**

Neurotransmitter System	Effect	Serotonin Receptor
Dopamine	Inhibit release	5-HT <sub>1A</sub>
	Increase release	5-HT <sub>3</sub>
Acetylcholine	Increase release	5-HT <sub>1A</sub>
	Inhibit release	5-HT <sub>3</sub>
Glutamate	Inhibit release	5-HT <sub>1A</sub>
	Potiation	5-HT <sub>2</sub>
Norepinephrine	Inhibit release	5-HT <sub>1</sub>
Cholecystokinin	Increase release	5-HT <sub>3</sub>

nations of different central serotonin “subsystems” or “neuronal networks” in recent literature. Heterogeneity is particularly evident in the existence of 15 different receptors upon which serotonin exerts its initial presynaptic or

postsynaptic actions. In different phyla, species, and locations, 5-HT can act as a classical neurotransmitter via actions on presynaptic and postsynaptic receptors. It can, alternatively or additionally, act as a neuromodulator or neurohormone, with less localized effects, and variably longer durations of action (Table 3).

The most pragmatic conclusion is that changes in global brain serotonin neurotransmission such as that produced by lesions or drugs that affect release or reuptake of 5-HT, or genetically engineered or spontaneous genetically based alterations in 5-HT reuptake,<sup>4</sup> will lead to a multitude of effects, both immediate and delayed. Some of these effects will depend upon the functional status of other neurotransmitter systems with which 5-HT interacts via different 5-HT receptors, including some with opposite effects on 1 or more of these other neurotransmitter systems (Table 4). Of course, repeated drug administration or the delayed, adaptive consequences of lesions or other enduring changes (e.g., knockouts of individual molecular components of 5-HT neurons) may lead to supersensitivity, tolerance, trophic changes, or other alterations in 5-HT-modulated CNS or peripheral functions.<sup>5-7</sup>

### WHY IS BRAIN SEROTONIN NEUROTRANSMISSION SO COMPLEX AND WHY ARE THERE 15 DIFFERENT SEROTONIN RECEPTORS IN VERTEBRATE BRAIN?

5-HT neurons in brain and other tissues use only 1 synthesis pathway, that from L-tryptophan to 5-hydroxytryptophan via tryptophan hydroxylase and then to 5-HT via L-amino acid decarboxylase. Likewise, a single molecule whose structure is highly homologous across species, the 5-HT transporter (5-HTT), is primarily responsible for terminating the action of 5-HT in brain and many other tissues via reuptake of released 5-HT. Metabolic degradation of 5-HT is primarily by MAO-A, although the closely related enzyme, MAO-B, is present in some serotonin-containing cells in brain, as well as in blood platelets, and can deaminate 5-HT when 5-HT is present at high concentrations.

As listed in Table 5, 15 molecularly-identified serotonin receptors are found in vertebrates. This far exceeds the number of receptors known for any other transmitter system. 5-HT receptors have been grouped into 7 families. The largest of these are the 5-HT<sub>1</sub> receptors (5-HT<sub>1A</sub>, B, D $\alpha$ , D $\beta$ , E, F), which are predominantly coupled to the G proteins, G<sub>i</sub> or G<sub>o</sub>, and generally act to inhibit cyclic AMP formation (G<sub>i</sub>) or open potassium channels (G<sub>o</sub>). 5-HT<sub>2A</sub>, B, C receptors are coupled to G<sub>q</sub> or G<sub>11</sub> and increase phosphatidylinositol (IP<sub>3</sub>) hydrolysis, diacylglycerol and cyclic GMP (cyclic guanosine monophosphate). The 5-HT<sub>3</sub> receptor is the only 5-HT receptor which is an ion channel, and thus, is the only subtype that does not share the general structural backbone of 7 or 8 transmembrane do-

mains, or the coupling to G proteins found for all other known 5-HT receptors. 5-HT<sub>4</sub>, 5-HT<sub>5 $\alpha$</sub> , 5-HT<sub>5 $\beta$</sub> , 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> have been more recently identified, and while less is known about these receptors, most are coupled to G<sub>s</sub> and act to increase cyclic AMP formation, although the signal transducing mechanisms of the 5-HT<sub>5</sub> receptors remain unknown.

One speculative rationale for this large number of receptors is that 5-HT has apparently been used as a neurotransmitter or neuromodulator dating back to very primitive organisms,<sup>8</sup> and thus, the multiplicity of these receptors could represent evolutionary mechanisms that over time permitted serotonin to modulate multiple functions. 5-HT can be found in all phyla that possess nervous systems, including invertebrates such as coelenterates, flatworms, nematodes (e.g., *C. elegans*), mollusks (e.g., aplysia), leeches, crustaceans (lobster, crayfish), and echinoderms (sea urchins, starfish).<sup>9</sup> In these organisms, 5-HT subserves sensory, motor, and cardiovascular functions, including those contributing to more complex behaviors, such as feeding, egg laying, defensive and aggressive behavior, and learning. In only a few instances have serotonin receptors from these organisms been molecularly identified and their homology compared with vertebrate 5-HT receptors. Several 5-HT receptors with homology to human 5-HT<sub>1A</sub> and 5-HT receptors are found in drosophila, however, and have been molecularly characterized.<sup>10,11</sup>

Some examples of the anatomical and physiologic complexity of serotonergic transmission are discussed in several following sections of this article. The basis for this complexity has been attributed to phylogenetic ancestry, multiple mechanisms of actions, and also the possible need for integration of the many physiologic functions subserved by 5-HT.<sup>12,13</sup>

## MULTIPLE SEROTONIN RECEPTORS AND PHARMACOLOGIC EFFECTS

For a long time, the pharmacology of serotonin neurotransmission has been complicated by the moderate-to-marked homology within and sometimes across receptor subtypes (except 5-HT<sub>3</sub> receptors, which have almost no structural homology to the other 5-HT receptors). Some older ligands with high affinity for almost all serotonin receptor subtypes (e.g., lysergic acid diethylamide, 5-CT, and metergoline) have provided the first clues used to identify some of the more recently discovered receptors (some discovered as "orphan" cloned receptors) as being serotonin receptors, e.g., 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors.<sup>13-16</sup>

Among some of the "classic" 5-HT receptor subtype agents, 8-OH-DPAT appeared to have highly selective affinity for 5-HT<sub>1A</sub> receptors sites and considerably lesser affinity for other 5-HT<sub>1</sub> sites, as well as 5-HT<sub>2</sub> sites. It constituted an example of 1 of the few agents with selective pharmacologic agonist effects on the 5-HT<sub>1A</sub> receptor

**Table 5. 15 Molecularly Identified Serotonin Receptors and Their Signal Transduction Mechanisms\***

Receptor	Effector	Signal Transduction
5-HT <sub>1A,B,D<math>\alpha</math>,D<math>\beta</math>,E,F</sub>	G <sub>i/o</sub>	↓Cyclic AMP, ↑K <sup>+</sup> channel
5-HT <sub>2A,B,C</sub>	G <sub>q/11</sub>	IP-3, DAG, cyclic GMP
5-HT <sub>3</sub>	...	Ligand-gated ion channel; IP-3
5-HT <sub>4</sub>	G <sub>s</sub>	↑Cyclic AMP
5-HT <sub>5<math>\alpha</math>,5<math>\beta</math></sub>		Unknown
5-HT <sub>6</sub>	G <sub>s</sub>	↑Cyclic AMP
5-HT <sub>7</sub>	G <sub>s</sub>	↑Cyclic AMP

\*Other former names and identities: 5-HT<sub>2A</sub> = 5-HT<sub>2</sub>, 5-HT<sub>2B</sub>; 5-HT<sub>2C</sub> = 5-HT<sub>1C</sub>; 5-HT<sub>3</sub> = M; 5-HT<sub>F</sub> = 5-HT<sub>1EB</sub>; also briefly designated 5-HT<sub>6</sub>. Abbreviations: AMP = adenosine monophosphate; DAG = diacylglycerol, GMP = cyclic guanosine monophosphate, IP-3 = phosphatidyl inositol.

across a wide range of physiologic functions regulated by 5-HT, including temperature, food intake, motor activity, and neuroendocrine functions. Recently it has become known that 8-OH-DPAT also has appreciable affinity for 5-HT<sub>7</sub> receptors.<sup>16</sup> Since, however, at present the pharmacology and function of the 5-HT<sub>7</sub> receptor remain undefined, it is not clear if any effects of 8-OH-DPAT previously related to 5-HT<sub>1A</sub> actions may actually represent 5-HT<sub>7</sub>-mediated actions.

Among agents acting at 5-HT<sub>2</sub> receptors, 1-(2,5-dimethoxy-4-phenyl)-2-aminopropane (DOI) and its congeners, DOB and DOM, have substantially greater affinity for 5-HT<sub>2</sub> sites than for any other sites (including 5-HT<sub>4,5,6,7</sub>). The agonist effects of DOI at 5-HT<sub>2A</sub> versus 5-HT<sub>2C</sub> receptors were difficult to separate, despite the fact that the 5-HT<sub>2A</sub> antagonist ketanserin (in vivo) and, more clearly, spiperone (in vitro only, because of its strong dopamine antagonist properties) were shown to possess greater 5-HT<sub>2A</sub> antagonist than 5-HT<sub>2C</sub> antagonist effects. Nonetheless, differences in the physiologic alterations produced via 5-HT<sub>2A</sub> versus 5-HT<sub>2C</sub> receptors became apparent only in paradigms that employed repeated administration of DOI versus *m*-chlorophenylpiperazine (*m*-CPP), a relatively selective 5-HT<sub>2C</sub> agonist, in investigations in rats.<sup>17,18</sup> Recently, antagonists with greater affinity for 5-HT<sub>2A</sub> vs. 5-HT<sub>2C</sub> (e.g., MDL-100,907; SB-206553) have been synthesized, and reports of their selective efficacy on functions thought to be mediated by 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> receptors are emerging, although, as yet, are incomplete.<sup>19,20</sup>

Among agents acting at 5-HT<sub>3</sub> receptors, highly selective antagonists, including granisetron, ondansetron, and tropisetron have been identified.<sup>21</sup> In contrast, few high affinity, high potency 5-HT<sub>3</sub> agonists have been found, although 2-methyl-5-HT and *m*-chlorylbiquanide exhibit some selectivity at 5-HT<sub>3</sub> sites.

The pharmacology of 5-HT<sub>4</sub> receptors has been aided by the identification of some selective agonists (ML-10302, RS-67506, and BIMU-8) and antagonists (SB-204070, GR-113808, and RS-39604). The pharmacology of the 5-HT<sub>7</sub> subtype is developing rapidly, but that

of the 2 5-HT<sub>5</sub> variants and the 5-HT<sub>6</sub> receptor subtype remain largely unknown at this time.<sup>13,16,22-24</sup>

With regard to 5-HT receptor pharmacology, one general issue needs to be emphasized. While many characteristics of molecules involved in serotonergic transmission are conserved across vertebrate species, this conservation cannot be assumed a priori. Some examples include the following: The human and rat 5-HT<sub>1B</sub> receptors share 97% sequence homology, yet their responses to pharmacologic agents differ greatly.<sup>25</sup> The human (and guinea pig) 5-HT<sub>1D</sub> receptors are 5-HT terminal autoreceptors, and this same function is subserved in rodents by 5-HT<sub>1B</sub> receptors. The pharmacology of 5-HT<sub>1D/1B</sub> receptor is very similar across primate and rodent species.<sup>25-31</sup>

5-HT<sub>1A</sub> presynaptic receptors subserve an autoreceptor function at somatodendritic sites located in the raphe area in both rodents and primates. The same 5-HT<sub>1A</sub> receptor molecule also subserves postsynaptic functions throughout the brain. All of the other serotonin receptors are located postsynaptically, although as noted below, some are found at some distance from serotonin-releasing terminals, especially in peripheral tissues, and thus have more in common with hormone receptors.<sup>13,32</sup>

#### **SOME EXAMPLES OF THE COMPLEXITY OF SEROTONERGIC INNERVATION IN SPECIFIC BRAIN REGIONS**

Rostral projections from the dorsal, median, and adjacent raphe nuclei have long been known to innervate various brain regions differentially. For example, the median raphe nucleus preferentially innervates the cingulate cortex, septal nuclei, and the hippocampus, whereas the dorsal raphe nucleus preferentially innervates the substantia nigra, striatum, amygdala, and nucleus accumbens.<sup>33,34</sup>

#### **Serotonin Neurotransmission in the Hippocampus**

The hippocampus is a clearly demarcated forebrain structure that is richly innervated by serotonergic, noradrenergic, and other neurotransmitter systems. It has long been regarded as a component of the limbic system, contributing to the appraisal and expression of both emotional behaviors and learning, particularly the learning of emotionally-related events.<sup>35</sup>

Different axonal pathways have been identified from the dorsal and median raphe 5-HT neurons to the hippocampus.<sup>33,34</sup> 5-HT neuronal cell bodies from the dorsal raphe nucleus project to the hippocampus via the fimbria-fornix and fasciculus cinguli pathways. Those 5-HT axons in the fimbria-fornix pathway are distributed to the hippocampal CA<sub>1</sub> and CA<sub>3</sub> layers and the molecular layer of the dentate gyrus of the hippocampus. These axons are very fine, with small varicosities, and are highly susceptible to damage by serotonin neurotoxins.<sup>32,36</sup> In contrast, axons from 5-HT neuronal cell bodies in the median raphe

nucleus reach the dentate gyrus, Ammon's horn, and subiculum regions of the hippocampus via the fasciculus cinguli pathway. These axons are thicker and have larger varicosities and greater resistance to damage by serotonin neurotoxins.

One illustration of how these separate anatomical fiber projections are accompanied by functional differences comes from studies of 5-HT<sub>1A</sub> receptor-mediated release of 5-HT in the hippocampus. The 5-HT<sub>1A</sub> agonist, 8-OH-DPAT, given systemically, has long been known to reduce 5-HT release in the hippocampus and other brain areas, such as the striatum and cortex, when measured via microdialysis cannulae placed in these brain areas. Electrophysiologic and other data identified the site of action of 8-OH-DPAT to be somatodendritic autoreceptors in the raphe nuclei area, and this was verified by the finding that 8-OH-DPAT, when administered directly into the microdialysis cannulae in the hippocampus, had no effect on 5-HT release.<sup>37</sup> However, injection of 8-OH-DPAT directly into the median raphe nucleus reduced 5-HT release in the hippocampus, while, interestingly, 5-HT release in the striatum was unchanged. In contrast, local injections of 8-OH-DPAT directly into the dorsal raphe nucleus did not reduce 5-HT release in the hippocampus, but did so in the striatum.<sup>37,38</sup>

#### **Serotonin Neurotransmission in the Cerebellum**

In comparison to other brain regions, 5-HT innervation of the cerebellum is sparse. Yet, recent investigations have revealed that this innervation is specifically organized along the same pattern as that of other more well-studied cerebellar neuronal networks. For example, the depolarization-induced release of glutamate from parallel/climbing fiber presynaptic terminals is inhibited by activation of 5-HT<sub>1D</sub> receptors.<sup>39,40</sup> Postsynaptic responses elicited by *N*-methyl-D-aspartate (NMDA) antagonists are inhibited by 5-HT via actions at 5-HT<sub>1A</sub> receptors<sup>40</sup> and also 5-HT<sub>2C</sub> receptors.<sup>41</sup>

Thus, a complex and well-organized serotonergic modulation of glutaminergic transmission via 3 5-HT receptors can be found in the cerebellum. Marcoli and co-workers<sup>41</sup> suggest that these interactions may play a role in the cerebral control of movement, including that associated with movement disorders such as cerebellar ataxia. This hypothesis is supported by recent data indicating some efficacy for 5-HT<sub>1A</sub> agents in clinical studies of cerebellar ataxia,<sup>42,43</sup> and another study demonstrating a relatively high density of 5-HT<sub>2C</sub> receptors in the cerebellum.<sup>44</sup>

#### **SEROTONIN-MEDIATED FUNCTIONS OUTSIDE THE BRAIN**

This review is primarily focused on brain serotonin neurotransmission, and is principally directed toward scientists and physicians with neuropsychiatric interests.

Brief mention needs to be made, nonetheless, of the function of serotonin in the periphery, first described in 1954.<sup>45</sup> Some of these functions, in fact, are directly mediated by the caudal raphe nuclei, which project into the cranial nerves and down the spinal cord. Other functions are found in cells that are embryonically associated with the neural crest, from which the raphe nuclei also differentiate, e.g., thyroid parafollicular cells.<sup>46</sup> Still other cells that transport, store, and release 5-HT by using the identical 5-HT transporter and MAO-B molecules as those found in brain have different embryologic origins, e.g., blood platelets and lung epithelial cells.<sup>47-49</sup> As a cautionary note, however, serotonin function has sometimes been studied in cultured cell lines, e.g., neuroblastoma cells. Many of these cell lines are of uncertain origin, and may exhibit ectopic gene expression. Thus, while they provide convenient models for studies, they may not contain normally present regulatory proteins or complete intracellular signaling elements; hence, studies in such systems could produce misleading conclusions.

The first identified physiologic function of serotonin was as a vasoconstricting substance.<sup>50</sup> It may not be a coincidence that the most recent and one of the most serious medical complications associated with an agent with a primary serotonergic mechanism of action was reported in 1997 when pulmonary hypertension and surprisingly common cardiac valve damage was discovered in obese individuals treated with fenfluramine—leading to the Federal Drug Administration (FDA) mandate to recall this drug.<sup>51,52</sup> It needs to be noted that several substituted amphetamines including fenfluramine and 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) have long been considered as potentially neurotoxic.<sup>53-56</sup> These agents act via the 5-HT transporter to release stored 5-HT. Other drugs like the SSRIs, which act by blocking reuptake of 5-HT, but which do not produce 5-HT release, have not been associated with neurotoxicity. In fact, in some models, SSRIs including fluoxetine and citalopram have been shown to prevent neurotoxicity, including apoptosis, produced by MDMA and fenfluramine.<sup>57,58</sup>

Serotonin has long been known to be present in most peripheral organs where it mediates, in part, the neural and local control of their functions.<sup>59</sup> High concentrations of 5-HT are present in the gut both as part of an enteric nervous system and in nonneural endocrine system cells (enterochromaffin cells).<sup>45,60,61</sup> 5-HT regulates many gastrointestinal functions, from peristalsis<sup>62,63</sup> to pancreatic secretion.<sup>64-67</sup> The cardiovascular system, including blood vessels, are now known to possess at least 4 different 5-HT receptors.<sup>68-70</sup> When they are examined comprehensively, some organs, such as the lumbar dorsal root ganglia and the cervical sympathetic ganglia, have been reported to have 6 and 7 different 5-HT receptors, respectively.<sup>71</sup>

The fundamental conclusion regarding incompletely studied serotonin subsystems in the periphery is that drugs

given to influence brain serotonin for therapeutic aims in neuropsychiatric disorders may also act in the periphery. Such actions may contribute to or complicate their effects in ways not yet completely understood.

## SEROTONIN NEUROTRANSMISSION AND CLINICAL NEUROPHARMACOLOGY

Despite the existence of 15 molecularly-identified serotonin receptors, most of which have been identified in human brain or cultured human cells, only a few 5-HT receptor subtype selective agents are available as pharmacologic therapeutic agents, and only for limited indications. Ondansetron and granisetron (5-HT<sub>3</sub> antagonists) are available for the treatment of emesis associated with anticancer chemotherapy. Sumatriptan (a 5-HT<sub>1D</sub> ligand) is available for the treatment of migraine headaches. One 5-HT<sub>1A</sub> partial agonist, buspirone, is available for the treatment of anxiety disorders.

While nonselective inhibitors of MAO-A/B are available as antidepressants, moclobemide, a more recently developed selective MAO-A inhibitor, is available in many countries, but not in the United States. No drugs acting on the serotonin synthesis pathway are available. L-tryptophan had been available as a nonprescription dietary supplement, but there are few data that increased oral L-tryptophan (at least in combination with a normal diet, or without coadministration with other drugs) leads to any increase in serotonin-mediated functions.

Thus, despite the intricacies of multiple serotonin subsystems served by 15 different serotonin receptors, SSRIs, such as fluoxetine, paroxetine, sertraline, and citalopram, remain the most widely-used class of serotonin-selective agents of therapeutic benefit available (Table 2). Their mechanisms of action are complex and may vary across different disorders (for reviews, see references 72-74). The SSRIs differ with respect to many properties, including 5-HT transporter affinity, pharmacokinetic properties (including absorption, duration of action, presence of active metabolites and interactions via drug metabolizing enzymes with other drugs), as well as other properties, such as additional direct effects on serotonin receptors in the case of some SSRIs and their metabolites,<sup>75-77</sup> and effects on other neurotransmitter systems.<sup>78-84</sup>

## CHANGES IN SEROTONIN-RELATED FUNCTIONS FOLLOWING TRANSGENIC DELETIONS OR ALTERATIONS OF MOLECULAR COMPONENTS OF THE SEROTONERGIC NEUROTRANSMITTER SUBSYSTEMS

The newest evidence demonstrating contributions of serotonergic transmission to physiology and behavior, particularly in the complex nervous system of vertebrates, is the use of transgenic methodology to delete single mo-

lecular components of the 5-HT neurotransmitter system. This has been accomplished for several 5-HT receptors and the 5-HT transporter. These models are in the early stages of study, but have provided both expected and unexpected additional knowledge of 5-HT-mediated functions.<sup>85-90</sup>

### 5-HT<sub>2C</sub>-Deficient Mice

These mice were generated by introducing a nonsense mutation into exon 5 of the gene encoding the 5-HT<sub>2C</sub> receptor, thereby placing a stop codon within the fifth putative transmembrane segment and eliminating the carboxy terminal half of the protein. These mice do not exhibit apparent developmental defects and are fertile. Their most obvious phenotypic difference is manifested by the occurrence of spontaneous seizures and a markedly greater susceptibility to sound-induced seizures.<sup>91,92</sup> These mice are also overweight and do not respond to *m*-CPP, an appetite-suppressant agent in rodents and humans whose principal effects long have been thought to be mediated by 5-HT<sub>2C</sub> receptors.<sup>91,93-95</sup>

### 5-HT<sub>1B</sub>-Deficient Mice

These mice also appeared developmentally normal. However, they were unresponsive to the locomotor enhancing effects of the 5-HT<sub>1A/1B</sub> agonist, RU-24969, and also demonstrated reduced sensitivity to selective 5-HT<sub>1B</sub> autoreceptor agonists.<sup>14,96</sup> Because a number of agents that are thought to act via 5-HT<sub>1B</sub>-mediated actions have anti-aggressive activity, aggressive behavior was investigated in these mice. After a period of isolation, mice lacking 5-HT<sub>1B</sub> receptors were found to show increased aggression in a standard resident-intruder paradigm of rodent aggression.<sup>14</sup>

### Other Transgenic Mice Models

Mice with a disrupted MAO-A gene were found to lack MAO-A enzyme activity and to have markedly elevated (up to 9-fold higher) brain serotonin concentrations during early development.<sup>97</sup> These mice displayed evidence of increased spontaneous aggression as well as increased aggression in the resident-intruder paradigm. They also exhibited altered mating behaviors and altered open-field behavior (more time in the center of the field).<sup>97-99</sup> While the latter change could be interpreted as an indication of a reduction in anxiety or fear-related behaviors, neuroanatomical evidence of alterations in the barrel fields of the somatosensory cortex raised the question of whether cognitive or sensory alterations might contribute to this behavioral difference. Of note, treating neonatal mice lacking MAO-A with the serotonin synthesis inhibitor, para-chlorophenylalanine (PCPA), partially restored the capacity to form cortical barrels.<sup>97,98</sup>

Increased aggressive behavior and decreased fear responses were also observed in mice deficient in

$\alpha$ -calcium-calmodulin kinase II ( $\alpha$ -CAMKII), a facilitator of presynaptic neurotransmitter release.<sup>100</sup> While alterations in 5-HT release were found in electrophysiologic studies of brain slices from these mice, further studies are required to evaluate a possible connection between serotonergic neurotransmission changes and the behavioral abnormalities they display.<sup>101</sup>

Further study also is needed of the deficit in fear conditioning observed when  $\alpha$ -CAMKII was transgenically expressed at high levels in the lateral amygdala and the striatum, but not in other forebrain areas.<sup>102</sup> Increased aggression, which was completely normalized by administration of 2 selective inhibitors of serotonin reuptake, zimelidine or clomipramine, also has been observed in a different transgenic model, mice overexpressing human growth factor.<sup>103,104</sup>

Preliminary data indicate that mice lacking the 5-HT transporter have apparently normal early development patterns, with intact feeding and mating behaviors.<sup>105</sup> However, these mice exhibit gene dose-dependent reductions in responses to serotonergic agents, including MDMA ("ecstasy") and 8-OH-DPAT.<sup>105-107</sup> While there is some evidence that serotonin regulates neural crest migration in rodents, and that excess serotonin, including that produced by SSRI administration, might lead to dysmorphogenesis,<sup>108,109</sup> the apparent physiologic and anatomical normality of these mice is in agreement with teratogenic surveys of pregnant humans exposed to SSRIs which indicated a lack or minimal risk of developmental problems.<sup>110-112</sup> These data raise the question of whether serotonergic neurotransmission, with all of its heterogeneity, is adaptively redundant, and that normal or near-normal function can be maintained despite a marked reduction or even total absence of a key component of this system, the 5-HTT, for example. This is in decided contrast with results from a similar knockout of the mouse dopamine transporter.<sup>113</sup> However, the possibility of localized, highly specialized alterations in somatosensory-related neuroanatomy and possibly function such as that found in some studies in rodents exposed to excess 5-HT or to SSRIs requires further investigation.<sup>97,98,114</sup>

## CONCLUSIONS

Unraveling the complexity of brain serotonergic transmission in attempts to link structure and function has proved to be a daunting task. The existence of different projection fields from the 2 rostral nuclei (dorsal raphe vs. median raphe), which use different pathways through the brain dually or singly to innervate some regions or specific neurons, has been demonstrated in vertebrate brain. The existence of 15 different serotonin receptors, some of which have opposite effects on other neurotransmitter system neurons (including dopamine, acetylcholine, and glutamate neurons), also has been demonstrated. Understand-

ing the mechanism of action of selective serotonergic agents that primarily target 1 serotonin receptor, e.g., the 5-HT<sub>3</sub> receptor, remains a reasonable goal.

The situation with drugs like the SSRIs, however, is far more complicated. These drugs, as well as serotonin-releasing drugs like fenfluramine, initially act by increasing synaptic and other extracellular serotonin concentrations that, theoretically, could affect all 15 serotonin receptors. The therapeutic effects of the SSRIs may require 3 to 6 weeks of continued administration in depressed patients and as long as 10 to 12 weeks in patients with obsessive-compulsive disorder. These therapeutic effects are likely to depend upon adaptive events involving changes in the multiple 5-HT receptors, their signal transducing mechanisms, expression of genes for these receptors or other components of the system (5-HT synthetic enzymes, the 5-HT transporter), or trophic effects.<sup>115–118</sup> Similar adaptive events may occur in the other neurotransmitter or neuromodulator systems that interact with the serotonin systems. Thus, while even partial understanding of the final mechanisms involved in the therapeutic effects of drugs like the SSRI antidepressants continues to be elusive, the search for these mechanisms has been enhanced by powerful new research strategies.

*Drug names:* buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), dopamine (Dopastat, Intropin), fenfluramine (Pondimin), fluoxetine (Prozac), granisetron (Kytril), L-tryptophan (Trofan and others), ondansetron (Zotran), paroxetine (Paxil), sertraline (Zoloft), spiperone (Spiropitan), sumatriptan (Imitrex).

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# Cardiovascular Effects of Antidepressant Drugs: Updated

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The cardiovascular effects of tricyclic antidepressants (TCAs), including the propensity of these agents to be fatal in overdose, have been well described. It has been established further that even at therapeutic doses the TCAs may have untoward cardiovascular effects in the context of underlying ischemic heart disease. By comparison, the selective serotonin reuptake inhibitors (SSRIs) as a class are less likely to affect cardiovascular parameters in depressed patients who are otherwise healthy. Importantly, the SSRIs in overdose situations are enormously safer than TCAs and rarely have been associated with cardiotoxic effects when ingested alone. More recently, the safety and efficacy of several of the SSRIs have been evaluated in patients with existing ischemic heart disease. Although the studies have involved a limited number of patients, the available data suggest that SSRIs are not associated with adverse cardiovascular effects in these patients and are safer than TCAs in the treatment of depression in patients with heart disease. The prevalence of cardiovascular disease and the evidence that comorbid depression with cardiovascular disease (for example, following myocardial infarction) increases the risk of mortality underscore the importance of understanding the cardiac effects of antidepressants and the need for effective antidepressants that are free of adverse cardiovascular effects. At present, the SSRIs should be considered first-line agents for the treatment of depressed patients with cardiovascular illness, particularly ischemic heart disease. Among the SSRIs, those with a lower potential for causing pharmacokinetic drug interactions generally are preferred.

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Shortly after the antidepressant efficacy of the first tricyclic compounds became apparent, reports appeared describing overdose fatalities with these new drugs. Within a few years, it was clear that the vast majority of these overdose deaths were cardiovascular in nature. When imipramine first was marketed, the vast majority of drug-related suicide attempts involved barbiturate overdoses. However, by the late 1960s and early 1970s, benzodiazepines had replaced barbiturates as the most commonly used sedative, hypnotic drugs, and tricyclic antidepressants (TCAs) had replaced barbiturates as the most commonly ingested drugs in suicide attempts. By the late 1970s, 1500 to 2000 individuals a year killed themselves in TCA overdoses.<sup>1</sup>

## CARDIOVASCULAR EFFECTS OF TCAs

Although the cardiovascular risks of TCAs in overdose were evident by the mid-1960s, the implications of the cardiovascular effects of TCAs at usual therapeutic levels was not evident for more than a decade. In the mid-1970s, for example, some National Institute of Mental Health (NIMH) reviewers of our original grant proposal to study the cardiovascular effects of TCAs maintained that these compounds had no cardiac effects at usual therapeutic levels. A decade of work subsequently established that their cardiovascular effects were, in fact, limited as long as depressed patients remained free of cardiovascular disease.<sup>2</sup> In otherwise healthy depressed patients, the cardiovascular complications are more or less restricted to orthostatic hypotension, which most likely causes falls in 2% to 3% of treated patients. The frequency of orthostatic hypotension rises modestly in elderly patients; however, the adverse consequences of falling increase dramatically in the elderly. Fortunately, the risk is not the same across all of the TCAs. Nortriptyline, although not free of this risk, appears to be significantly less likely to result in falls than imipramine, desipramine, clomipramine, or amitriptyline.<sup>3</sup>

All TCAs have been shown to delay cardiac conduction and increase heart rate; however, in otherwise healthy adult patients, these effects seldom, if ever, are of any clinical significance. In children, the story is somewhat

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more complex. Here, this class of drugs regularly produces sustained elevation of blood pressure, and there persists a suspicion that treatment with TCAs, especially desipramine, can, on rare occasions, result in sudden death.<sup>4</sup>

In adults, the safety of the TCAs changes significantly in patients with overt heart disease. The frequency of orthostatic hypotension increases. In part, this may result from interactions with other drugs, but the change is particularly dramatic in patients with left ventricular impairment. Here, several studies have observed the development of orthostatic falls in as many as 50% of patients.<sup>5,6</sup> Another problem recognized many years ago is that the moderate prolongation of conduction characteristic of TCAs can become problematic in patients who already have conduction disease, especially bundle branch block,<sup>7</sup> since the TCA-induced delay could easily result in symptomatic rhythm disturbances and even death.

Another potential problem has become apparent that was not originally appreciated. In 1977, it was first reported that TCAs were class I antiarrhythmic drugs.<sup>8</sup> Originally this was thought to be beneficial in that if a depressed patient also had a ventricular arrhythmia, these compounds would seem likely to improve both conditions. In the late 1980s, to almost everyone's surprise, studies revealed that, although the usual class I drugs (which block sodium channels) were powerful antiarrhythmics, their long term use *increased* rather than decreased mortality.<sup>9</sup> It gradually became clear that, although these class I antiarrhythmic drugs under usual conditions suppress ventricular arrhythmia, they regularly become proarrhythmic when cardiac tissue becomes anoxic. This has proven to be true with quinidine, flecainide, encainide, and moricizine. Although no study has been conducted specifically to test whether, under anoxic conditions, a TCA would increase mortality, because the action of TCAs on the heart is so similar to other class I antiarrhythmics, it would be prudent to assume they would carry the same risk in patients with ischemic heart disease.<sup>10</sup>

Considering the problems associated with class I antiarrhythmics and the conduction and orthostatic effects, TCAs probably should never be the initial treatment in a depressed patient with cardiac disease, especially ischemic disease. The TCAs remain potent antidepressant drugs and under certain conditions their use in depressed patients with heart disease might still be warranted; however, one would need to balance carefully the risks and benefits for each individual patient.

### OVERDOSE EXPERIENCE WITH SSRIs

The initial concern that TCAs might have cardiotoxic properties came from experience with these drugs in overdose. One of the dramatic differences between the TCAs and the selective serotonin reuptake inhibitors (SSRIs) is that SSRIs are remarkably less likely to be life-threatening

even when ingested in fairly dramatic overdoses.<sup>11</sup> There is a propensity to wonder whether an SSRI ingested alone ever can cause death, and the answer is clearly yes. However, it is important to remember that for many years TCA usage resulted in 1500 to 2000 overdose deaths per year. Although the prescribing information for all SSRIs alludes to rare occurrences of fatal overdoses with these drugs, there are only 2 well-documented deaths reported in the literature from ingestion of SSRIs alone during the decade since they were introduced: one with fluoxetine<sup>12</sup> and the other with citalopram.<sup>13</sup> In both cases the patients ingested what would amount to a 6-month supply of drug at the usual dose of 20 mg per day.

Overdose cases can be informative about potential cardiovascular problems at normal therapeutic levels. This was certainly true for the TCAs for which conduction delays and arrhythmia were absolutely characteristic of overdose, even when only moderately severe. With SSRIs there is no similar clear signal. Most SSRI overdoses result in no significant clinical symptomatology; however, when symptoms develop following ingestion of large doses of SSRIs, the most common serious event is seizure—not cardiotoxicity.

The majority of cases in which SSRI ingestion was associated with mortality involved the coingestion of either alcohol or benzodiazepines; however, without more detailed descriptions of pathologic findings in deaths following SSRI overdose, it is not possible to establish the mechanism of toxicity. It is conceivable that the seizurogenic qualities of the SSRIs in overdose, combined with the effect of alcohol and benzodiazepine withdrawal to lower the seizure threshold, could produce status and death. It has been reported in some cases of mixed SSRI/alcohol/benzodiazepine overdoses that QRS or QT prolongations have occurred. However, status itself can result in such prolongations, and, as a result, it is unclear if the cardiac changes are a direct effect of the drug or secondary to seizures.

There are 2 large reported series of overdose cases with SSRIs. One regional group of the U.S. Poison Control Center reported 234 fluoxetine cases,<sup>14</sup> and, similarly, a Swedish Poison Information Centre reported 159 cases of citalopram ingestion.<sup>15</sup> The 2 studies involved over 400 overdoses, and both are notable for the lack of fatalities. Curiously, the citalopram overdose cases reported in the Swedish study involved, on average, a considerably higher level of ingestion. Five of the Swedish cases were known to have ingested more than 1900 mg (about 100 times the usual daily dose), and all of these patients had either seizures or conduction delays (wide QRS) or both. Of 18 cases in which 600 mg–1900 mg of citalopram was ingested, 6 experienced QRS widening and seizures.

None of the fluoxetine cases reported in the U.S. series involved ingestion of more than 1500 mg of drug, and none showed QRS widening, although seizures occurred

in 2 of the 7 cases in which 600 mg–1200 mg of fluoxetine was ingested. Thus, even in cases of rather substantial SSRI overdose, except for tachycardia and occasional QRS widening, there is little evidence for cardiovascular toxicity. The most common serious problem, if any serious problem at all arises, is seizures. Although less evidence is available with either paroxetine or sertraline, the story would seem to be the same.

### CARDIOVASCULAR EFFECTS OF SSRIs

Although the relative lack of toxicity in SSRI overdose is reassuring, the ultimate test of safety comes only from treating depressed patients with coexisting cardiovascular disease. Until very recently, no such studies were available. Some information was available from studies with each of the SSRIs in which cardiovascular measures were obtained in otherwise healthy depressed patients.<sup>16–19</sup> These studies frequently showed a very modest slowing of pulse rate, but no influence on either resting or postural blood pressure and no influence on PR, QRS, or QT<sub>c</sub> intervals. Measures of cardiac contractility or irritability were not likely to be informative in patients with healthy hearts and were not obtained.

The only potential problem that could be documented from early clinical experience with SSRIs was a very occasional report of severe sinus bradycardia.<sup>20</sup> These reports have occurred with all of the SSRIs, and no clear mechanism has been established. Paradoxically, there also are infrequent reports of supraventricular tachycardia, particularly with fluoxetine.<sup>21</sup> However, the reports of tachycardia are so rare that it is not obvious that these cases are drug-induced.

#### Use of SSRIs in Patients With Cardiovascular Disease

In 1996, the first systematic studies of SSRIs in patients with preexisting cardiac disease have appeared. The first of these studies examined 27 inpatients with both serious depression and serious, but stable, cardiovascular disease, who were treated with fluoxetine.<sup>22</sup> These patients had conduction disease, arrhythmia, impaired contractility, or some combination of the 3 conditions. In most cases, these symptoms were the result of ischemic heart disease. However, none of the patients was less than 4 months post-myocardial infarction. These patients were started on fluoxetine 20 mg/day and, after 2 weeks, if they could tolerate it, were raised to 60 mg/day. The average dose after 6 weeks actually reached 50 mg/day. In spite of this unusually high dose in a group of patients who averaged 77 years of age, almost no cardiovascular effects and certainly no evidence of cardiac harm were seen. Pulse rate did slow slightly as had been reported previously, but that slowing did not increase even though the average blood level almost quadrupled between weeks 2 and 6. There were negligible effects on both resting and postural blood pressure

and no evidence of orthostatic hypotension, even in patients with impaired left ventricular function (in whom TCAs are particularly problematic). There was no effect of fluoxetine treatment on conduction, even in patients with preexisting conduction disease. In those patients with ventricular ectopy at baseline, there was no evidence of either proarrhythmic or antiarrhythmic activity. The one surprise was that among those patients with evidence of impaired cardiac contractility at baseline, ejection fraction improved during treatment with fluoxetine. The improvement—though modest—was clinically significant; however, since the finding was post hoc and because the number of patients with baseline impairment of ejection fraction was small, replication is needed.

The second study in depressed patients with heart disease involved 40 patients treated with paroxetine compared with 40 treated with nortriptyline.<sup>23</sup> All were outpatients who suffered from chronic but stable cardiovascular disease. Both the degree of cardiac impairment and the severity of depression were less than that in the patient population exposed to fluoxetine. Those issues notwithstanding, the cardiovascular effects of paroxetine were very similar to those observed with fluoxetine. As with fluoxetine treatment, there was observed a modest (4 beat per minute) decrease in heart rate at 2 weeks among patients treated with paroxetine. The dose of paroxetine also was raised after 2 weeks—but only by 50%. Thus, a less dramatic increase in blood levels was observed, compared with the fluoxetine study. Somewhat surprisingly, the initial bradycardia observed at week 2 had disappeared by week 6, and heart rate returned essentially to baseline values even though the paroxetine dose was higher. As with fluoxetine, there was no influence of paroxetine on resting systolic or diastolic blood pressure, nor evidence of orthostatic hypotension. Similarly, there was no evidence of intracardiac conduction delays. The study's authors further noted that, compared with nortriptyline, paroxetine was associated with a lower incidence of adverse cardiovascular effects.<sup>23</sup>

#### Effects of SSRIs on Platelet Activity

While the paroxetine study did not measure drug effects on left ventricular function, it did include measures of platelet function. An increasing awareness of the role thrombus formation plays in the onset of myocardial infarction and an increasing awareness of the association between depression and ischemic heart disease have led to increased attention to issues of platelet function. The marked effect of SSRIs on platelet serotonin has been known for some time, although the effect of SSRIs on platelet function had not been investigated previously. In the paroxetine study, the Pittsburgh site elected to examine platelet factor 4 and  $\beta$ -thromboglobulin. Both proteins are extruded when the platelet shifts into an activated or more “sticky” state, and a rise in levels of these proteins is associated with increased readiness of the platelet to aggregate.

Pollock and Laghrissi-Thode made 2 striking observations: prior to treatment, depressed cardiac patients had markedly elevated levels of these 2 proteins compared with non-depressed cardiac patients, and, when depressed patients were treated with paroxetine but not with nortriptyline, these levels returned significantly toward control values.<sup>24,25</sup> The baseline elevations in these markers of platelet activation are consistent with recent epidemiologic data indicating that not only are depressed individuals more likely to die of cardiovascular disease, but they are also more likely to develop a first myocardial infarct than their non-depressed counterparts.<sup>26</sup> In this study, the reduction in platelet stickiness observed with paroxetine treatment was in addition to the contribution of aspirin, which most of these patients were receiving to reduce the propensity of their platelets to aggregate. There are some data with citalopram to suggest that this characteristic is a general property of the SSRI drugs and not unique to paroxetine.

Indeed, the putative antiplatelet activity of SSRIs possibly could explain the occasional episode of bleeding that has been reported with these agents. However, in patients who are post-infarction or at risk for other thrombotic diseases, an SSRI effect to reduce platelet "stickiness" might serve a beneficial function.

### Use of SSRIs Post-Myocardial Infarction

Evidence also has been accumulating that patients experiencing depression in the immediate post-infarction period are at markedly increased risk for death. The 1993 study by Frasure-Smith and colleagues in particular raised the issue of treating depression in the immediate post-infarction period.<sup>27</sup> However, treatment of these patients with TCAs would be of concern because of the TCAs' class I antiarrhythmic activity. It is not yet clear whether another antidepressant would be less troublesome. The SSRIs are a reasonable choice because of their widespread use and their lack of obvious toxicity. However, even the 2 studies just described, with fluoxetine and paroxetine, avoided including patients within 4 to 6 months of infarction.

The only data available in the immediate post-infarction period are from a pilot study of 26 patients treated with sertraline.<sup>28</sup> These patients were identified as depressed while still hospitalized after an infarction, and treatment began, on average, within 1 month of infarction. In spite of focusing on this high-risk period, again there was no evidence of harm. As in the other studies, neither blood pressure (supine or standing) nor conduction measures showed any evidence of change. Unlike the fluoxetine and paroxetine study groups, the post-infarction population was followed for 12 rather than 6 weeks. One difference between the studies' findings was that sertraline-treated patients never showed any evidence of bradycardia. As was observed in the fluoxetine study, sertraline-treated patients showed an increase in ejection fraction over the course of the study. However, this observation is harder to interpret since the

initial measure generally was made within 2 weeks after infarction, and, if the patient survives, the pump function of the heart often will show evidence of recovery. The same is true of ventricular arrhythmia. Arrhythmia is not uncommon in the post-infarction period and, again, if the patient survives, the incidence often decreases over time. In fact, this was observed in the sertraline study. To determine whether the antiarrhythmic effect or the improvement in ejection fraction is the result of sertraline treatment or whether such changes merely reflect recovery in patients who survive infarction would require a placebo-controlled group. Nevertheless, it is encouraging that patients could tolerate an SSRI in the immediate post-infarction period without difficulty.

There had been some question about the effect of a serotonergic drug on a patient with a recently injured coronary artery. Serotonin in healthy coronary arteries produces vasodilation; however, serotonin injected in human coronary arteries with evidence of intimal damage results in vasoconstriction.<sup>29</sup> It is not clear to what extent administering an SSRI may increase free serotonin levels in circulating blood, especially blood reaching the coronary arteries. The accepted wisdom has been that, at least initially, SSRIs increase serotonin in the synaptic cleft and that, because reuptake is blocked, some of the excess will find its way into the plasma. Ordinarily a large fraction of that plasma serotonin is taken up into platelets, but the SSRIs block this uptake as well as that in the cleft. The largest source of this excess serotonin comes from the gut, and, although platelet reuptake is reduced, this serotonin-rich blood enters the liver via the portal circulation before reaching the general circulation. The liver is rich in monoamine oxidase (MAO) and can readily deaminate serotonin. Thus, it remains unclear to what degree serotonin in the general circulation actually rises. One of the few reports that attempted to measure the level of circulating serotonin after SSRI treatment found it to be reduced rather than increased.<sup>30</sup> Whatever happens and regardless of theoretical considerations, it is reassuring that no clinical evidence of coronary vasoconstriction following SSRI treatment was observed.

Taking this information together certainly suggests that the SSRIs as a class are safe in depressed patients with heart disease. However, it is important to recognize that the total number of patients in the 3 studies described here is only 96, and of that number, only 26 are patients in the immediate post-infarction period. Ninety-six patients do not establish safety. There is a wide variety of cardiac pathology, and what may be safe in one situation may not be safe in another. For example, it is not understood why very occasionally patients taking SSRIs develop severe bradycardia. In general, it would seem that SSRIs slow the heart a few beats per minute and that, after a few weeks, even this modest slowing seems to diminish or disappear. Interestingly, in overdose, the characteristic effect on heart

rate is not bradycardia, but rather tachycardia. Rare cases of supraventricular tachycardia have been reported at normal therapeutic levels of these drugs. Why these rare deviations in heart rate occur remains unclear, and whether this might pose a problem for patients with unrecognized sinus node disease also is uncertain. For the vast majority of patients, however, even those with heart disease, rate changes are not a problem with SSRIs.

### Other Cardiovascular Effects of SSRIs

The SSRIs show no propensity to produce either systolic or diastolic hypertension. In contrast, both bupropion and venlafaxine in adults and TCAs in children and adolescents can raise blood pressure.<sup>31</sup> Most importantly, and in marked contrast to the TCAs and MAOIs, the SSRIs show no proclivity to produce orthostatic hypotension. This appears true even in those with impaired left ventricular function at baseline. Again, in contrast to the TCAs, there has been no evidence of conduction prolongation by SSRIs in either the large data sets collected by the manufacturers in essentially healthy patients or in the limited number of cases with preexisting conduction disease. Conduction changes have been reported in a small number of very severe overdose ingestions of SSRIs. However, even in those limited cases, at least some of the changes may be secondary to seizures that are reported to occur in SSRI overdose situations.

Similar to the TCAs, there has been no evidence of SSRIs causing harm to the pump function of the heart. In a post hoc analysis, there was even the suggestion that patients with impaired left ventricular ejection fraction at baseline improved following SSRI treatment, but this is an observation that needs replication. The influence, if any, of SSRIs on arrhythmia is the most difficult to establish. This is because the only patients that are informative are those who suffer both depression and arrhythmia. In addition, ventricular arrhythmia is inherently a highly variable condition, so to make any evaluation certainly requires an unusually large sample. The number of patients studied to date is quite limited, and any statement at this time must be guarded. Nevertheless, the data available show no evidence of any antiarrhythmic activity and, even in massive overdoses, SSRIs have not been associated with malignant arrhythmia.

### DRUG-DRUG INTERACTIONS WITH SSRIs

While the use of SSRIs for the treatment of depression in cardiac patients generally appears to be safe, it is important to remember that these patients frequently will be receiving other medications for their conditions. The potential for SSRIs to cause pharmacokinetic drug-drug interactions is therefore of concern, and the risk is not the same for all agents.<sup>32</sup> For example, fluoxetine and paroxetine are highly potent inhibitors of the P450 2D6 isozyme, which

is responsible for the metabolism of a number of cardiovascular medications. In contrast, sertraline and fluvoxamine are nearly an order of magnitude less potent than fluoxetine and paroxetine in 2D6 inhibition, and citalopram and venlafaxine are at most only weak inhibitors of 2D6. With respect to the 2C19 isozyme, fluvoxamine is a highly potent inhibitor, whereas fluoxetine and sertraline are moderate inhibitors, paroxetine is a mild inhibitor, and citalopram and venlafaxine cause minimal or no inhibition. Thus, in selecting an antidepressant for the treatment of a depressed cardiac patient, an SSRI with a lower potential for causing pharmacokinetic drug interactions generally is preferred.

### COMMENT

It is clear that the use of SSRIs in cardiac patients is associated with considerably less risk than the use of TCAs. There is little or no information available on other antidepressant drug classes in patients with overt cardiac disease. Neither venlafaxine nor mirtazapine have been studied in populations with known heart disease. Bupropion has been examined in depressed patients with stable but significant heart disease and no problems with conduction, contractility, or orthostatic hypotension were observed.<sup>33</sup> There was some evidence of antiarrhythmic activity. The only obvious concern with bupropion involved the occasional occurrence of significant elevation of blood pressure; however, only 27 patients in total were studied. Even with the SSRIs, for which 3 different studies have looked at a total of 96 patients with comorbid heart disease, the power to see a problem—if one exists—is quite limited. This is particularly true for the period following myocardial infarction, for which only a pilot study with 26 patients treated with a single drug, sertraline, has been conducted. Although the available information is limited, both the commonness of cardiovascular disease in later life and the strong evidence that depression after a heart attack greatly increases the risk of death make the need for antidepressant drugs that can be used safely in this group imperative. To determine whether treating depression after a heart attack will reduce the risk of mortality, it is essential first to prove that there are antidepressant drugs that are both safe and effective in this clinical population.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), flecainide (Tambocor), fluoxetine (Prozac), imipramine (Tofranil and others), mirtazapine (Remeron), moricizine (Ethmozine), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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# Drug Interactions With Newer Antidepressants: Role of Human Cytochromes P450

David J. Greenblatt, M.D.; Lisa L. von Moltke, M.D.;  
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Selective serotonin reuptake inhibitors and related antidepressant compounds have the secondary pharmacologic property of inhibiting the activity of human cytochrome P450 enzymes responsible for the oxidative metabolism of many drugs. A number of clinically important pharmacokinetic drug interactions are a consequence of these cytochrome inhibiting effects. This review evaluates the clinical implications of the metabolic profiles of the newer antidepressants, the relative activities of various new antidepressants as inhibitors of human cytochrome P450, and the various in vivo and in vitro methodologies that can be used for identification and quantification of drug interactions.

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The selective serotonin reuptake inhibitor (SSRI) and related "mixed mechanism" antidepressants are not clearly superior to traditional antidepressants in terms of therapeutic efficacy,<sup>1-3</sup> but the profile of clinical pharmacologic properties and side effects of these newer compounds clearly differs from that of the older antidepressants.<sup>4-16</sup> Of particular importance is the capacity of SSRIs and related antidepressants to inhibit the activity of human cytochrome P450 enzymes responsible for the oxidative biotransformation of many drugs used in clinical practice.<sup>17-24</sup> The possibility of pharmacokinetic drug interactions must be carefully considered during clinical use of the current generation of antidepressants. This is a com-

plex problem, since each new antidepressant and/or its pertinent in vivo metabolites can be anticipated to have a different activity or potency as an inhibitor of each specific human cytochrome. Understanding of the clinical issues has been helped by advances in the discipline of cytochrome chemistry, including the biochemistry, molecular genetics, and clinical functions of the human cytochromes P450.<sup>25-31</sup> Most clinical observations and studies of drug interactions with new antidepressants are in fact largely consistent with models based on molecular and in vitro data.<sup>32-36</sup> This field is advancing so rapidly that secondary sources as well as approved labeling language may be out of date or not in context. Review articles, product labeling information, and promotional material therefore should be evaluated critically, and recent primary sources consulted whenever possible.

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## METABOLISM OF ANTIDEPRESSANTS IN HUMANS

Clinically important metabolic products of some newer antidepressants are listed in Table I. Among the SSRIs, fluoxetine, sertraline, and citalopram all undergo *N*-demethylation in humans; the respective metabolites are norfluoxetine, desmethylsertraline, and monodesmethylcitalopram.<sup>19-24,37,38</sup> Some of these metabolites appear in plasma at levels similar to or higher than those of the parent drug, and the metabolites have values of elimination half-life longer than those of the respective parent compounds. Fluoxetine and norfluoxetine are similar to each other in SSRI activity,<sup>38</sup> as are citalopram and monodesmethylcitalopram.<sup>39,40</sup> Therefore parent drug and principal metabolite both contribute to clinical efficacy and

side effects during clinical treatment with fluoxetine or citalopram. In addition, fluoxetine and norfluoxetine both have cytochrome-inhibiting activity, and both will contribute to pharmacokinetic drug interactions. However, citalopram and monodesmethylcitalopram have weak or negligible cytochrome inhibiting activity. Desmethylsertraline, the principal metabolite of sertraline, has only weak SSRI activity compared to its parent compound<sup>41</sup>; both have equivalent, although generally weak, cytochrome inhibiting activity. In the case of paroxetine and fluvoxamine, clinically important metabolites in human plasma have not been identified.<sup>42,43</sup>

Nefazodone has the most complex metabolic profile among the "mixed-mechanism" antidepressants.<sup>44</sup> Nefazodone undergoes parallel biotransformations, yielding: (1) hydroxy products formed by hydroxylation at 2 sites on the molecule; (2) a triazoledione derivative; and (3) meta-chlorophenylpiperazine (*mCPP*) following cleavage of the molecule.<sup>45,46</sup> The triazoledione and the aliphatic hydroxy metabolite are present in human plasma in significant concentrations during chronic treatment with nefazodone, whereas *mCPP* levels are relatively low.<sup>46</sup> The antidepressant activity of the metabolites of nefazodone is not established. Venlafaxine is biotransformed by parallel demethylation reactions at 2 sites on the molecule.<sup>47</sup> The *O*-desmethyl derivative appears in plasma in levels exceeding those of the parent drug,<sup>48,49</sup> and both compounds have antidepressant activity. *N*-desmethylvenlafaxine is a relatively minor metabolite. Mirtazapine is biotransformed to *N*-desmethylmirtazapine as the principal metabolite.<sup>50</sup>

### IDENTIFICATION OF RESPONSIBLE CYTOCHROMES

Knowledge of the specific human cytochromes mediating biotransformation of antidepressants allows health care professionals to anticipate a number of clinically important factors contributing to regulation of metabolism of the antidepressants. Examples of such factors include the possibility of genetic polymorphism, as occurs with drugs metabolized by P450 2D6 or 2C19<sup>51-59</sup>; the possibility of extrahepatic contributions to metabolism as occurs with substrates of P450 3A that may be biotransformed in part in the gastrointestinal tract mucosa; and the profile of other compounds that may induce or inhibit metabolism (Table 2).

#### Research Methods

Cytochrome identification may be accomplished through a combination of clinical pharmacologic approaches as well as in vitro models. For specific cytochromes (P450 2C19 or 2D6) whose activities are regulated by a genetic polymorphism, that cytochrome may be inferred to participate in clearance of the drug under study, if that drug's clearance cosegregates with the clearance or metabolic ratio of a test substrate for the corresponding

**Table 1. Newer Antidepressants, Their Principal Metabolic Products, and Cytochromes Responsible for Biotransformation\***

Parent Compound	Important Metabolite(s)	Responsible Cytochrome(s)
Predominant SSRI Mechanism		
Fluoxetine	Norfluoxetine	2C9 (3A, 2D6)
Sertraline	Desmethylsertraline	2C9, 3A (others not established)
Citalopram	Monodesmethylcitalopram (Didesmethylcitalopram)	2C19, 3A (2D6)
Paroxetine	None described to date	2D6
Fluvoxamine	None described to date	1A2, 2D6
"Mixed" Mechanism		
Nefazodone	Triazoledione	3A
	Hydroxynefazodone ( <i>mCPP</i> )	3A
	<i>O</i> -Desmethylvenlafaxine ( <i>N</i> -Desmethylvenlafaxine)	2D6
Venlafaxine	<i>O</i> -Desmethylvenlafaxine ( <i>N</i> -Desmethylvenlafaxine)	3A, 2C19
Mirtazapine	Desmethylmirtazapine	3A (1A2, 2D6)
	(8-Hydroxymirtazapine)	2D6 (1A2)
	(Mirtazapine <i>N</i> -oxide)	3A (1A2)

\*Parentheses indicate metabolic products of relatively small quantitative importance.

**Table 2. Representative Index Reactions and Specific Chemical Inhibitors for Studies of Human Cytochromes P450**

Cytochrome P450	Index Substrates	Specific Inhibitor
1A2	Phenacetin	$\alpha$ -Naphthoflavone;
	Caffeine	furafylline <sup>a</sup>
2C9	Phenytoin	Sulfaphenazole
	Tolbutamide	
2C19	<i>S</i> -Mephenytoin	Omeprazole <sup>b</sup>
2D6	Dextromethorphan	Quinidine <sup>c</sup>
	Desipramine	
	Bufuralol	
	Sparteine	
	Debrisoquin	
	Chlorzoxazone	Diethyldithiocarbamate <sup>a,c</sup>
	Midazolam	Ketoconazole <sup>c</sup> ;
3A	Triazolam	troleanomycin (TAO) <sup>a</sup> ;
	Alprazolam	gestodene <sup>a</sup>
	Testosterone	
	Nifedipine	

<sup>a</sup>Mechanism-based inhibitor.

<sup>b</sup>Suitable as specific inhibitor in vitro (up to 10  $\mu$ M); less suitable in vivo due to metabolite, omeprazole sulfone.

<sup>c</sup>Suitable for human in vivo studies.

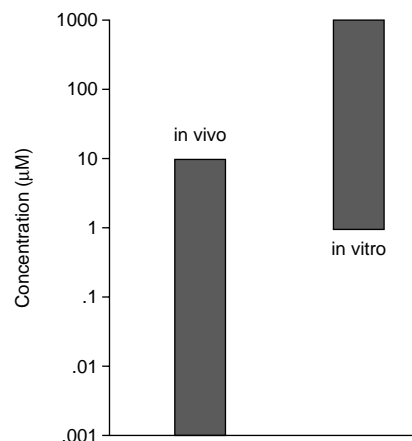
cytochrome, such as dextromethorphan for 2D6 or *S*-mephenytoin for 2C19. This population cosegregation approach has provided important data, but also has limitations and drawbacks. It is useful only when metabolism is mediated by polymorphically regulated cytochromes and qualitative (but not quantitative) contributions of a specific cytochrome can be identified. Furthermore, the method is indirect, and assumes that subject groups divided as "normal" and "slow" metabolizers are otherwise comparable with respect to activity of all other cytochromes. Confounded associations cannot be excluded and may lead to misidentification of responsible cyto-

chromes. Conclusions based on plasma concentrations of metabolites as opposed to parent drug may also be confounded, since the area under the plasma concentration curve for a metabolite depends on both its rate of formation from the parent compound as well as its own clearance, which may be mediated by a different cytochrome. A controlled crossover study of clearance of the drug in question, with and without coadministration of specific chemical inhibitor (Table 2), may presumptively identify the corresponding cytochrome if clearance is substantially reduced by the specific inhibitor. However such inhibitors must be safe and appropriate for clinical use, as well as have reasonable inhibitory specificity for the cytochrome in question.

In vitro models are being increasingly applied to identification of cytochromes mediating specific metabolic biotransformations.<sup>25-36</sup> Microsomal preparations of human liver in vitro contain the various human cytochromes in proportion to their quantitative representation in human liver in vivo. The capacity of a relatively specific chemical inhibitor (Table 2) to inhibit biotransformation of a specific substrate to its initial metabolite constitutes evidence supporting the participation of the corresponding cytochrome. The in vitro approach using chemical inhibitors has the obvious advantages over clinical studies of being less costly, more rapid in implementation, free of risk of human drug exposure, as well as offering a larger number of potential chemical inhibitors for this purpose and the possibility of assigning both quantitative and qualitative contributions of specific cytochromes. Antibodies with relatively specific inhibitory activity against the various human cytochromes can also be used to support or confirm data from in vitro chemical inhibition studies.<sup>60</sup> In recent years, the versatility of in vitro models has been increased by the availability of microsomes containing pure human cytochromes as expressed by cDNA-transfected human lymphoblastoid cells,<sup>61</sup> or other expression systems.<sup>62</sup>

Among the limitations of in vitro approaches is the need to utilize substrate concentrations that are one or more orders of magnitude higher than those encountered clinically, even accounting for the extensive uptake of some lipophilic drugs into liver that produces intrahepatic concentrations higher than those in plasma (Figure 1). In vitro studies of high substrate concentrations can be extrapolated down to a clinically relevant concentration range as long as mathematical models remain valid over the entire range.<sup>63</sup> However, a "high-affinity" metabolic reaction (i.e., one with a low  $K_m$ ) that contributes importantly to a drug's biotransformation at clinically relevant concentrations could be overlooked or underestimated in vitro if assay sensitivity limits impede study of substrate concentrations in that low range. The specificity of chemical inhibitor probes is of concern for in vitro as well as in vivo models. No inhibitory probe is completely specific for its corresponding cytochrome—all ultimately become

**Figure 1. Schematic Representation Showing a Typical Range of Antidepressant (and Metabolite) Concentrations Encountered in Human Plasma and Liver In Vivo, Compared With the Range Typically Studied Using In Vitro Models**

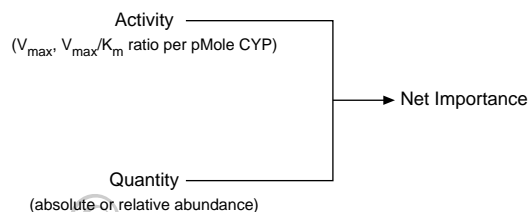


nonspecific at higher concentrations.<sup>64</sup> Ketoconazole, for example, has a relatively high specificity as an index inhibitor for P450 3A, as long as concentrations are below 1.0 µM; at higher concentrations specificity diminishes.<sup>64-66</sup> Omeprazole appears to have acceptable specificity as a P450 2C19 inhibitor at concentrations up to 10 µM. Above this range, specificity diminishes.<sup>67</sup> In vivo, omeprazole is biotransformed to a sulfone metabolite that has P450 3A inhibiting capacity. The SSRI fluvoxamine is not specific enough to serve as an index inhibitor, since it has moderate to strong inhibitory activity against P450 1A2, 2C19, 2C9, and 3A. Finally, the inferential strength of data from cDNA-expressed human cytochromes must be weighed against the intrinsic (and deliberate) limitations imparted by study of a single cytochrome removed from its usual cytochrome "mix." Studies of individual cytochromes can yield specific quantitative data on their activity as mediators of a specific reaction. However, an inference about the relative activity of different cytochromes either in vivo, or in liver microsomes in vitro, requires an independent estimate of the relative quantitative abundance of the cytochromes in question (Figure 2).<sup>61</sup>

### Cytochromes Mediating Biotransformation of Antidepressants

In vivo and in vitro studies have collectively provided estimated contributions of specific cytochromes to the metabolism of the newer antidepressants (Table 1). Clearance of fluoxetine in human subjects cosegregates with the P450 2D6 metabolic polymorphism, suggesting the conclusion that fluoxetine clearance is mediated by that cytochrome.<sup>68</sup> In vitro, however, 2D6 appears to be relatively unimportant, whereas 2C9 is the principal cytochrome, with a possible further contribution of 3A.<sup>69,70</sup> The discrepancy between in vivo and in vitro results could be ex-

**Figure 2. The Net Importance of a Specific Cytochrome as a Contributor to a Metabolic Biotransformation In Vivo, or in Liver Microsomal Preparations In Vitro, Depends on Two Factors\***



\*The two factors are the activity of that cytochrome as a mediator of the reaction, related to the  $V_{max}$  and to the  $V_{max}/K_m$  ratio (intrinsic clearance), and the quantitative abundance of that cytochrome.

plained by a confounded association of 2D6 phenotype in vivo with extremes in 2C9 activity. The in vitro methods may also have overlooked the participation of a low  $K_m$  (high-affinity) reaction mediated by P450 2D6 at low substrate concentrations that cannot be reliably studied. Sertraline clearance in vivo did not cosegregate with 2D6 metabolizer phenotype,<sup>68</sup> but the cytochromes contributing to its metabolism are not clearly established. P450 2C9 and 3A are likely to be involved to some degree, but the other contributing cytochromes are not known. Data on paroxetine and fluvoxamine are mostly indirect. Clearance of paroxetine cosegregates with 2D6 phenotype in vivo<sup>71,72</sup>; involvement of 2D6 is also supported by in vitro data.<sup>73</sup> Fluvoxamine clearance is associated with 1A2 and 2C9 activity in vivo, based on population cosegregation data,<sup>74,75</sup> as well as the observation of induced fluvoxamine clearance in cigarette smokers.<sup>76</sup> Biotransformation of citalopram to monodesmethylcitalopram depends on both 3A and 2C19 in vitro, with a possible small contribution of 2D6<sup>77,78</sup>; citalopram clearance in vivo cosegregates with 2C19 phenotype.<sup>38</sup> Nefazodone clearance is essentially completely dependent on P450 3A, based on in vitro data.<sup>79</sup> Formation of the principal metabolite of venlafaxine (*O*-desmethylvenlafaxine) is dependent mainly on 2D6; production of *N*-desmethylvenlafaxine, the minor metabolite, depends on a combination of 3A and 2C19.<sup>80,81</sup> Formation of the principal demethylated product of mirtazapine is mediated mainly by 3A, with additional contributions of 1A2 and 2D6.<sup>50</sup>

## INHIBITION OF HUMAN CYTOCHROME ACTIVITY BY ANTIDEPRESSANTS

### Research Methods

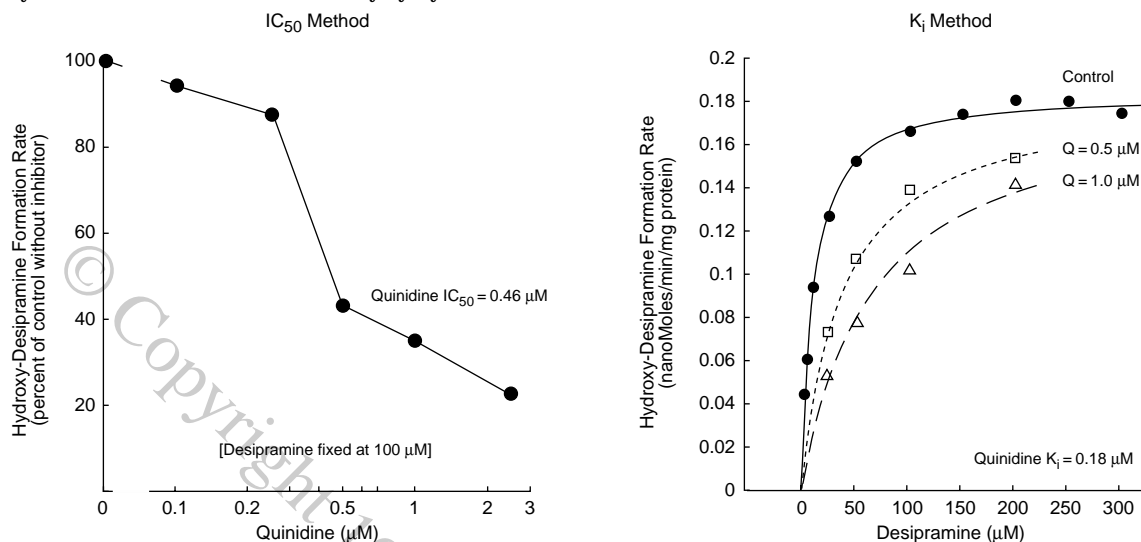
In vivo and in vitro approaches similar to those used for cytochrome identification are applicable to evaluation of antidepressants and their metabolites as potential inhibitors of specific human cytochromes. A controlled clinical pharmacokinetic study design, in which clearance of an index substrate (Table 2) is determined with and without

coadministration of the antidepressant in question, directly addresses the question in the human context. However, such studies have drawbacks, since they are costly, time-consuming, and involve finite (although small) risks of human drug exposure. Furthermore when the antidepressant being studied undergoes in vivo biotransformation itself,<sup>82</sup> any metabolic inhibition that is observed could be due to parent drug, metabolites, or both. There is no direct method to resolve the relative contributions of multiple potential inhibitors that are present simultaneously, nor of estimating the quantitative inhibitory potency of any one inhibitor.

Using in vitro models of human liver microsomes, a series of drugs and/or their metabolites can be screened relatively quickly at low cost, and with no human drug exposure, to determine quantitative inhibiting potency against specific index reactions presumed to reflect the activity of specific cytochromes with relatively high specificity (Table 2).<sup>32,36,83</sup> One approach uses a fixed concentration of the index substrate coincubated with variable concentrations of the inhibitor. The relation of decrement in metabolite formation rate versus inhibitor concentration yields an estimate of a 50% inhibitory concentration ( $IC_{50}$ ) (Figure 3). Values of  $IC_{50}$  are suitable for comparing the relative potency of a series of inhibitors, and are independent of the specific biochemical mechanism of inhibition. On the other hand,  $IC_{50}$  values depend on substrate concentration when inhibition is competitive, and cannot be directly applied to in vitro-in vivo scaling models, except when inhibition is established as having a noncompetitive mechanism.

A second approach utilizes the inhibition constant ( $K_i$ ), which reflects inhibitory potency in reciprocal fashion. Determination of  $K_i$  involves more work, time, and expense, since it requires study of multiple substrate concentrations and multiple inhibitor concentrations (Figure 3).  $K_i$  is model-dependent, since it depends upon the specific mechanism of inhibition,<sup>84</sup> which may not be established. Once determined,  $K_i$  is independent of substrate concentration and can be used under some defined conditions for quantitative in vitro-in vivo scaling of drug interactions.<sup>32-36</sup> Although  $K_i$  is less than or equal to  $IC_{50}$  as a general rule,  $K_i$  will be equal to  $IC_{50}$  if inhibition is noncompetitive, or if inhibition is competitive and the substrate concentration is far below the reaction  $K_m$ .  $K_i$  and  $IC_{50}$  both provide similar estimates of relative inhibitory potency for a series of inhibitors of a specific reaction, but the absolute values of  $K_i$  and  $IC_{50}$  do not cross different substrates for the same cytochrome. As an example, the inhibitory  $K_i$  values for SSRIs versus sparteine oxidation<sup>85</sup> do not equal the corresponding  $K_i$  values versus desipramine hydroxylation,<sup>65,86</sup> although the 2 metabolic reactions are mediated mainly by 2D6. However the relative inhibitory potency should be maintained across substrates for the same cytochrome.

**Figure 3. Comparison of Two In Vitro Methods for Determining the Inhibitory Potency of Quinidine Versus Desipramine Hydroxylation, a Reaction Mediated Mainly by Cytochrome P450 2D6\***



\*Studies were performed using microsomal preparations from human liver.

Left: A fixed concentration of desipramine (100 µM), considerably higher than the K<sub>m</sub> value of 10.2 µM, was incubated with varying concentrations of quinidine. Reaction velocities were expressed as a percentage of the control value without inhibitor. Nonlinear regression was used to determine the quinidine IC<sub>50</sub> value of 0.46 µM.

Right: Varying concentrations of desipramine were incubated with liver microsomes in the control conditions (without inhibitor), and with coaddition of two concentrations of quinidine. Control data were analyzed by nonlinear regression to determine the reaction V<sub>max</sub> and K<sub>m</sub>. Data with coaddition of quinidine were analyzed under the assumption of Michaelis-Menten kinetics with competitive inhibition. Note that the K<sub>i</sub> value for quinidine is smaller than the IC<sub>50</sub> value.

**Table 3. Inhibition of Human Cytochromes P450 by Newer Antidepressants\***

Antidepressant	Cytochrome P450					
	1A2	2C9	2C19	2D6	2E1	3A
Fluoxetine	+	++	+ to ++	+++	—	+
Norfluoxetine	+	++	+ to ++	+++	—	++
Sertraline	+	+	+ to ++	+	—	+
Desmethylsertraline	+	+	+ to ++	+	—	+
Paroxetine	+	+	+	+++	—	+
Fluvoxamine	+++	++	+++	+	—	++
Citalopram	+	0	0	0	0	0
Desmethylcitalopram	0	0	0	+	0	0
Nefazodone	0	0	0	0	—	+++
Triazolodione	0	0	0	0	—	+
Hydroxynefazodone	0	0	0	0	—	+++
Venlafaxine	0	0	0	0	—	0
O-Desmethylvenlafaxine	0	0	0	0	—	0
Mirtazapine	0	—	—	+	—	0

\*0 = minimal or zero inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = strong inhibition. Dash (—) indicates no data available.

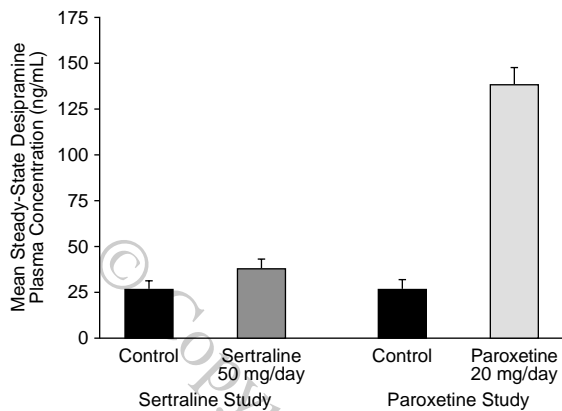
### Review of the Data Base (Table 3)

All sources consistently identify fluvoxamine as a highly potent inhibitor of P450 1A2,<sup>66,87,88</sup> causing large reductions in clearance of 1A2 substrates such as caffeine, clozapine, tacrine, and chloroguanide.<sup>89-93</sup> Although no systematic study has been published, a significant interaction of fluvoxamine with theophylline should be anticipated. Some of the other antidepressants show a weak to moderate capacity to inhibit 1A2 in vitro,<sup>66</sup> but significant

interactions in vivo are not clearly documented. Fluvoxamine also is the most potent of the newer antidepressants as an in vitro inhibitor of P450 2C9.<sup>94</sup> Labeling information describes a highly significant interaction of fluvoxamine with warfarin in a controlled pharmacokinetic study, but no published data are available. Fluoxetine (in particular the S-enantiomer) also is a significant 2C9 inhibitor in vitro,<sup>94</sup> and a number of case reports describe interactions with phenytoin in vivo.<sup>95</sup> Sertraline and desmethylsertraline are weak 2C9 inhibitors in vitro,<sup>94</sup> and sertraline did not interact with tolbutamide or phenytoin in vivo.<sup>96,97</sup> Nefazodone also produced no interaction with phenytoin in a clinical study.<sup>98</sup> Fluvoxamine is a highly potent inhibitor of 2C19, and significant interactions with 2C19 substrates should be anticipated in vivo.<sup>93,99,100</sup> Some of the other antidepressants demonstrate some degree of 2C19 inhibition in vitro, but the clinical significance of this is not established.

Inhibition of P450 2D6 activity by newer antidepressants is a topic receiving considerable attention in pharmaceutical promotional materials, which not uncommonly encourage the implication that inhibition of 2D6 by SSRIs is not clinically important, or that differences among SSRIs are unclear or indistinct. Particular studies or results may be cited out of their proper context to support this view. However, the scientific data on antidepressants and P450 2D6 are unequivocal, with close agreement of in vitro and in vivo results.<sup>32,65,86</sup> Fluoxetine, norfluoxetine,

**Figure 4. Mean  $\pm$  SE Steady-State Plasma Desipramine Concentrations in Studies of Human Volunteer Subjects\***



\*Adapted in part from reference 104. One group of volunteers received desipramine 50 mg daily in the control condition and with coadministration of sertraline 50 mg daily. A second group of volunteers received the same dose of desipramine in the control condition, and with coadministration of paroxetine 20 mg daily. Sertraline causes a small and statistically significant increase in plasma desipramine levels, whereas paroxetine causes a very large increase. The differential inhibition of desipramine clearance by sertraline and paroxetine in vivo is entirely consistent with changes anticipated based on in vitro studies.

and paroxetine are highly potent inhibitors of P450 2D6.<sup>65,86,101,102</sup> Usual therapeutic doses of fluoxetine or paroxetine, producing a usual range of steady-state plasma concentrations, typically impair clearance of 2D6 substrates such as desipramine by 70% or more, with steady-state plasma desipramine concentrations increasing 4-fold or more (Figure 4).<sup>102-108</sup> Interactions of this magnitude obviously are of clinical importance.<sup>102</sup> In contrast, sertraline, desmethylsertraline, and fluvoxamine have nearly an order of magnitude lower potency as 2D6 inhibitors than do fluoxetine, norfluoxetine, and paroxetine.<sup>65,86</sup> Coadministration of sertraline with desipramine will increase steady-state desipramine concentrations by 20% to 50%, depending on the daily dose and plasma concentration of sertraline (and desmethylsertraline) (Figure 4).<sup>103,104,108</sup> Citalopram, nefazodone, venlafaxine, and mirtazapine are at most weak 2D6 inhibitors.<sup>50,80,89,101,109,110</sup> It should be emphasized that inhibition of 2D6 activity will be evident only in subjects of the genetically "normal" metabolizer phenotype. Genetically "poor" metabolizers lack functional enzyme and already have low clearance of 2D6 substrates regardless of inhibitor coadministration.<sup>105,111</sup>

Biotransformation of drugs by cytochrome P450 3A is strongly inhibited by nefazodone both in vitro<sup>79,112</sup> and in vivo.<sup>113,114</sup> In clinical studies, nefazodone produces large decrements in clearance of 3A substrates such as alprazolam and triazolam.<sup>113,114</sup> Inhibition is attributable to nefazodone itself and to the hydroxylated metabolite, but not to the triazolidione metabolite or to *m*CPP.<sup>79</sup> Among the other antidepressants, fluoxetine itself is a weak 3A inhibi-

tor, but *N*-demethylation of this compound to form norfluoxetine results in moderate 3A inhibiting potency. This is a consistent finding across many in vitro studies (see review in reference 23). In clinical studies, coadministration of fluoxetine with substrates biotransformed partly or entirely by P450 3A isoforms (such as diazepam, alprazolam, carbamazepine, and amitriptyline) causes impaired clearance and elevated plasma concentration of these substrates (reviewed in reference 23). Some publications encourage the incorrect conclusion that fluoxetine and norfluoxetine are unlikely to be clinically important 3A inhibitors.<sup>115,116</sup> In any case it is clear that inhibition of 3A activity in vivo by fluoxetine, when it occurs, is attributable mainly to norfluoxetine,<sup>23</sup> which reaches significant plasma concentrations when fluoxetine treatment proceeds for a period of time.<sup>19,20</sup> A reported noninteraction of fluoxetine and terfenadine, for example, is attributable to the relatively low plasma norfluoxetine concentrations in the study participants,<sup>116</sup> inasmuch as norfluoxetine clearly inhibits terfenadine metabolism in vitro.<sup>117</sup> When fluoxetine treatment is discontinued, 3A inhibition may persist for some time thereafter due to slow elimination of norfluoxetine.<sup>118</sup> Understanding of 3A inhibition by fluoxetine is nonetheless incomplete, since fluoxetine did not importantly inhibit triazolam clearance<sup>119</sup> despite adequate plasma norfluoxetine levels and clear evidence of inhibition in vitro.<sup>112</sup> Sertraline, desmethylsertraline, and paroxetine are weak 3A inhibitors in vitro.<sup>86</sup> Sertraline produces small or undetectable clinical interactions with 3A substrates such as diazepam,<sup>120</sup> alprazolam (S. H. Preskorn, M.D., et al., unpublished data), and carbamazepine<sup>121</sup>; paroxetine produced no interaction with terfenadine. Fluvoxamine is a moderate 3A inhibitor in vitro<sup>86</sup> and in vivo.<sup>122,123</sup> Citalopram (L. L. von Moltke et al., unpublished data), venlafaxine,<sup>109,124</sup> and mirtazapine<sup>50</sup> are weak or negligible 3A inhibitors.

Citalopram and monodesmethylcitalopram are negligible inhibitors of P450 2E1 (L. L. von Moltke et al., unpublished data). The activity of other antidepressants as inhibitors of P450 2E1 has not been determined.

## COMMENT

The new generation of antidepressant agents made available over the last decade has broadened the therapeutic options for depressive illness, but also poses new complexities in terms of differences among drugs in metabolic disposition as well as the propensity to produce drug interactions. Treatment of depression in the current era requires application of therapeutic skills together with principles of clinical pharmacology. The use of multiple medications by depressed patients may contribute to increasing the probability of drug toxicity due to drug interactions. Clinicians can utilize in vitro and in vivo data to make a more informed choice among the newer antidepressants and anticipate and avoid possible drug interactions.<sup>83,102,125</sup>

*Drug names:* alprazolam (Xanax), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlorzoxazone (Paraflex), citalopram (Celexa), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), ketoconazole (Nizoral), midazolam (Versed), nefazodone (Serzone), nifedipine (Adalat, Procardia), omeprazole (Prilosec), paroxetine (Paxil), phenytoin (Dilantin and others), sertraline (Zoloft), terfenadine (Seldane), tolbutamide (Orinase), triazolam (Halcion), venlafaxine (Effexor).

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# The Use of Selective Serotonin Reuptake Inhibitors in Eating Disorders

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The introduction of selective serotonin reuptake inhibitors (SSRIs), which are, in general, safer and more easily tolerated than conventional antidepressants, has had a profound effect on the treatment of affective illnesses and obsessive-compulsive disorder (OCD). A number of symptoms associated with eating disorders overlap those of depression and OCD, suggesting a theoretical and practical case for evaluating the SSRIs in the treatment of anorexia nervosa, bulimia nervosa, binge-eating disorder, and obesity. Despite the expectations for SSRIs in the treatment of eating disorders, clinical investigations have yielded mixed results. In this paper, results from clinical studies of SSRIs (with and without concomitant psychotherapy) in the treatment of anorexia and bulimia nervosa, binge eating disorder, and obesity are reviewed, directions for future research are suggested, and practical recommendations for the clinician are provided. (*J Clin Psychiatry 1998;59[suppl 15]:28-34*)

The introduction of the selective serotonin reuptake inhibitors (SSRIs) has revolutionized the practice of psychopharmacology. Although not devoid of side effects, they are often less dangerous and better tolerated than their predecessors. Their efficacy in the treatment of psychiatric disorders such as depression and obsessive-compulsive disorder is now well established. Because of the frequent overlap in symptoms between these disorders and eating disorders, the utility of SSRIs in the treatment of eating disorders is of substantial clinical and theoretical interest. This paper reviews the clinical studies of the SSRIs for the treatment of the eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating disorder) and obesity.

There is substantial uncertainty regarding the role of medication in the therapy of eating disorders. Results of clinical trials of medication in the treatment of anorexia nervosa and obesity have been generally disheartening, and work with SSRIs in binge-eating disorder is just beginning. The efficacy of antidepressant agents in studies of the treatment of bulimia nervosa has been much more encouraging. However, because forms of short-term, focused psychotherapy are at least equally effective and may

have superior long-term benefits, the precise role of medication in the treatment of bulimia nervosa requires further study. Additionally, despite the fact that anorexia nervosa and bulimia nervosa typically have their onset during adolescence, clinical trials have focused entirely on adults. The utility and safety of SSRIs in pediatric populations have yet to be addressed.

## ANOREXIA NERVOSA

Anorexia nervosa is a psychiatric illness that predominantly affects adolescent girls and young women. It is associated with distorted perceptions about shape and body image, leaving the teenager or young adult thinking she is fat and disgusting. In the most severe cases, the relentless cycle of dieting and weight loss can result in death.

The American Psychiatric Association (APA) Practice Guideline for Eating Disorders<sup>1</sup> recommends a multidisciplinary approach for the treatment of anorexia nervosa. The primary interventions are family and individual psychotherapies, incorporating a major cognitive-behavioral component, and with pharmacotherapy often used as an adjunct.<sup>2</sup> Although basic and clinical research has greatly contributed to our knowledge about various neurotransmitter and neuroendocrine disturbances associated with starvation, the etiology of anorexia nervosa remains unknown. Therefore, despite recent advances, behavioral and psychosocial treatments remain the standard, and the search for effective pharmacologic interventions actively continues.

## Antidepressant Medication

Patients with anorexia nervosa often present with symptoms consistent with major depressive disorder (in-

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cluding depressed mood, low energy, and poor concentration) and obsessive-compulsive disorder (such as extensive food-related rituals and obsessional preoccupations with weight and shape). These observations have prompted trials of the efficacy of SSRIs in the treatment of anorexia nervosa. Although there is little evidence that the efficacy of one SSRI is superior to another, controlled studies regarding use of SSRIs in the treatment of anorexia nervosa have used fluoxetine exclusively. Ferguson<sup>3</sup> reported that fluoxetine treatment was successful for a woman with anorexia nervosa who had previously developed significant side effects to other antidepressants, and thus been difficult to treat. In an open trial of fluoxetine, Gwirtsman and colleagues<sup>4</sup> described 6 patients with anorexia nervosa who all showed improvement in depressive symptoms and an increase in weight. Our own group at Columbia<sup>5</sup> has recently completed what we believe to be the only placebo-controlled trial of fluoxetine among underweight patients with anorexia nervosa. Analysis of these data suggests that the impact of fluoxetine, provided in the context of a behaviorally oriented inpatient program, was disappointing.

More encouraging findings regarding the utility of fluoxetine in the treatment of anorexia nervosa come from research with a slightly different focus. Most controlled studies of medication for anorexia nervosa have concentrated on the weight gain phase of treatment, usually in hospitalized patients participating in a structured, behavioral program. Such programs are effective in helping patients gain weight, and thus make detecting a supplementary benefit of medication more difficult. However, the subsequent phase of treatment, the weight maintenance phase, which occurs in the less structured outpatient setting, is quite challenging, and typically is associated with a substantial rate of relapse. There are hints that fluoxetine might be helpful during this phase. A preliminary report of Kaye and colleagues<sup>6</sup> describes the course of 35 patients, all of whom met criteria for anorexia nervosa, restricting subtype, and who had successfully completed an inpatient hospitalization. They were randomly assigned to either fluoxetine or placebo and discharged to the community for continuing psychosocial care. The fluoxetine-treated patients were better able to maintain their weight and had a significantly lower rate of relapse than those receiving placebo. On the other hand, a naturalistic follow-up study by Strober et al.<sup>7</sup> suggested little benefit from fluoxetine. Data from 33 patients who had received fluoxetine during and after a successful inpatient hospitalization were compared with data from 33 historical control patients who had not received medication. Follow-up outpatient treatment, although not standardized, included at least weekly psychotherapy, with the addition of family therapy and dietary counseling as needed. Assessments were made during face-to-face interviews performed by the research staff at 6-month intervals for 2 years' duration. No patient was

lost to follow-up, and compliance with medication was high, with only 4 patients discontinuing medication by the end of the second year follow-up visit. Overall, the authors found no significant difference between the fluoxetine-treated and control groups on measures of compensatory behaviors, need for rehospitalization, and tendency to drop below target weight. Although interpretation of these data is limited due to the naturalistic design of this study, they cannot be summarily dismissed. Thus, whether treatment with fluoxetine is helpful in preventing relapse remains an active and important question for further research. There have been no controlled trials of other SSRIs in the treatment of anorexia nervosa. Whether the alternative agents in this class offer significant benefit, either to the underweight patient with anorexia nervosa or as a preventative measure against relapse for those who have regained weight, remains an open question. In addition, there is substantial clinical and biological heterogeneity among patients with anorexia nervosa. It is possible that only patients with specific, as yet unidentified characteristics respond to pharmacologic intervention. Thus, trials conducted including patients with a variety of characteristics may obscure the benefits of the medication. It may be helpful, in future studies, to focus on subgroups, such as patients with the restricting or binge/purge subtypes, patients with short duration of illness, or, as previously described, patients who have already attained a certain level of weight restoration.<sup>6</sup>

## BULIMIA NERVOSA

The development of pharmacologic treatments for bulimia nervosa has been much more successful than for anorexia nervosa. Several factors have presumably contributed to this difference. The higher prevalence of bulimia nervosa, compared with that of anorexia nervosa, eases recruitment into clinical trials. Secondly, the medical condition of patients with bulimia nervosa is typically much less precarious, which allows more patients to be treated on an outpatient basis, thereby reducing the cost of clinical trials. In addition, it is possible that the more normal physiologic state of patients with bulimia may be necessary for the therapeutic impact of antidepressant medications.

### Antidepressant Medication

The antidepressant medications, in general, have been shown repeatedly to be effective in curbing the binge-purge cycle,<sup>8-16</sup> and the SSRIs are no exception. Again, fluoxetine is the most rigorously studied,<sup>17,18</sup> although case reports and open trials of sertraline,<sup>19</sup> fluvoxamine,<sup>20,21</sup> and paroxetine<sup>22</sup> exist.

Because of the high frequency of depressive symptoms seen in bulimia nervosa, it was plausible that the effective dose for bulimia nervosa would be identical to that for depression. A single study of fluoxetine directly addressed

this issue.<sup>17</sup> In this large trial (N = 387), one group of 129 patients with bulimia nervosa was randomly assigned to receive the “standard” dose of 20 mg/day of fluoxetine, a second group of 129 patients received 60 mg/day, and a third group of 129 received placebo. The results showed that 20 mg/day of fluoxetine was, at most, marginally superior to placebo. On the other hand, 60 mg/day of fluoxetine was clearly superior. Subsequent studies of fluoxetine in bulimia nervosa have generally used 60 mg/day, which is usually tolerated with minimal side effects.

There is further evidence of a divergence between depression and bulimia nervosa. Although depressive symptoms and bulimia tend to co-occur, the presence of depressive symptoms does not predict the degree of improvement in bulimic symptoms with antidepressant treatment<sup>8,10,15</sup>; that is, the eating disorder symptoms of patients with bulimia nervosa who are depressed do not respond more dramatically to antidepressant medication than do those of patients with bulimia nervosa who are not depressed. These data, and the preferential effectiveness of the 60 mg/day dose of fluoxetine, suggest that the mechanism of action of antidepressants in bulimia nervosa may be different than that in depression.

It should be noted that the pharmacologic studies of bulimia nervosa have, for the most part, been restricted to normal weight, adult women who purge through vomiting, and the results may not be generalizable to other populations including men, overweight patients, or patients with bulimia nervosa who use alternate methods of compensation such as fasting or exercise.

### Medication and Psychotherapy

Compelling data have emerged in the last decade demonstrating that focused forms of short-term psychotherapy, particularly cognitive behavioral therapy (CBT), are effective in the treatment of bulimia nervosa.<sup>23</sup> The existence of effective forms of both pharmacotherapy and psychotherapy has complicated therapeutic recommendations, particularly because many important clinical questions cannot be directly answered with the data available. For example, concerns regarding the comparative efficacy of medication and psychotherapy and, especially, regarding the long-term outcome of medication treatment leave the precise place of antidepressant medication in the treatment of bulimia nervosa unclear. The studies that have compared medication and psychotherapy and evaluated the potential benefits of combined treatment have yielded somewhat inconsistent results. Several studies have been published comparing the combination of focused psychotherapy and fluoxetine.

Fichter and colleagues,<sup>24</sup> in Germany, examined the effect of fluoxetine (60 mg/day) compared with placebo in a population of patients hospitalized for bulimia nervosa who were actively engaged in a program of intensive behavioral psychotherapy. The authors found no significant

difference between the fluoxetine and placebo groups and suggested that a “ceiling effect” may have limited the power of the study to detect a benefit from medication; that is, the intensive inpatient psychotherapy was so effective that no additional medication effect could be observed.

An interesting study by the same group examined the value of fluvoxamine in preventing relapse following inpatient treatment.<sup>25</sup> In a double-blind, placebo-controlled study, 72 patients completing inpatient psychotherapy treatment for bulimia nervosa were randomly assigned to receive 12 weeks of outpatient fluvoxamine or placebo treatment. Despite a high dropout rate in the fluvoxamine-treated group, both intent-to-treat and completer analyses showed active medication to have a significant effect in reducing return of binge purge behavior.

Goldbloom et al.<sup>26</sup> conducted a 16-week, randomized trial of individual CBT, fluoxetine, and the combination in 76 women with bulimia nervosa. All groups improved over the course of the study, and intent-to-treat analysis yielded no statistically significant differences in outcome. Completer analysis showed a significantly lower subjective binge frequency in the CBT-treated group compared with the group that received fluoxetine alone. Interpretation of these data is limited by the absence of placebo and control groups and by a surprisingly high dropout rate (43%). It is uncertain whether the absence of differences in outcomes reflects similar treatment effects (that is, that fluoxetine treatment is equivalent to CBT, and that the combination is no better than either alone) or limited power to detect group differences.

Beumont et al.<sup>27</sup> conducted a randomized, placebo-controlled trial of intensive nutritional counseling combined with fluoxetine. In an 8-week trial, with follow-up at 12 and 20 weeks, they compared 60 mg of fluoxetine with placebo in 67 patients receiving weekly nutritional counseling. Both the active medication and placebo groups showed substantial improvement over the course of the study. During active treatment, fluoxetine was superior to placebo only on measures of dietary restraint, weight concern, and shape concern. Although there were suggestions that bulimic symptoms reemerged after fluoxetine was discontinued, the fluoxetine- and placebo-treated groups had statistically similar levels of behavioral symptoms both at end of treatment and at follow-up. While this study suggests that fluoxetine does not dramatically add to the benefit of nutritional counseling, the rate of improvement from nutritional counseling was quite impressive with 61.5% of patients reporting no binge eating episodes during the last week of active treatment. This impressive degree of improvement may have limited the ability to detect any benefit from medication.

Our group recently published the results of a placebo-controlled trial designed to compare 2 forms of psychotherapy for bulimia nervosa (individual CBT and indi-

vidual supportive psychotherapy) and to examine the benefit of combining medication with psychotherapy.<sup>28</sup> The medication intervention was unique in that it was 2-stage: patients randomly assigned to receive active medication were first treated with desipramine; if they could not tolerate this medication, or did not show sufficient improvement, they were switched to fluoxetine. The study was large (120 patients were randomized) and placebo-controlled. The short-term results clearly document that CBT was superior to supportive psychotherapy and also indicate that the 2-stage medication intervention modestly but significantly augmented the effect of psychotherapy. It was also of interest that the group of patients receiving only medication had an outcome on most measures similar to that of patients receiving CBT and placebo.

Although the results of these trials are by no means entirely consistent, they emphasize that, in most patients, the symptoms of bulimia nervosa respond both to structured psychotherapeutic interventions and to antidepressant medication. There are hints that combining medication and psychotherapy may confer some additional benefit, at least in the short-term, but hard evidence for superiority of combined treatment is limited. The most convincing data come from our own study in which the effects of psychotherapy were not as dramatic as reported from other centers. Conceivably, it is easier to detect the additive benefit of medication in a population of patients relatively resistant to the effects of psychotherapy.

It is safe to conclude that we have at least 3 effective treatment strategies to employ in the treatment of bulimia nervosa: CBT alone, antidepressant medication alone, and combination therapy. Pressing questions for clinical research are how to match patients with treatments and what interventions are useful for the significant number of patients who fail to respond to these established treatments.

### **BINGE-EATING DISORDER**

Binge-eating disorder is a newly proposed diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Appendix B: Criteria Sets and Axes Provided for Further Clinical Study. Binge-eating disorder is characterized by repeated episodes of the consumption of a large quantity of food associated with feelings of loss of control (similar to bulimia nervosa), but without the inappropriate compensatory measures such as vomiting, laxative abuse, fasting, or excessive exercise that follow binges in bulimia nervosa. Other similarities to bulimia nervosa include marked concern with body image, shape, and weight,<sup>29-31</sup> and a high prevalence of mood symptoms including depression, worthlessness, and low self-esteem. Although the diagnostic criteria for binge-eating disorder do not require the presence of obesity, most patients presenting with these symptoms are overweight. The number of controlled treatment trials for

binge-eating disorder is limited, and the number of clinical trials investigating the efficacy of pharmacotherapy for this disorder is fewer still. Preliminary results regarding the efficacy of SSRIs in the treatment of binge-eating disorder are mixed.

De Zwaan et al.<sup>32</sup> examined a group of 64 obese patients, recruited specifically for complaints of "emotional problems" to attempt to better characterize the subpopulation of binge eating. Although "emotional problems" were not defined, they recruited 64 overweight women and randomly assigned them to 1 of 4 treatment conditions: CBT and fluvoxamine, CBT and placebo, dietary management and fluvoxamine, or dietary management and placebo. They conservatively estimate that roughly 22% of their sample met DSM-IV criteria for binge-eating disorder (disregarding the frequency criteria). Fluvoxamine (100 mg/day) did not seem to confer additional benefit to those with binge eating in terms of weight loss.

Prats et al.<sup>33</sup> conducted a 16-week open clinical trial in 9 patients of the efficacy of paroxetine on binge frequency. Preliminary results suggested a significant reduction in binge eating. However, these results are difficult to interpret as the cohort included patients with both binge-eating disorder and bulimia nervosa.

An open clinical trial by Devlin<sup>34</sup> attempted to assess the efficacy of phentermine and fluoxetine for binge eating when used in conjunction with CBT. Although a more complete data analysis is currently in progress, preliminary results suggest that phentermine, fluoxetine, and CBT might be more helpful than CBT alone in decreasing binge frequency and weight and improving mood and body image symptoms in the short-term (less than 6 months). However, recommendations regarding long-term efficacy and safety remain premature, and given the recent concerns regarding phentermine and dexfenfluramine, it would be prudent to await completion of data analysis and the results of controlled trials before arriving at clinical recommendations.

The only randomized, double-blind, placebo-controlled trial of an SSRI specifically focusing on binge-eating disorder to date is that of Hudson et al.<sup>35</sup> which examined fluvoxamine. A preliminary report indicates that fluvoxamine was of benefit in reducing binge frequency.

One additional, double-blind, placebo-controlled trial has relevant information. In the context of a multisite trial of the long-term efficacy of fluoxetine for weight loss in the obese, Marcus et al.<sup>36</sup> further divided their obese population into binge and nonbinge eaters. All patients received 52 weeks of behavioral treatment, while half also received fluoxetine (60 mg per day). At the end of 1 year, those subjects who had received both fluoxetine and behavioral modification had lost significantly more weight than those receiving placebo and behavioral modification, but there was no significant difference between binge and nonbinge eaters.

Thus, although there are a number of clinical similarities between binge-eating disorder and bulimia nervosa, and although a few open trials suggest clinical utility of the SSRIs for promoting weight loss and reducing binge frequency, convincing data regarding the use of SSRIs in binge-eating disorder have not yet been published.

## OBESITY

Although obesity is primarily considered a medical disorder, interest in this condition on the part of psychiatry appears to have increased in recent years. Obesity results when energy intake exceeds energy expenditure over an extended period and carries with it many serious medical complications such as diabetes mellitus and hypertension. Although dieting and exercise are clearly effective in producing short-term weight loss, long-term maintenance of this loss is very difficult for most individuals. Whereas the treatment of depression with tricyclic antidepressants was often associated with significant weight gain, the initial clinical trials of SSRIs in depression suggested it sometimes had a more welcome side effect: weight loss. This observation, along with the known role of serotonin in the regulation of appetite, led to trials of SSRIs as a pharmacologic treatment for obesity.

A decade ago, Ferguson and Feighner<sup>37</sup> enthusiastically reported preliminary data suggesting fluoxetine to be equivalent to benzphetamine and superior to placebo as an appetite suppressant. A 6-week, double-blind trial of fluoxetine (60 mg per day) in 23 obese, nondepressed women by Pijl et al.<sup>38</sup> reported significant weight loss in the fluoxetine-treated group ( $3.6 \pm 0.5$  kg vs.  $0.3 \pm 0.5$  kg). Levine et al.<sup>39</sup> conducted a similar, but larger study. An 8-week, randomized, placebo-controlled, double-blind trial of fluoxetine (60 mg) evaluated weight loss in 120 nondepressed, obese subjects. As early as the first week of the study, the fluoxetine-treated group showed significantly greater weight loss compared with placebo, a finding that persisted for the duration of the trial. The degree of weight loss was correlated with initial weight; that is, the greater the degree of obesity at baseline, the larger the amount of weight lost while taking the drug. Overall, fluoxetine was well tolerated, the only significant side effect being asthenia. A second, large study was designed to evaluate the relationship between the dose of fluoxetine and weight loss.<sup>40</sup> Six hundred fifty-five patients were randomly assigned to 5 groups and treated for 8 weeks either with placebo or with 10 mg, 20 mg, 40 mg, or 60 mg of fluoxetine. Findings supported a dose-dependent relationship, with those receiving the highest dose of fluoxetine showing the greatest amount of weight loss. This result contrasts with studies of fluoxetine for major depression in which adverse side effects outweighed the beneficial mood effects at higher doses, leading to the recommendation of 20 mg/day as the standard dose for depression.

Although these studies provided new and potentially exciting information regarding the utility of fluoxetine for obesity, they were limited by the relatively brief duration of treatment. Thus, a large ( $N = 458$ ), multisite study was designed to assess the effect of fluoxetine on weight loss over 1 year.<sup>41</sup> The results were interesting, albeit discouraging. The fluoxetine-treated group showed significantly greater weight loss than the placebo group for the first 20 weeks. After week 20, however, those who received fluoxetine began to regain weight, despite continued treatment with active medication. Overall, although both the fluoxetine and the placebo groups ended the study at weights less than baseline values, there were no significant differences between the groups at the end of the 1-year period. The reasons for this weight gain remain unclear. Possibilities include development of tolerance to the drug (a concept that may be worth pursuing, given the observation that some depressed patients treated with fluoxetine seem to lose the antidepressant effect over time). Another explanation offered related to a decrease in the frequency of visits which occurred after the first 8 weeks of treatment. Whatever the reason, fluoxetine appears to be a successful short-term weight loss treatment, but its long-term efficacy is not established.

Two of the sites published their own results from this large trial. Darga et al.<sup>42</sup> added dietary counseling to both groups. This added intervention, however, did not appear to augment the weight loss effect of fluoxetine, nor prevent weight regain. However, the results (mentioned above) of Marcus et al.<sup>36</sup> portray a slightly different picture. In addition to receiving fluoxetine or placebo, all patients at this site received behavioral modification counseling and were encouraged to restrict their caloric intake and to exercise. Unlike the results at the other sites, at the end of 1 year, there was a significant difference in weight between the drug- and placebo-treated groups. The patients receiving fluoxetine lost an average of 13.9 kg over the course of the year, whereas the placebo group gained 0.6 kg ( $p < .004$ ) (this analysis was based only on the 21 patients who completed the entire year). This study leaves open the possibility that a combination of fluoxetine with more intensive behavioral treatment might assist long-term weight loss.

An examination of another SSRI, citalopram, for obesity was disappointing. Szkudlarek and Elsborg<sup>43</sup> randomly assigned 72 severely obese patients to either citalopram or placebo. All patients also received instruction in the consumption of a low-calorie diet. Over the succeeding 3 months, both the citalopram and the placebo groups lost between 5 and 10 lb. However, citalopram provided no significant additional benefit compared with placebo.

Wadden et al.<sup>44</sup> were interested in the potential utility of an SSRI in maintaining weight loss. Specifically, these investigators examined the utility of sertraline in preventing weight regain following a very low-calorie diet.

Fifty-three women who had lost at least 10% of their initial weight during a very low-calorie diet in the prior 26 weeks were randomly assigned to receive either 200 mg of sertraline or placebo for 1 year. During the initial 6 weeks of the study, those patients receiving sertraline continued to lose weight, while those receiving placebo began to gain weight. However, this difference promptly disappeared, and, at the end of 1 year, both groups had regained similar amounts of weight, and there was no significant difference between the sertraline- and placebo-treated groups.

## PRACTICAL RECOMMENDATIONS

### Anorexia Nervosa

As reviewed above, no pharmacologic agent has been established to be of benefit in the treatment of anorexia nervosa. The mainstay of treatment is an eclectic approach, including psychological, nutritional, and behavioral elements aimed at restoring body weight and normalizing the distorted thinking concerning food, body shape, and weight. In addition, for children and adolescents with this disorder, involvement of the family in treatment is essential.

Antidepressant medications may be considered when evidence of a significant mood disturbance or of OCD persists or emerges after weight restoration. Because of its side effect profile, extensive experience in the treatment of bulimia nervosa, and more limited experience in anorexia nervosa, fluoxetine is probably the preferred agent. Treatment may be initiated at 10 to 20 mg/day. If target symptoms include OCD, higher doses (e.g., 60 mg/day) should be employed and can be reached for most patients over 1 to 2 weeks. The limited data available suggest that fluoxetine can be used safely for patients with anorexia nervosa, but the physiologic disturbances associated with this disorder merit careful monitoring of medication side effects and interactions. It is likely that other SSRIs have similar effects, but there is very limited information concerning their use in anorexia nervosa.

### Bulimia Nervosa

The major pharmacologic intervention to consider for patients with bulimia nervosa is the use of an antidepressant. Because it has been extensively studied and because information concerning the effective dose is available, fluoxetine should be considered the drug of first choice. The preferred dose is 60 mg/day; most patients of normal weight with bulimia nervosa can be started immediately on this amount or can increase from 20 to 60 mg/day over the course of a week. Side effects are rarely a major problem. Anecdotal information suggests that other SSRIs are probably also effective and should be considered if the use of fluoxetine is complicated by the need for other medications with which it may interact.

### Binge-Eating Disorder

Data are too limited to support a recommendation for a specific course of pharmacologic treatment for binge-eating disorder with any confidence. The utility of SSRIs in bulimia nervosa suggests that these agents also may be useful for binge-eating disorder. On the other hand, the discouraging outcome of most long-term studies of SSRIs for obesity may portend difficulties with such agents among obese individuals with binge-eating problems. More work is clearly needed.

### Obesity

There is enormous clinical and economic interest in the development of an effective and safe pharmacologic intervention for obesity. The SSRIs, while full of short-term promise, appear unable to sustain weight loss in the long-term. It is of some interest that sibutramine, which has just been approved for marketing in the treatment of obesity, combines the blockade of serotonin reuptake with reuptake blockade of norepinephrine. This development offers hope that medications related to the currently available SSRIs will eventually prove to be useful adjuncts in the treatment of obesity.

*Drug names:* citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), phentermine (Regitine), sertraline (Zoloft), sibutramine (Meridia).

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# Treatment of Antidepressant Nonresponders: Augmentation or Switch?

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Selective serotonin reuptake inhibitors (SSRIs) are now commonly used in the treatment of major depression. In all patients starting treatment, the intent-to-treat response rate is about 50%. The other 50% will require some change in treatment, either augmentation or switch to a different agent. In this report, augmentation strategies are reviewed, with special attention to those strategies that have been used with the SSRIs. The data for switching antidepressants also are reviewed. Although there are no direct comparison studies of augmentation strategies versus switching that address the question of relative efficacy, the tactical issues that pertain to augmentation or switching are discussed.

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The treatment of refractory depression is a common challenge for the psychiatrist. There are several reasons for this. First, a substantial portion of all patients starting pharmacologic treatment either fail to respond or cannot tolerate the drug. A comprehensive review of 102 controlled trials of tricyclic antidepressants found that the overall intent-to-treat response rate in depressed outpatients was 51%.<sup>1</sup> This means that about half of those starting one antidepressant will need another. The overall intent-to-treat rate for selective serotonin reuptake inhibitors (SSRIs) was 47% in 39 studies. In addition, the most common methods of defining response, 50% improvement over baseline or a Clinical Global Impressions (CGI) rating of much improved, result in a level of response that would be unacceptable for many patients. Further, clinical trial patients are usually carefully selected and are less complicated than the patients clinicians often treat. Finally, psychiatrists are likely to treat a disproportionate number of treatment-resistant patients since this is a common reason for referral.

When faced with a refractory patient, the clinician has essentially 2 choices—to switch to another antidepressant or to augment the first medication. Ideally, this decision would be based on data that indicate the most effective treatment. Yet, at this time there are no parallel comparison studies that directly test these 2 approaches. The avail-

able data, presented subsequently, do not indicate a clear advantage for switching or augmentation in terms of efficacy. For these reasons, the decision to switch or augment is based more on practical issues than efficacy data.

Switching to another antidepressant is simpler. For a patient who is reluctant to take medication, monotherapy may improve compliance. In addition, there are reasonably good data on continuation and maintenance treatment for most marketed antidepressants used alone, while the information on continuation treatment following augmentation is scant.

Cost and side effects are also important considerations but do not necessarily favor one strategy over another. Costs vary with the specific antidepressants and augmenting agents. Several of the augmenting agents, e.g., lithium and thyroid hormone, are inexpensive. Thus, the combination of lithium and low-dose SSRI treatment may be less expensive than another SSRI given at a higher dose. Side effects of the augmenting strategies also vary considerably. Thyroid and bupropion appear to cause fewer side effects than a higher dose of an SSRI. Alternatively, combinations of 2 antidepressants, for example, an SSRI plus a tricyclic antidepressant (TCA) or an SSRI and bupropion may have more side effects than monotherapy.

Augmentation strategies have some advantages. First, they may be rapidly effective. Effects within 48 hours have been reported.<sup>2</sup> Second, patients who have had some degree of response may be reluctant to risk losing this improvement, and, in this situation, augmentation may be preferred. Augmentation with another marketed antidepressant may improve response and ultimately “bridge” to monotherapy with the second agent. Finally, in very refractory patients, the psychiatrist may wish to exhaust each drug trial with augmentation before switching to another agent, especially if most drug classes have already been tried.

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## AUGMENTATION STRATEGIES

Several augmentation strategies have been described and the list continues to grow. Described below are those for which there are multiple reports in the literature. They are presented roughly in the order that controlled trials support their efficacy. In this report the term *augmentation* is used to describe the use of 2 agents to enhance the response of the core symptoms of depression. These combinations include the use of an established antidepressant with an agent not approved for use as an antidepressant, e.g., fluoxetine and pindolol, and combinations of 2 marketed antidepressants, e.g., fluoxetine and bupropion. These combinations are to be distinguished from combinations in which the second agent is used for other target symptoms, for example, the addition of a benzodiazepine to reduce anxiety or the addition of an antipsychotic to treat delusions. Special attention will be given to the issue of augmentation of the SSRIs, although some of the early augmentation strategies were tested before the SSRIs became the first-line drugs for depression.

**Lithium augmentation** is the best studied approach. Since its initial description in 1981,<sup>2</sup> it has been studied in 9 placebo-controlled trials, of which 7 were positive.<sup>3-11</sup> It is effective with essentially all types of antidepressants including the SSRIs—fluoxetine,<sup>10,12</sup> citalopram,<sup>11</sup> fluvoxamine,<sup>13</sup> and sertraline.<sup>14</sup> Recent work indicates a single dose of 250 mg/day is no more effective than placebo, but in that study, 250 t.i.d. was effective.<sup>9</sup> In most North American studies, the dose has been 300 mg t.i.d. At this dose, serum levels vary between 0.4 mEq/L and 1.0 mEq/L, and within this range there appears to be no relationship of serum levels to response.<sup>15</sup> These data suggest that levels above 0.4 mEq/L will usually be adequate but that 1 pill a day or levels below 0.4 mEq/L are not likely to be effective. Although response can occur within 48 hours, 2 weeks has been the usual period of observation and 2 studies suggest patients continue to improve over a 3- to 6-week period.<sup>16,17</sup>

In 4 of the largest controlled lithium augmentation studies,<sup>7-10</sup> response rates of 44%, 48%, 52%, and 53% were reported. In other words, about 50% of patients will show at least much improvement. This is likely to vary with how refractory the patients are. Less treatment-resistant patients are likely to have a higher response rate,<sup>15</sup> while patients who have failed several prior trials will have a lower rate.<sup>13</sup> There is little information available about predictors of response to lithium. We have reported that lithium augmentation was most effective in patients with a possible history of hypomania or a family history of bipolar illness,<sup>18</sup> but this observation has not been replicated.

Lithium at the doses used has mild side effects. Tremor is most common. In my experience, a more common obstacle to the use of lithium is the patient's view that lithium

is used for serious mental illness and, as a result, the patient is reluctant to take it.

**Thyroid augmentation** is the next best studied strategy in refractory patients. Thyroid augmentation has a long history. It was first suggested by Prange et al. in 1969.<sup>19</sup> Several open studies in refractory patients followed, and to date, 4 systematic or controlled studies have been reported.

Goodwin et al.<sup>20</sup> substituted T<sub>3</sub> for placebo in 12 patients who had failed at least 4 weeks of tricyclic treatment. Eight had marked response. Thase et al.,<sup>21</sup> however, failed to observe any effect of T<sub>3</sub> addition in 20 patients who had failed 12 weeks of imipramine and psychotherapy. In this study, patients receiving T<sub>3</sub> augmentation were compared with a group of historical controls who continued on imipramine treatment.

Gitlin et al.<sup>22</sup> reported the first placebo-controlled study. Sixteen patients who had failed prior tricyclic treatment were given either T<sub>3</sub> or placebo for 2 weeks and were then crossed over. No difference between T<sub>3</sub> and placebo was observed. The most recent controlled study<sup>8</sup> compared T<sub>3</sub> with lithium and placebo in 50 depressed outpatients who had failed a tricyclic. Both T<sub>3</sub> and lithium were effective with rates of response of 59% and 54%, respectively, while response to placebo was low at 19%. The latter study provides the best support for T<sub>3</sub> augmentation and indicates it is comparable to lithium.

All of the systematic studies added T<sub>3</sub> to patients who had not responded to a TCA. There are few data addressing T<sub>3</sub> augmentation of SSRIs, although Joffe has reported 3 cases.<sup>23</sup>

T<sub>3</sub> is the preferred form of thyroid (a comparison study<sup>24</sup> found T<sub>3</sub> more effective than T<sub>4</sub>), and Joffe and Sokolov<sup>25</sup> have suggested that T<sub>3</sub> acts by lowering circulating T<sub>4</sub>, the form of thyroid that enters the brain. They argue that contrary to the usual view that the addition of thyroid is treating something akin to subclinical hypothyroidism, in fact, depressed patients display relative hyperthyroidism. They note that depressed patients have elevated T<sub>4</sub> levels and that most antidepressant treatments lower T<sub>4</sub> levels. While this remains an area of controversy, T<sub>3</sub> is the form of thyroid usually employed. The usual dose of T<sub>3</sub> has been 25 to 50 µg/day. Despite the controlled evidence supporting its use, thyroid augmentation does not appear to be a popular strategy according to a poll of northeastern psychiatrists.<sup>26</sup>

**Pindolol augmentation** was first reported by Artigas and colleagues in 1994,<sup>27</sup> but has already received considerable attention. In theory, pindolol would block the presynaptic 5-HT<sub>1A</sub> autoreceptor at the outset so that the compensatory reduction in the presynaptic firing rate, which usually occurs following the administration of an SSRI, would not occur or would be attenuated. This would help to reduce the delay in effect of the antidepressant. Artigas also suggested this might be an effective strategy for refractory patients and presented a small open series of pa-

tients. Subsequently Blier and Bergeron<sup>28</sup> reported similar results from an open trial.

Five placebo-controlled studies have now been reported. Berman et al.<sup>29</sup> described a comparison of pindolol and placebo in 40 outpatients with major depression. They found no difference between the 2 groups of patients in the rate of response. Alternatively, Tome et al.,<sup>30</sup> in a placebo-controlled study of pindolol and paroxetine in 80 patients with major depression, found an early advantage of pindolol over placebo but no difference at the end of treatment. In the third controlled study, Perez et al.<sup>31</sup> reported a positive placebo-controlled trial of pindolol and fluoxetine in 111 patients in Barcelona. Pindolol reduced the mean time to response (50% improvement) from 29 days to 19 days and resulted in a higher response rate (75% vs. 59%). In another study,<sup>32</sup> the Barcelona group compared the effects of paroxetine 20 mg/day given with placebo for 4 weeks, with pindolol for 4 weeks, or with pindolol for the first week only. Sixty-three patients with major depression were recruited and equally distributed among the 3 groups. Patients receiving paroxetine and pindolol for the full 4 weeks did significantly better than those taking paroxetine and placebo after each week of treatment. The group receiving paroxetine and pindolol for 1 week showed greater improvement at weeks 1 and 2 than those taking paroxetine and placebo, but at weeks 3 and 4 did not differ from the group receiving paroxetine and placebo. The study suggests pindolol does augment response as early as week 1, but that pindolol needs to be continued to sustain the improved response. In each of these studies, the usual dose of pindolol was 2.5 mg t.i.d., and at this dose, side effects were minimal.

The study of pindolol has generated considerable interest and has led to preliminary reports describing the value of adding pindolol to nefazodone<sup>33</sup> and buspirone.<sup>34</sup> Yet, it should be noted that the controlled studies of pindolol, described above, focus on speed of response. They do not address the issue of the effectiveness of pindolol augmentation in refractory patients. In fact, in 1 of these studies,<sup>29</sup> the patients were treatment naive. Data on the use of pindolol in refractory patients are limited. A recent placebo-controlled trial in 10 refractory patients found no advantage of pindolol over placebo.<sup>35</sup> Consequently, the status of pindolol as an augmentation strategy in refractory depression remains unclear.

**SSRI-TCA combinations** were first suggested by Weilburg et al. in 1989.<sup>36</sup> They described 30 patients who had been refractory to prior antidepressant treatment, usually with a tricyclic. Fluoxetine was added and 26 patients had a good response. Subsequently, Seth et al.<sup>37</sup> described 8 very refractory elderly patients who had failed various treatments including ECT. All responded to a combination of an SSRI and nortriptyline.

We described the first systematic comparison study of a TCA-SSRI combination.<sup>38</sup> We treated 14 severely de-

pressed inpatients with the combination of fluoxetine and desipramine for 4 weeks and compared these patients with 52 similar patients treated with desipramine alone. This was not a randomized parallel comparison study; however, patients were similar descriptively, were treated in the same setting, and were rated during treatment with the same instrument. In all patients, desipramine dose was adjusted using a 24-hour blood level to achieve a therapeutic plasma desipramine level and, in the combined group, to anticipate the effect of fluoxetine on desipramine levels. In this comparison, the combination of fluoxetine and desipramine was more effective than desipramine alone. The advantage of the combination was significant and meaningful at 1 week and continued through the trial. For example, at 2 weeks, the mean improvement in the patients taking desipramine alone was 30% versus 60% for the patients taking desipramine and fluoxetine. The combination appeared effective in some patients who had been quite refractory to other treatments including ECT. Because dose was adjusted early with blood level monitoring, the desipramine levels achieved were reasonably comparable in the 2 groups. The usual dose of desipramine required during combined treatment was 75 to 125 mg/day.

Usually the combination was well tolerated although side effects can result from either the SSRI or the TCA. There is the potential for more serious adverse reactions because of the effect of the SSRI on tricyclic metabolism.<sup>39</sup> Paroxetine and fluoxetine both raise desipramine levels 3- to 4-fold.<sup>38,40,41</sup> Sertraline has a more modest effect, on average raising desipramine levels 30% to 40%.<sup>40</sup> Citalopram appears to have a modest inhibitory effect on desipramine metabolism similar to that of sertraline.<sup>42</sup> Fluvoxamine has minimal effects on the 2D6 isoenzyme, which metabolizes desipramine.<sup>43</sup> The effects of the SSRIs on nortriptyline have not been well studied but interactions do occur.<sup>44</sup> The effects of the SSRIs on the tertiary tricyclics differ because the demethylation of these compounds is mediated by different isoenzyme pathways; however, if the intent of combined treatment is to use a potent norepinephrine reuptake blocker with an SSRI, there is no reason to use a tertiary tricyclic. Desipramine or nortriptyline would be the TCAs of choice. Because of potential drug interactions, this strategy is best administered with blood level monitoring and/or the use of an SSRI less likely to interact with a TCA.

From a practical perspective, combined treatment can be a very useful strategy for patients admitted to the hospital who have failed treatment with an SSRI. In these patients, there may not be time to withdraw the SSRI before starting a new treatment. A noradrenergic TCA can be added to ongoing SSRI treatment. This combination has another advantage. In a responding patient, the SSRI can be tapered and the patient continued on the TCA. Thus the augmentation period serves as a bridge to the new treatment.

There are yet no controlled data supporting the SSRI-TCA combination. One small controlled study failed to find augmentation of fluoxetine with desipramine or lithium effective<sup>45</sup>; however, as we have argued elsewhere, the doses used in that study were below those usually found to be effective.<sup>46</sup> While controlled studies are needed, the rationale for combining a potent serotonergic blocking agent with a noradrenergic reuptake blocker is compelling.

**Stimulant augmentation** has been described in several open cases or series of cases previously reviewed.<sup>47</sup> In 2 of the largest series, stimulants were used to augment monoamine oxidase inhibitor (MAOI) agents. In one, Fawcett and colleagues reported that 78% of the 32 patients responded.<sup>48</sup> The patients had all been clearly refractory to prior treatment, and the authors documented that the response was sustained. The usual dose of stimulants used was 10 mg t.i.d. for methylphenidate or 5 mg t.i.d. for dextroamphetamine. When coadministered with the MAOIs, lower doses usually have been used. Most of the stimulant augmentation reports involved the addition of stimulants to either the TCAs or the MAOIs. One recent report suggests they are effective when given with the SSRIs.<sup>49</sup> There are no controlled studies of stimulant augmentation; however, there have been controlled studies of the use of stimulants in depressed patients. Although the extended use of a stimulant as the primary antidepressant has been disappointing,<sup>50</sup> the acute effects of stimulants in depressed patients have been well established in controlled studies, which have been reviewed elsewhere.<sup>51</sup> Thus, the addition of stimulants might be expected to have rapid effects.

Side effects of stimulants are usually mild.<sup>50</sup> At the doses reported, cardiovascular effects are minimal. Those side effects that do occur are usually behavioral and include irritability, anxiety, and sometimes paranoia. Stimulants are usually not given to patients already anxious or agitated.

**Buspirone augmentation** has been described in 3 reports,<sup>52-54</sup> based on the idea that a 5-HT<sub>1A</sub> partial agonist might add to the postsynaptic effects of a serotonergic agent. In each of the 3 reports, bupirone 10 mg t.i.d. was added to an SSRI, usually fluoxetine. In the 2 larger studies,<sup>52,54</sup> 10 of 17 patients and 17 of 25 patients responded over a 3-week period. The advantages of bupirone augmentation are that it has minimal side effects, it has independent anxiolytic effects, and it has been studied primarily with the SSRIs.

**Bupropion augmentation** has been described in 2 reports.<sup>55,56</sup> In each study, patients were refractory to either an SSRI or bupropion. The second agent was then added. In the first study, 8 (35%) of 23 responded. In the second, 19 (70%) of 27 responded. In the second study, the mean dose of bupropion was 243 mg/day. Side effects with this combination are mild to moderate. A disadvantage of this combination is that the kinetic interaction of bupropion and SSRIs is not well described; yet, there are reports of

bupropion being of benefit for the reversal of sexual dysfunction occurring with the SSRIs.<sup>57</sup>

**Other augmentation strategies** have been described. In fact, tryptophan augmentation has been studied in 7 previously reviewed placebo-controlled studies.<sup>58</sup> Tryptophan was an effective adjunct when used with the MAOIs or with clomipramine. It was not more effective than placebo when used with other tricyclics. Tryptophan, however, has been withdrawn from the U.S. market because of its association with eosinophilia-myalgia syndrome.<sup>59</sup> The use of tryptophan with the SSRIs has not been well studied, but clinicians should be aware that 5 cases of severe serotonergic side effects were reported when tryptophan was added to high dose (50 to 100 mg/day) fluoxetine treatment in OCD patients.<sup>60</sup> Although the addition of tryptophan appeared to trigger the side effects, it seems likely that the high doses of the SSRI were a contributing factor.

MAOI-TCA combinations have also been reported in refractory depression. In 6 open series, over 200 patients were studied. Only one study<sup>61</sup> reported a controlled comparison and in that study the combination of an MAOI and trimipramine was no more effective than trimipramine alone; however, this study was not limited to refractory patients. Although this combination can be safely administered, it is potentially hazardous. Certainly its use should be restricted to clinicians experienced in the use of the MAOI compounds. Because there are many other safer alternatives, the use of this combination is not recommended. Given the current infrequent use of the MAOIs, the clinician would be better advised to consider whether an MAOI alone would be a worthwhile alternative.

The list of augmentation strategies continues to grow. Those with favorable findings, reported by more than one group, have been described. The reader is referred to other sources for a further discussion of augmentation strategies.<sup>62-64</sup>

## SWITCHING STRATEGIES

The most common approach to patients who are treatment-resistant is to switch to another drug. Prior to the introduction of the SSRIs, the best studied switch was from a TCA to an MAOI. Four controlled studies<sup>65-68</sup> found rates of response for switching from TCA to MAOI of 50%, 59%, 65%, and 75%; however, the higher rates of response were noted in atypical depressed patients<sup>66</sup> or anergic bipolar patients.<sup>67</sup> This was further illustrated in a systematic study reported by Thase et al.,<sup>69</sup> who found that 55% (23 of 42) of patients who failed imipramine therapy responded to either phenelzine or tranylcypromine. However, the rate in atypical anergic patients was higher, 67% (18 of 27), than in typical patients, 31% (4 of 13).

Surprisingly, switching from one TCA to another has not been well studied, and when studied, has not been found to be very effective. Two small studies<sup>70,71</sup> found

rates of response of 9% and 27% when TCA failures were treated with another TCA. These low rates are consistent with the rationale for switching to a drug with a different mechanism.

Following the introduction of the SSRIs, several studies, reviewed elsewhere,<sup>72</sup> examined the switch from a TCA to an SSRI. Beasley et al.<sup>73</sup> reported that 51% (18 of 35) of patients who failed a TCA responded to an open-label trial with fluoxetine. Reimherr et al.<sup>71</sup> observed that 17 (43%) of 40 patients who failed a TCA responded to fluoxetine. The rate was higher among the atypical patients. In a small series of 10 patients who failed a TCA, Peselow et al.<sup>74</sup> found 50% (N = 5) responded to paroxetine. Rates of response to fluvoxamine following TCA failure have been variable, with rates of 4%, 28%, and 75% reported in 3 studies,<sup>75-77</sup> giving an overall pooled rate of 18.5%.

Other agents have also been examined in patients failing TCAs. Both bupropion<sup>78</sup> and trazodone<sup>79</sup> appear to be effective following a switch.

Perhaps the most controversial current question is the value of switching from one SSRI to another. The data from the TCA studies argue against a switch within a class. The logic is that if a patient fails to respond to a drug whose primary mechanism is serotonin reuptake blockade, then giving another drug with the same mechanism is less likely to work than a drug with a different action. The counter argument is that the secondary effects of the SSRIs are sufficiently different that there may be differences in efficacy. The empirical data are limited and mixed. Two studies examined this switch in patients intolerant of the first drug. Brown and Harrison<sup>80</sup> found sertraline effective in fluoxetine-intolerant patients, while Apter et al.<sup>81</sup> found fluoxetine effective in patients who failed or were intolerant of sertraline. Another report was less favorable. Zarate et al.<sup>82</sup> examined 42 patients treated with sertraline who had previously failed to respond or were intolerant of fluoxetine. Among the 31 patients with unipolar or bipolar depression at follow-up, only 8 (26%) of 31 responded. Patients with side effects on sertraline tended to have had the same side effects on fluoxetine therapy. Only 1 study examined a switch to another SSRI in a sample limited to nonresponders. Joffe et al.<sup>83</sup> found 55 patients with unipolar nonpsychotic major depression in their mood disorders clinic who failed 1 SSRI and then received a second. Twenty-eight (51%) of the 55 patients responded.

There are few data on other switches in patients starting treatment with an SSRI. In a study of 15 patients failing paroxetine, Peselow et al.<sup>74</sup> found 11 (73%) responded to imipramine in a double-blind crossover study.

### COMPARISON OF SWITCHING AND AUGMENTATION

The practical considerations bearing on the question of whether to switch or augment have been discussed above.

One other issue might be raised. Clinical lore suggests that augmentation may be more useful in partial responders with the implication that augmentation should not be used in patients showing little response. It does seem likely that partial responders are more apt to respond to future interventions of any sort than patients having no response, but it is not clear that patients having minimal response will necessarily respond better to a switch. In a large open study<sup>16</sup> that provided detailed data, 84 depressed inpatients received lithium augmentation after failing a 4- to 6-week tricyclic trial. The average improvement on the tricyclic was only 13% or 4.5 points on a 25-item Hamilton Rating Scale for Depression. Yet, after 3 weeks of lithium augmentation, 56% were at least much improved. There was essentially no difference between lithium responders and nonresponders with respect to their prior improvement on the TCA (15% vs. 11%). Thus, while it may be that augmentation is beneficial in partial responders in order to maintain improvement, it is not clear that augmentation will be ineffective in patients with minimal prior improvement.

As mentioned above, no controlled study has directly compared an augmentation strategy with a switch under similar conditions. Response rates of separate studies can be compared. As noted, the response rates for lithium augmentation in controlled studies are about 50%. In the single positive controlled study of T<sub>3</sub>, the response rate was 59%.<sup>8</sup> The rates of response for switching from a TCA to an MAOI, from a TCA to an SSRI, or from an SSRI to another SSRI are about 50%. These data suggest the efficacy of the 2 approaches is similar but comparisons across studies are hazardous. A response rate of 50% in a sample of 30 patients means that it is 95% likely that the true rate is between 32% and 68%, a fairly large range. In addition, the studies vary in terms of how refractory the samples were, how response was defined, and other factors. The safest conclusion is that the relative efficacy of augmentation and switching is unknown, and that until there are data to the contrary, treatment decisions are likely to be based on practical considerations rather than differences in efficacy.

*Drug names:* bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil), methylphenidate (Ritalin), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), pindolol (Visken), sertraline (Zoloft), tricyclicpromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

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# SSRI Safety in Overdose

Jean T. Barbey, M.D., and Steven P. Roose, M.D.

**Background:** The morbidity and mortality caused by tricyclic antidepressant (TCA) overdose are well recognized. Among newer antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are thought to be safer in overdose. This study was designed to describe the signs, symptoms, and mortality associated with SSRI overdose. **Method:** English-language articles identified through MEDLINE (1985 through 1997), and case reports from the American Association of Poison Control Centers (AAPCC) (1987 through 1996) and United States Food and Drug Administration (FDA) adverse event database (through 1997) that describe findings of fatal and nonfatal overdoses involving SSRIs alone or in combination with other ingestants were reviewed. **Results:** SSRI antidepressants are rarely fatal in overdose when taken alone. During the 10 years that SSRI antidepressants have been marketed, there have been remarkably few fatal overdoses reported in the literature or to the AAPCC or FDA involving ingestion only of an SSRI. Moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms, while ingestions of greater amounts typically result in drowsiness, tremor, nausea, and vomiting. At very high doses (> 75 times the common daily dose), more serious adverse events, including seizures, electrocardiogram (ECG) changes, and decreased consciousness may occur. SSRI overdoses in combination with alcohol or other drugs are associated with increased toxicity, and almost all fatalities involving SSRIs have involved coingestion of other substances. **Conclusion:** The SSRI antidepressants are far safer than the TCAs in overdose. There is no apparent difference among SSRIs with respect to overdose safety.

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The lethality of tricyclic antidepressant (TCA) overdose is well established. In fact, clinicians and researchers first became aware of the deleterious cardiovascular effects of tricyclics because patients who took overdoses of TCAs died a cardiac death, from either heart block or arrhythmias. Not only is TCA overdose associated with significant morbidity and mortality, but also there is a relatively narrow range between therapeutic and toxic levels of drugs. Significant symptoms can result from ingestion of as little as 3 to 4 times the therapeutic daily dose. Not surprisingly, there was a time when tricyclic overdose resulted in thousands of deaths per year.

Despite the robust efficacy of tricyclic antidepressants, overdose fatality, along with anticholinergic side effects,

weight gain, orthostatic hypotension, and adverse impact on preexisting cardiovascular disease, have limited the clinical utility of the TCAs.

The selective serotonin reuptake inhibitors (SSRIs) have documented efficacy, in most circumstances, comparable to the tricyclics.<sup>1-5</sup> However, collectively the SSRIs are generally better tolerated than the tricyclics, and although the SSRIs are not without problematic side effects (e.g., anorgasmia), they do not have anticholinergic effects nor do they induce weight gain. Perhaps most importantly, the SSRIs do not have adverse cardiovascular effects and appear vastly safer than the tricyclics when taken in overdose.

The purpose of this article is to review the data available on SSRI overdose. There are significant problems inherent in reviewing overdose data:

1. Most overdoses are not of a single drug, but rather multiple substances, most often antidepressants in combination with benzodiazepines and/or alcohol. Thus, the attribution of symptoms or mortality to a single agent is not possible.
2. For many reasons, the reporting of overdoses is sporadic, and so it is impossible to establish true numerators and denominators with respect to rates of symptoms, severe adverse events, or mortality.
3. Reports of overdose often combine accidental ingestion by infants or young children with intentional overdose by adults.

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4. Most often, it is only possible to estimate the amount of medication ingested in an overdose.
5. The data recorded in an overdose situation are not standardized, so there rarely are complete data on the consequences of the overdose.

Thus, there are obstacles to the definitive characterization of the symptom and mortality profile of a medication when taken in overdose, and it is especially difficult to make comparisons between medications. Nonetheless, there are sufficient data available to describe the impact of an SSRI overdose.

## METHOD

A MEDLINE search was conducted for the period 1985 through 1997 for all English-language reports (using keywords including *overdose*, *poisoning*, *toxicity*, and *suicide*) of overdose experience with any of 5 SSRIs—fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. Published articles describing the safety experience during premarketing development and FDA-approved labeling for each of these drugs also were reviewed.

Additionally, the annual report of the AAPCC Toxic Exposure Surveillance System was reviewed for the years 1987–1996,<sup>6–15</sup> and individual case reports for each fatality involving ingestion of an SSRI alone were obtained from the AAPCC. Through the Freedom of Information Act, all reports contained in the FDA's database of spontaneously reported adverse events with fluoxetine, sertraline, paroxetine, and fluvoxamine were requested. This database was then searched for keywords including *overdose*, *poisoning*, *toxicity*, and *suicide*, and individual case reports were obtained.

Cases drawn from the AAPCC's annual compilation of fatal overdoses and the FDA's database of adverse drug reactions have been submitted voluntarily directly to the AAPCC, the FDA, or to a drug manufacturer, both by consumers and members of the health profession. Thus, the information has been spontaneously reported, and not verified, scientifically or otherwise, as to a cause and effect relationship.

Due to the spontaneous nature of the reporting systems, the cases reported to the AAPCC and the FDA are in many instances incomplete, making it difficult to rule out the involvement of other drugs or alcohol. In many cases, neither a specific cause of death (other than "drug overdose") nor pathology results are included in the reports.

Additionally, reported overdoses comprise both accidental ingestions (typically involving young children who may ingest only a small amount of drug) as well as overdoses with clear suicidal intent. It also is possible that some overlap in cases reported to each organization may have occurred. Finally, the absolute incidence of fatalities associated with overdoses of SSRIs alone cannot be cal-

**Table 1. Fatal Overdoses Reported to AAPCC or FDA Involving Ingestion of an SSRI Alone\***

Drug	Source	No. of Fatalities	Dose Ingested <sup>a</sup> (mg)	Plasma Drug Concentration <sup>a</sup> (ng/mL)
Fluoxetine	FDA	34	260–6000	Fluoxetine: 1300–7000 Norfluoxetine: 800–4152
Sertraline	AAPCC	2 <sup>b</sup>	Unknown	Unknown
	FDA	8	1100	Sertraline: 672–700 Desmethylsertraline: unknown
Paroxetine	AAPCC	1 <sup>b</sup>	Unknown	Unknown
	FDA	6	530–600	Paroxetine: 1000
Fluvoxamine	FDA	1	Unknown	Unknown

\*Abbreviations: AAPCC = American Association of Poison Control Centers, FDA = U.S. Food and Drug Administration.

<sup>a</sup>Not all case reports contained information on ingested dose or plasma concentrations. Ranges are given if more than one report contained such information.

<sup>b</sup>One case reported to the AAPCC involved an overdose with unknown amounts of both sertraline and paroxetine.

culated, as both the numerators and denominators are uncertain.

Because citalopram has only recently been approved for marketing in the United States, data on citalopram overdose situations come from non-FDA sources, such as the Swedish Poisons Information Centre.

Requests also were made to the manufacturers of each of the drugs for data on file regarding overdose experience, to which several (SmithKline Beecham Pharmaceuticals and H. Lundbeck A/S) responded in detail.

## RESULTS

During the period 1985 through 1997, there were only 6 verified overdose deaths involving ingestion of an SSRI alone, 2 published in the literature<sup>16,17</sup> and 4 confirmed by the drugs' manufacturers. An additional 51 cases of fatal overdoses with an SSRI in which no other substances were said to have been ingested have been reported to the AAPCC or FDA; these are summarized in Table 1. A detailed description of the experience with each drug follows.

### FLUOXETINE

#### Clinical Trials

Two deaths were reported by the manufacturer among 38 reports of fluoxetine overdose with or without concomitant drugs or alcohol during clinical trials.<sup>18</sup> One death involved 1800 mg of fluoxetine combined with an undetermined dose of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4570 ng/mL and 4180 ng/mL, respectively. The other fatality involved 3 drugs, resulting in plasma concentrations of 1930 ng/mL for fluoxetine, 1100 ng/mL for norfluoxetine, 1800 ng/mL for codeine, and 3800 ng/mL for temazepam.

Nausea and vomiting were the most frequently reported symptoms associated with the remaining nonfatal fluoxetine overdoses that occurred during clinical trials conducted by the manufacturer.<sup>18</sup> Other prominent symptoms reported in overdose situations were agitation, restlessness, hypomania, and other signs of CNS excitation. One patient who reportedly ingested 3000 mg of fluoxetine (150 times the common daily dose of 20 mg, almost 40 times the maximum recommended daily dose of 80 mg) experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment.<sup>18</sup>

### Published Reports

**Case series.** During the 10 years that fluoxetine has been available for the treatment of depression, several prospective studies as well as a number of case reports have been published describing the effects of fluoxetine in acute overdose situations. For example, 4 studies reported findings on 106, 44, 234, and 16 fluoxetine overdoses in 1990, 1990, 1992, and 1997, respectively.<sup>19-22</sup> These cases included 229 fluoxetine overdoses in which coingestants were reported, and 137 in which patients reported that fluoxetine was ingested alone. Of the cases in which fluoxetine was ingested alone, at least 48 patients experienced no symptoms. The largest ingestion of fluoxetine among asymptomatic patients was 1500 mg (75 times the common daily dose of 20 mg). The most frequent symptoms experienced by those who ingested fluoxetine alone were tachycardia, and lethargy or drowsiness. Additional symptoms included QT prolongation, tremor, nausea, and vomiting.

With the exception of gastric decontamination, treatment beyond general supportive care was not required for the majority of patients who ingested fluoxetine alone. Most were treated in the emergency department only, and many were subsequently transferred to a psychiatric unit, whereas others were admitted to a medical floor for further observation or treatment. Patients recovered without sequelae.

The potential for serious toxicity appears higher in cases involving coingestion of fluoxetine with alcohol or other drugs. In the prospective study of 234 overdoses,<sup>21</sup> patients ingesting fluoxetine and alcohol or other drugs were more likely to be symptomatic than those ingesting fluoxetine alone; 5 of 147 patients ingesting other drugs in combination with fluoxetine developed cardiac arrhythmias, 3 developed seizures, 3 suffered respiratory arrest, and 3 experienced dystonic reactions.

**Case reports.** Feierabend<sup>23</sup> described a 4-year-old girl who was believed by her family to have ingested 700 mg (approximately 43 mg/kg) of her mother's fluoxetine, resulting in plasma levels of 3080 ng/mL and 459 ng/mL of fluoxetine and norfluoxetine, respectively. She experienced sinus tachycardia, some degree of psychomotor agitation and dyskinesia, and an episode of unconsciousness,

all of which were transient, and subsequently resolved without sequelae.

Braitberg and Curry<sup>24</sup> reported that a 15-year-old girl ingested 900 mg of fluoxetine and experienced a seizure 9 hours after ingestion that remitted spontaneously. She then recovered fully.

Another case report<sup>25</sup> describes a 13-year-old boy with Tourette's syndrome and obsessive-compulsive disorder who ingested approximately 1880 mg of fluoxetine and had a generalized tonic clonic seizure 3½ hours later that remitted spontaneously. Plasma samples taken 15 hours after ingestion revealed a fluoxetine level of 1142 ng/mL and a norfluoxetine level of 322 ng/mL.

Only one case of a pure fluoxetine overdose resulting in fatality has been reported in the literature.<sup>16</sup> In this case, a 58-year-old woman with a history of suicide attempts was found dead at home. She had 6000 mg of fluoxetine available to her at the time of her death, as she reportedly had obtained several prescription refills in the few weeks before her death. Postmortem blood levels were 6000 ng/mL and 5000 ng/mL of fluoxetine and norfluoxetine, respectively.

Rohrig and Prouty<sup>26</sup> report that a 28-year-old woman died after ingesting an overdose of fluoxetine and ethanol. Heart blood levels of ethanol were measured at 48 mmol/L and fluoxetine and norfluoxetine blood levels were 800 ng/mL and 650 ng/mL, respectively.

Graudins et al.<sup>27</sup> describe a case in which a patient ingested an overdose of fluoxetine and acetaminophen, resulting in plasma concentrations of 901 ng/mL fluoxetine, 451 ng/mL norfluoxetine, and 174 mg/L acetaminophen. The patient presented with lethargy and cardiac conduction delays (QRS complex of 110 milliseconds, QTc interval of 458 milliseconds) and experienced a seizure 16 hours after ingestion. After therapy with intravenous sodium bicarbonate therapy, the QRS complex narrowed to 90 milliseconds, and the patient subsequently recovered fully.

### AAPCC Reports

There have been 7 fatalities resulting from overdose of fluoxetine with concomitant drugs or ethanol reported by the AAPCC since the release of fluoxetine in 1987.

### FDA Reports

Since the release of fluoxetine in the United States in 1987, 34 fatal overdoses have been reported to the FDA in which fluoxetine was the only documented ingestant (see Table 1). Many of the reports are incomplete and lack information regarding exact cause of death, dose of fluoxetine ingested, and resulting plasma levels. However, 7 case reports listed plasma levels of fluoxetine and norfluoxetine ranging from 1300 to 7000 ng/mL and from 800 to 4152 ng/mL, respectively. None of these 7 case reports listed dosage ingested or exact cause of death.

Thirty-five nonfatal overdoses in which fluoxetine was the only reported ingestant resulted in serious adverse events. Of these, 30 cases involved patients who experienced convulsions (dose range, 100 mg–4000 mg). The remaining 5 case reports involved patients who experienced other serious adverse events such as cardiac arrest, torsades de pointes, QT prolongation, and ECG changes.

## SERTRALINE

### Clinical Trials

During premarketing clinical trials with sertraline, there were 79 reports of nonfatal overdoses, 28 of which were overdoses of sertraline alone.<sup>18</sup> The reported overdoses ranged from 500 mg to 6000 mg (10 to 120 times the recommended starting dose of 50 mg/day, 2.5 to 30 times the maximum recommended daily dose of 200 mg), resulting in plasma sertraline concentrations ranging from < 5 ng/mL to 554 ng/mL. Resulting symptoms included drowsiness, nausea, vomiting, tachycardia, and ECG changes.

Ingestion of sertraline alone did not result in fatalities during clinical trials; there were 4 deaths involving overdoses of sertraline in combination with other drugs.<sup>18</sup>

### Published Reports

In 1996, Klein-Schwartz and Anderson<sup>28</sup> performed a 2-year retrospective and a 6-month prospective study to characterize the toxicity of sertraline-only overdose. Of 52 patients who ingested up to 3500 mg of sertraline alone, 34 (11 children and 23 adults) experienced no symptoms (adult dose range, 250 mg–1800 mg). Those adults with symptoms (dose range, 250 mg–3500 mg) experienced lethargy, tachycardia or bradycardia, vomiting, and abdominal pain. Treatment consisted of supportive care including monitoring of vital signs and gastric decontamination.

Lau and Horowitz<sup>29</sup> prospectively studied sertraline overdoses reported to 5 western regional poison control centers. Of 40 nonfatal overdoses reported (dose range, 50 mg–8000 mg), 17 were sertraline-only overdoses. The most common symptoms reported in the sertraline-alone overdoses were tremor, lethargy, and nausea. There were 23 cases of sertraline overdose that involved ingestion of other medications; 4 of these patients were asymptomatic, whereas others reported lethargy, nausea, and vomiting. All patients recovered.

Caracci<sup>30</sup> described a 32-year-old woman who ingested an overdose of nearly 4000 mg of sertraline and experienced tremors, dizziness, and nausea for the following 2 days, insomnia for the following week, and then recovered fully.

### AAPCC Reports

The AAPCC has reported 4 fatalities resulting from sertraline overdose in combination with other drugs, and 1

case in which it is not known whether concomitant ingestants were involved (see Table 1). In this case, the emergency medical services crew found an empty bottle of sertraline next to the patient and brought her into the emergency department in cardiac arrest. She was pronounced dead after 15 minutes. No other information about this case is available, thus it is not known whether concomitant drugs or alcohol may have contributed to the fatality.

A sixth fatality involved a mixed overdose of sertraline and paroxetine (see Table 1). In this case, a 36-year-old woman was unresponsive upon arrival to the emergency department after ingesting unknown amounts of the 2 SSRIs. She remained unresponsive after being placed on a ventilator and administered naloxone. The patient remained comatose with fixed and dilated pupils, and expired within 24 hours. No other information was reported and no postmortem examination was performed. Thus, it is unclear whether this fatality involved coingestion of substances other than the 2 SSRIs.

### FDA Reports

Since 1992, 8 fatal overdoses have been reported to the FDA in which sertraline was the only drug believed to have been involved (see Table 1). Although the data reported are incomplete, in 2 cases the blood concentrations of sertraline were recorded at 700 ng/mL and 672 ng/mL. The patient whose blood levels were measured at 700 ng/mL presented to the emergency room in cardiac arrest and died later that day. None of the other reports documented the exact cause of death, with the exception of 1 case in which the patient ingested 22 sertraline tablets and experienced ECG changes prior to death.

Three additional cases were reported in which possible pure sertraline overdose resulted in ECG abnormalities. In 1 such case, a 13-year-old female ingested 650 mg of sertraline, and in another, a 22-year-old woman ingested 500 mg of sertraline. In the final case, a 23-year-old man had a seizure and QT prolongation after ingesting an unknown amount of sertraline. In all 3 cases, the patients recovered fully.

Finally, 4 cases were reported in which patients ingested overdoses of sertraline and experienced seizures (dose range, 500 mg–1000 mg).

## PAROXETINE

### Clinical Trials

In cases of reported overdoses on paroxetine alone or in combination with other drugs during premarketing trials, patients experienced nausea, vomiting, drowsiness, dizziness, sinus tachycardia, sweating, and dilated pupils.<sup>18</sup> In cases where hospitalization was required, medical treatment included gastric lavage or administration of activated charcoal or syrup of ipecac. No ECG abnormalities,

coma, or convulsions were reported following pure paroxetine overdose. All patients recovered fully, including those who ingested up to 2000 mg of paroxetine (100 times the common daily dose of 20 mg, 40 times the maximum recommended daily dose of 50 mg).<sup>18</sup>

Postmarketing reports to SmithKline Beecham through 1995 include 188 (135 validated) overdoses which occurred while a patient was treated with paroxetine, 19 of which were fatalities (S. Wiejowski, Pharm.D., written communication, December 1997). Of these, 17 involved ingestion of substances in addition to paroxetine or other factors. Of 2 fatalities in which only paroxetine was ingested, 1 patient (who ingested 800 mg) was found dead in an automobile with the cause of death attributed to hypothermia. Little information is available about the other fatality; however, autopsy reports suggested elevated plasma levels of paroxetine. In the remaining reports of overdose, the patients recovered without sequelae.

### Published Reports

Myers et al.<sup>31</sup> reviewed paroxetine overdoses reported to the Pittsburgh Poison Control Center over a 12-month period. Among 35 people (26 adults) who ingested from 10 mg to 1000 mg of paroxetine, 8 experienced no symptoms, while others experienced symptoms such as vomiting, drowsiness, and tremors. The 16 overdoses involving coingestants had symptoms consistent with the coingestant.

Myers and Krenzelok<sup>32</sup> further reviewed 28 ingestions by children (10 months to 17 years of age) of paroxetine alone reported to the Pittsburgh Poison Control Center over a 24-month period. Ingested amount ranged from 10 mg to 800 mg. Twenty-two of the children were asymptomatic, and the remaining 6 suffered symptoms such as drowsiness, vomiting, orthostatic hypotension, and tachycardia. All patients recovered fully without sequelae.

Gorman et al.<sup>33</sup> reported a case in which a patient took 400 mg of paroxetine alone and experienced no symptoms.

### AAPCC Reports

The AAPCC has reported 3 fatalities in which paroxetine was ingested concomitantly with other drugs (including the sertraline/paroxetine ingestion previously described). To date, no cases of fatalities resulting from paroxetine-only overdose have been reported to the AAPCC.

### FDA Reports

Six fatalities have been reported to the FDA in which paroxetine was the only known ingestant (Table 1). One patient had blood paroxetine levels that were 10 times above normal. In another report, the heart blood level was measured at 170 ng/mL. An additional case reported that a 42-year-old male ingested 26 to 28 tablets of paroxetine

and subsequently died of cardiac arrest after several seizures. The medical examiner reported that screens for alcohol and other drugs were negative. Finally, a patient ingested 600 mg of paroxetine, presented with a hypotensive episode, and then "appeared to go into cardiogenic shock."

One possible pure paroxetine overdose caused ECG abnormalities, followed by full recovery. Two others resulted in seizures.

## FLUVOXAMINE

### Clinical Trials

In contrast to other SSRIs, fluvoxamine is not approved in the United States for the treatment of depression, but is approved for the treatment of obsessive-compulsive disorder. A total of 354 cases of overdose involving fluvoxamine were reported during clinical trials and postmarketing surveillance in Europe, including 19 fatalities.<sup>18</sup> Of the reported fatalities, 17 involved coingestion of fluvoxamine with other drugs, and 2 involved ingestion of fluvoxamine alone. No further information is available on these fatalities. At least 309 of the remaining 335 patients recovered completely after gastric lavage and symptomatic treatment. One patient ingested 10,000 mg of fluvoxamine (100 times the minimum effective daily dose, about 33 times the maximum recommended daily dose of 300 mg) and fully recovered with no sequelae. Common symptoms associated with pure fluvoxamine overdose included drowsiness, diarrhea, vomiting, and dizziness.<sup>18</sup>

### Published Reports

Garnier et al.<sup>34</sup> reviewed 221 cases of intentional fluvoxamine overdose that were reported to the Paris Poison Centre, and 78 cases of fluvoxamine overdose collected by the International Drug Safety Department of Duphar BV (the Dutch subsidiary of Solvay S.A.). In 69 cases, fluvoxamine was ingested alone (dose range, 150 mg–9000 mg). Symptoms including drowsiness, tremor, nausea, vomiting, abdominal pain, moderate bradycardia, and/or anticholinergic effects, such as dry mouth, mydriasis, sinus tachycardia, and urinary retention, were observed when the fluvoxamine dose was less than 1000 mg. At higher doses, other symptoms (e.g., decreased consciousness) were reported.

Ingestion of fluvoxamine with concomitant drugs or alcohol resulted in more serious toxicity. For example, seizures occurred in 5 cases in which higher doses (>1500 mg) and concomitant drugs were ingested. Thirteen cases in which patients ingested large doses of fluvoxamine (range, 2500 mg–6100 mg) concomitantly with other substances resulted in fatalities.

### AAPCC Reports

The AAPCC has not reported any fatalities involving fluvoxamine to date.

### FDA Reports

The single report of a fatal overdose in which fluvoxamine was the only drug reported to have been ingested did not include the blood levels of fluvoxamine, pathology findings, or exact cause of death (see Table 1).

### CITALOPRAM

#### Clinical Trials

Citalopram, an approved antidepressant in more than 60 countries worldwide, recently was approved for marketing by the United States Food and Drug Administration. During premarketing clinical trials involving 4422 citalopram-treated patients, 15 overdoses (up to 2000 mg) with citalopram, either alone or in combination with other ingestants, were reported (Forest Laboratories, Inc., data on file, 1998). There were no fatalities. Of the patients who ingested citalopram alone, 2 were asymptomatic, and in other cases symptoms such as nausea, somnolence, increased sweating, and tachycardia were reported. In several patients ingesting citalopram and other substances, including benzodiazepines and alcohol, more serious symptoms, including loss of consciousness, were observed.

During postmarketing surveillance outside the United States (1989 through mid-1998), there have been 2 reports to H. Lundbeck A/S of fatalities from overdose of citalopram alone, 1 of which also has been published in the literature<sup>17</sup> (see below). In the other case, a 17-year-old female with a previous suicide attempt ingested 2800 mg of citalopram (140 times the common daily dose of 20 mg). The patient developed generalized seizures approximately 4 hours after ingestion and did not regain consciousness. Serum citalopram concentration was 2993 ng/mL 6 hours postingestion (Forest Laboratories, Inc., data on file, 1998).

#### Published Reports

Recently, a Swedish poison control center published findings from 108 cases of citalopram-only overdoses reported since 1993.<sup>35</sup> In 94 cases, the dose taken ranged from 140 mg to 5200 mg (7 to 260 times the common daily dose of 20 mg, approximately 2.5 to 90 times the maximum recommended daily dose of 60 mg). In overdoses of less than 600 mg, symptoms such as nausea, dizziness, tachycardia, tremor, drowsiness, and somnolence were reported. Higher doses (30–100 times the common daily dose) were associated with convulsions and tachycardia. There were no instances of arrhythmia, and all patients, including 1 who ingested 5200 mg, the highest known overdose, recovered without sequelae.

Among 6 reported cases of fatal citalopram overdose, 5 involved other sedative drugs or ethanol, as well as large doses of citalopram (range, 840 mg–3920 mg).<sup>17</sup> The single pure citalopram fatality resulted from an ingestion of nearly 4000 mg of citalopram—more than a 6-month supply of the drug at the common daily dose of 20 mg. In this

case, a 56-year-old male was found dead in his car in a parking lot. The concentrations of citalopram and demethylcitalopram in blood samples taken from the femoral vein were 16,000 ng/mL and 500 ng/mL, respectively, more than 75 times the therapeutic concentration.

Grundemar et al.<sup>36</sup> described in detail 5 cases of massive citalopram overdose in which all patients survived. At least 3 of the 5 cases involved coingestion of citalopram with ethanol or other drugs. Four of the 5 patients had seizures, and the fifth (in which the patient also ingested 375 mg of oxazepam) was amnesic. ECG changes, including prolongation of QT<sub>c</sub> interval (to values > 440 milliseconds) were reported. All patients recovered without sequelae.

Since citalopram was only recently approved in the United States, neither the AAPCC nor the FDA has received any postmarketing case reports involving citalopram overdose.

### DISCUSSION

Results of both prospective studies and individual case reports indicate that the potential for toxicity in overdose of SSRIs (including fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) is very much less than that of TCAs. Whereas approximately 100 to 150 fatal overdoses with TCAs were reported to the AAPCC each year, only 16 fatal overdoses involving SSRIs (with or without concomitant coingestants) were reported to the same organization during the period 1987 through 1996.

In general, overdoses with SSRIs alone very rarely result in fatality, and most patients recover without sequelae. Moderate overdoses (up to 30 times the common daily dose) are associated with minor or no symptoms. Acute ingestion of SSRIs at doses up to 50–75 times the common daily doses typically result in symptoms including drowsiness, tremor, nausea, and vomiting. At higher doses, more serious adverse events, including seizures, ECG changes, and decreased consciousness may occur. With exceptionally large acute overdoses of these drugs ( $\geq 150$  times the common daily therapeutic dose), fatalities have been reported. Not surprisingly, SSRI overdoses in combination with alcohol or other drugs appear to be associated with increased toxicity, and most fatalities involving SSRIs have involved coingestion of other substances.

The signs and symptoms of acute overdoses with fluoxetine and with citalopram are more thoroughly characterized than overdoses with other SSRIs, as both fluoxetine and citalopram have been marketed for approximately 10 years. During this time, both fluoxetine and citalopram have been ingested in hundreds of overdose situations, yet each has caused only 1 well-documented fatality in cases of SSRI-only overdose.<sup>16,17</sup> As with all antidepressants, more fatalities are reported when there is coingestion with other substances.

Although much less is known about overdoses with other SSRIs, the very few instances of fatalities suggest that SSRIs generally share the favorable safety in overdose profile observed with fluoxetine and citalopram. The relatively benign profile of SSRI overdose represents a distinct advantage compared with the TCAs. However, coingestion is very common, especially with alcohol and benzodiazepines, and can greatly increase toxicity.

*Drug names:* citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), naloxone (Narcan and others), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril).

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