

Toxicology News

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Selective Serotonin Reuptake Inhibitors are Diverse Group

By Diana Garside

The selective serotonin reuptake inhibitors (SSRIs) are a group of newer antidepressants named for their principal mechanism of action. Fluoxetine was the first SSRI, approved for use in the United States by the Food and Drug Administration in the late 1980s, with several more compounds approved in the 1990s and 2000s.

Developed as an alternative to the classic tricyclic antidepressants (TCAs), SSRIs are considered safer in overdose and easier to tolerate, with fewer adverse side effects. SSRIs are used to treat not only major depressive disorders, but a range of other psychiatric conditions, including generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, premenstrual dysphoric disorder, bulimia nervosa, and social anxiety disorder.

The SSRIs are a chemically diverse group of compounds (Figure 1). They include fluoxetine (Prozac, Sarafem; Eli Lilly), fluvoxamine (Luvox; Solvay), sertraline (Zoloft; Pfizer), paroxetine (Paxil; GlaxoSmithKline), and citalopram (Celexa, Lexapro; Forest). Venlafaxine (Effexor; Wyeth-Ayerst) has a dual mechanism of action. At lower concentrations, it is an SSRI. It also blocks the reuptake of norepinephrine and dopamine in a dose-dependent manner, and is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI). SSRIs are also marketed worldwide under a variety of trade names not mentioned above. They are administered orally in tablet or suspension form. Fluoxetine, paroxetine, and venlafaxine are also formulated for extended release. For dosing information, see Table 1.

SEROTONIN

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) is synthesized in vivo by the

hydroxylation and decarboxylation of the amino acid L-tryptophan. Ninety percent of the body's serotonin is found in the small intestine in the enterochromaffin cells, with the remainder stored in platelets and throughout the central nervous system (CNS). Serotonin elicits a variety of pharmacological responses, both peripherally and centrally. Peripherally, it increases small intestine motility, modulates cardiovascular function, and affects platelet homeostasis. Serotonin is more widely recognized as a centrally acting neurotransmitter, however, and as such it affects mood, memory and learning, appetite, sleep, sexual behavior, motor function, and endocrine and temperature regulation.

PHARMACOLOGIC ACTION

The mechanisms of action associated with SSRIs and other antidepressants are not completely understood, but mood disorders have been linked to a deficit of monoamine neurotransmitters, notably norepinephrine, dopamine, and serotonin, in the CNS. Drugs that enhance the concentration of these neurotransmitters in the CNS, either by promoting their release from storage vesicles (sympathomimetics), inhibiting their metabolic breakdown (monoamine oxidase inhibitors), or preventing their reuptake (SSRIs and TCAs), appear to alleviate many of the symptoms of psychiatric disorders (the so-called biogenic amine theory). SSRIs are designed to specifically inhibit the reuptake of serotonin and have little effect on the abundance of norepinephrine and dopamine. They also have little to no affinity for histaminergic (H_1), adrenergic (α_1), or muscarinic (M_1) receptors, unlike the TCAs. This specificity makes SSRIs more desirable than TCAs in therapy because they exhibit similar efficacy yet

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Inside...

Estimated GFR 2

Ask the Experts

Q Our lab reports estimated glomerular filtration rate (GFR) as recommended by the National Kidney Disease Education Program (NKDEP). Should clinicians use this information to adjust the dosage of renally cleared drugs?

Answered by Greg King

A In an effort to improve the early detection of chronic kidney disease, the NKDEP recommends that laboratories report an estimated GFR using a formula empirically derived from the modification of diet in renal disease (MDRD) study. The measurement of microalbuminuria is also recommended as a screening test. Early intervention in renal disease in the form of better diabetic control, antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors, and low-protein diet can reduce the risk of progression of chronic renal disease (estimated GFR 30–60) to renal failure (estimated GFR <30) and the eventual need for hemodialysis. This preventive approach has the potential to reduce the high mortality and morbidity rates of individuals with renal failure and save billions of health-care dollars.

The abbreviated equation uses a test commonly available in laboratories—serum creatinine—along with age and gender to calculate an estimated GFR standardized to average adult body surface area (mL/min/1.73 m²). An additional factor of 1.21 is used to upwardly adjust the estimated GFR in African Americans. The formula has been validated in adults and has been most extensively evaluated in individuals with some degree of renal insufficiency (estimated GFR <60).

A number of formulas have been used to calculate estimated GFR or its proxy, creatinine clearance. Alternative compounds have been proposed as a better marker of GFR (including inulin, iothalamate, or cystatin C), but these tests are considerably more expensive and not as readily available as creatinine. Creatinine is filtered in the glomerulus with a small amount secreted in the renal tubules, which complicates the relationship with true glomerular filtration. Difficulties collecting a complete 24-hour urine specimen limit the accuracy of the creatinine clearance result.

The Cockcroft-Gault equation is widely used; however, recent data suggests the MDRD equation gives a more accurate estimated GFR, at least when mild renal impairment is present. Little published data is available using the MDRD equation for drug dosing purposes. Given the relatively low therapeutic index of some drugs dosed using the Cockcroft-

Gault formula, formal studies comparing dosing using the two different equations with correlations to toxicity and patient outcomes are needed.

The NKDEP does not currently recommend that the MDRD equation be used for pharmacologic dosing. The equation should be used only to screen for individuals at risk of chronic renal disease.

The MDRD estimated GFR equation is: Estimated GFR (mL/min/1.73m²) = 186 × (P_{cr})^{-1.154} × Age^{-0.203} × (0.742 if female) × (1.21 if African American). It can be found at: www.nkdep.nih.gov/professionals/gfr_calculators/mdrd.htm

The Schwartz estimated GFR calculator for children can be found at: www.nkdep.nih.gov/professionals/gfr_calculators/gfr_children.htm

Suggested reading

1. NKDEP “Frequently asked questions about estimated GFR values”: www.nkdep.nih.gov/professionals/gfr_calculators/gfr_faq.htm
2. Report of an NKDEP meeting, “Creatinine assay and reporting estimated GFR”: www.nkdep.nih.gov/about/meetings/01062003gfr_report.pdf
3. “Validating GFR information via data mining and practical aspects of embedding GFR data in the LIS/HIS,” by Jay Jones, a question and answer session: www.aacc.org/access/gfr/index.asp

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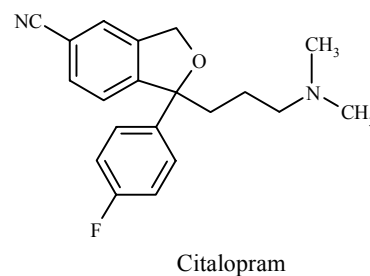
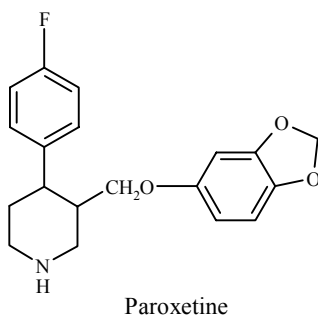
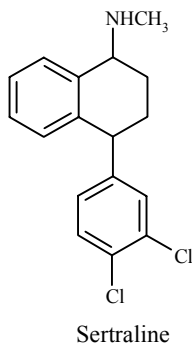
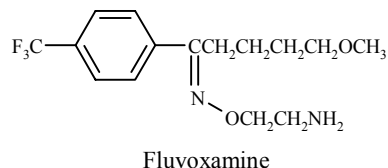
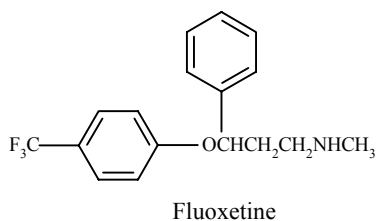
SSRIs

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produce fewer side effects, which in turn results in increased compliance.

Despite the extensive and ongoing neurobiological research into exactly how SSRIs elicit their physiologic responses, the hypotheses remain equivocal. Although preventing serotonin reuptake is a key pharmacological property of SSRIs, there remains one flaw to this being the entire explanation for the mechanism of action. The transport block and reuptake inhibition increase the level of serotonin in the synaptic cleft immediately. The clinical efficacy of SSRIs, however, takes several weeks to manifest, which suggests the mechanism is at least biphasic (1). The serotonin increase occurs not only at the axon but predominantly at the dendrites, where over time it desensitizes the somatodendric 5-HT_{1A} autoreceptors of the presynaptic neuron and reduces the inhibitory control they exert on the synthesis and release of serotonin. The desensitization leads to the release of more serotonin at the axon and into the synaptic cleft. In addition, there is some evidence that the postsynaptic serotonin receptor subtypes

Figure 1. SSRI Chemical Structures



may be down-regulated by the increased serotonin stimulation of these receptors. 5-HT_{2A} receptor down-regulation, in particular, has been implicated in antidepressant therapy (2). Indeed, some of the side effects observed with SSRIs and the subsequent development of tolerance to them may also be explained by an increase in serotonin receptor stimulation followed by their down-regulation. Suffice it to say, the mechanism of action is convoluted but appears to be due to the potentiation of serotonergic transmission in the CNS resulting from inhibition of neuronal reuptake of serotonin. SSRIs have no effect on the undepressed population and treated individuals respond differently to the various SSRIs.

PHARMACOKINETICS: Absorption

SSRIs are well-absorbed after oral ingestion but are subject to first pass hepatic metabolism, leading to reduced bioavailability. Peak serum concentrations occur 3–8 hours after a single dose. Food doesn't affect the bioavailability, although it can affect absorption by 1–2 hours. Except for sertraline and citalopram, SSRIs display non-linear kinetics; the increase in blood concentrations is disproportionate to dose increase. In addition, the half-lives of SSRIs tend to increase with increasing doses. SSRIs don't have a predictable correlation between plasma concentration and therapeutic efficacy.

Distribution

SSRIs are lipophilic drugs and have large volumes of distribution (Vd), indicating extensive tissue

distribution (Table 1). SSRIs cross the placenta and enter the breast milk.

Fluoxetine has the largest Vd of all the SSRIs and is approximately 94% protein bound. Fluoxetine is supplied as a racemate with both enantiomers, *R*- and *S*-, having equivalent pharmacological activity. Fluoxetine and its major metabolite, norfluoxetine, both have long half-lives and accumulate in the blood after chronic dosing. *S*-Fluoxetine is eliminated more slowly than *R*-fluoxetine and is the predominant isomer present at steady state. *S*-Norfluoxetine is as potent at inhibiting serotonin reuptake as the parent enantiomers, while *R*-norfluoxetine is less so. After chronic dosing in a therapeutic regimen, the concentration of fluoxetine is less than that of norfluoxetine because the metabolite has a significantly longer elimination half-life than the parent compound. This fact can be useful in interpreting postmortem drug levels because the mean whole blood fluoxetine/norfluoxetine ratio at therapeutic levels is 0.8, but with overdose reaches 4.17 (3). Fluoxetine accumulates in lysosome-rich lung tissue and is approximately 2.5 times more concentrated in the brain than in plasma, although the brain concentrations are lower than for the other SSRIs.

Fluvoxamine has the lowest plasma protein binding at 77%, making drug interactions with highly protein-bound drugs less likely than with some of the other SSRIs. Fluvoxamine has a relatively short half-life, which results in steady-state plasma concentrations occurring after about a week.

Sertraline is the second most potent SSRI and

Table 1. SSRI Pharmacokinetic Parameters (4–9)

Drug (active metabolite)	Dose (mg/day)	Elimination half-life	Vd (L/kg)	% Plasma protein binding	Time to steady-state conc.	Therapeutic plasma conc. (mg/L)	Isoenzymes involved in metabolism	Inhibited isoenzymes
Fluoxetine (Norfluoxetine)	20–80	4–6 days (4–16 days)	12–42	94	4–5 weeks	0.03–0.47 (0.02–0.47)	CYP2D6, 3A4, 2C9, 2C19	CYP2D6, 3A4, 2C9, 2C19
Fluvoxamine	50–300	8–28 h	25	77	1 week	0.09–0.55	CYP1A2, 2C19	CYP1A2, 2C9, 2C19, 3A4
Sertraline (Norsertraline)	50–200	24 h (60–100 h)	>20	98	1 week	0.02–0.21 (167% of parent)	CYP3A4	CYP2D6
Paroxetine	20–50	21 h (mean)	3–28	95	7–10 days	0.06 (mean)	CYP2D6	CYP2D6, 3A4
Citalopram	20–40	35 h (mean)	12	80	10 days	0.04–0.10	CYP2C19, 3A4, 2D6	Negligible

All values are subject to inter-individual variation.

is marketed as a single enantiomer despite having two chiral centers. Sertraline has an elimination half-life similar to that of fluvoxamine and consequently also reaches steady state after about one week. Sertraline's major metabolite, norsertraline, like norfluoxetine, has a much longer half-life than the parent drug, which results in an accumulation after chronic dosing. Norsertraline, however, has less than 20% of the pharmacological activity of sertraline. The mean postmortem whole blood sertraline/norsertraline ratios for therapeutic and supratherapeutic ingestion have been reported at 0.74 and 2.0, respectively (3).

Paroxetine is the most potent SSRI, although it is less selective at inhibiting serotonin over norepinephrine reuptake than the other SSRIs. In addition, paroxetine has an affinity for muscarinic acetylcholine receptors similar to that of TCAs. Despite this, the anticholinergic effects are minimal. Paroxetine is a chiral molecule but is marketed as the pure *S*-enantiomer. It is approximately 95% protein bound and is widely distributed in the body, including the CNS, with less than 1% left in the plasma.

Citalopram is the most selective of the SSRIs at inhibiting serotonin over norepinephrine reuptake, although it does have some affinity for α_1 - and H_1 -receptors. Citalopram is the second-lowest SSRI in the level of protein binding (80%). Like sertraline, it displays linear kinetics under steady-state conditions. Citalopram is marketed as a racemate, but it is only the *S*-enantiomer that possesses SSRI activity. This distinction between the isomers led to the production of escitalopram (Lexapro), which is pure *S*-citalopram (10). Citalopram's major metabolite, *N*-desmethylcitalopram, has some SSRI activity, but because it is only present in plasma at 50% of the concentration of the parent, its overall pharmacological activity is considered to be insignificant.

Metabolism

SSRIs are extensively metabolized in the liver through Phase I oxidative reactions followed by Phase II glucuronide conjugation. The oxidative reactions involve catalysis by the cytochrome P450 (CYP) mono-oxygenases and involve several families and isoforms. Table 1 indicates which enzymes are involved with which SSRIs. The non-linear kinetics mentioned above are probably due to saturable elimination pathways and autoinhibition of the various P450 isoenzymes. Also, polymorphic distribution of some isoenzymes, such as CYP2D6, leads to genetic differences in the population. For example, approximately 4–10% of the Caucasian population lack the CYP2D6 isoenzyme and are classified as poor metabolizers, while the remainder are extensive metabolizers. Poor metabolizers have an increased risk of adverse effects arising from higher concentrations of unmetabolized drugs that utilize this enzyme, primarily fluoxetine and paroxetine (11).

Fluoxetine undergoes *N*-demethylation to its major and active metabolite, norfluoxetine, primarily due to the actions of isoenzyme CYP2D6. Studies also suggest that additional contributions may come from CYP2C9, CYP2C19, and CYP3A4. Both fluoxetine and norfluoxetine have been implicated in the inhibition of these same enzymes, leading to many potential drug–drug interactions that could persist for weeks, even after cessation of use, due to the long elimination half-lives of both analytes.

The major metabolic pathways for fluvoxamine biotransformation are oxidative demethylation and deamination, although all the enzymes responsible have not been clearly identified. It is known, however, that CYP1A2 plays a prominent role and that CYP2C19 is also probably involved. The main metabolite of fluvoxamine, fluvoxamine acid, is one of 11 known metabolites and is a weak serotonin reup-

take inhibitor. Fluvoxamine is an inhibitor of isoenzymes CYP2C19, CYP21A2, CYP23A4, and CYP22C9. As with fluoxetine, this widespread inhibition causes many potential pharmacokinetic side effects.

In sertraline's major metabolic pathway, the isoenzyme CYP3A4 converts sertraline to norsertraline through *N*-demethylation. Both sertraline and norsertraline also undergo deamination, hydroxylation, and glucuronidation. Sertraline shows only possible inhibition of the P450 enzymes, the most probable being CYP2D6. This means that drug-drug interactions with sertraline are of minor importance.

Paroxetine undergoes oxidative cleavage of the methylenedioxy bridge by the CYP2D6 isoenzyme, followed by methylation at both the *meta*- and *para*-positions. These metabolites are further biotransformed by glucuronide and sulfate conjugation. The metabolites have negligible potency as SSRIs and are considered inactive. Paroxetine is the most potent inhibitor of CYP2D6 and may also show weak inhibition of CYP3A4. Despite this potent inhibition, CYP2D6 is the only enzyme of significance that paroxetine inhibits, and the inhibition lasts only as long as paroxetine does in the body. There is, therefore, less drug-drug interaction potential with paroxetine than with fluoxetine.

Citalopram is converted by enzymes CYP2C19 and CYP3A4 to *N*-desmethylcitalopram. *N*-Desmethylcitalopram is then further metabolized to di-desmethylcitalopram by CYP2D6. The ratio of *S/R* citalopram and the corresponding ratio of desmethylcitalopram are less than unity, suggesting that the *R*-enantiomers of citalopram and its metabolite are metabolized more slowly than the *S*-enantiomers (10). Citalopram doesn't appear to inhibit any CYP isoenzymes, although *N*-desmethylcitalopram weakly inhibits CYP2D6. Consequently, citalopram doesn't appear to have any relevant drug-drug interactions and is the safest SSRI in this respect.

Elimination

SSRIs undergo extensive hepatic metabolism followed by renal excretion. The extensive metabolism of these drugs results in less than 10% of fluoxetine and citalopram, 2% of fluvoxamine and paroxetine, and 0.2% of sertraline being excreted unchanged in the urine. As one might expect, liver disease impairs the plasma clearance of SSRIs, up to 30% with fluvoxamine and 37% with citalopram, although renal disease appears to have little effect.

PEDIATRICS AND GERIATRICS (4)

Generally, in the geriatric population, SSRIs display an increase in plasma concentration and

elimination half-life with reduced clearance. Paroxetine shows the most dramatic effects. Few of these drugs have been studied in the pediatric population. The plasma concentrations of fluoxetine and sertraline have been shown to be higher at a given dose compared with adults, but the difference is attributable to lower body weight. Sertraline may be metabolized slightly more efficiently than in adults. The differences in pharmacokinetics in geriatric and pediatric populations are best accounted for by using lower doses and titrating more cautiously.

ANALYSIS

SSRIs are organic bases that are traditionally analyzed after chemical separation from the biological matrix using gas chromatography with mass spectroscopy or nitrogen phosphorous detection. More affordable technology is leading to the application of high-performance liquid chromatography coupled with mass spectroscopy to this analysis.

TOXICITY

There are numerous potential adverse side effects of SSRIs (Table 2), although most are fairly benign and chronic users will form a tolerance to them. A potentially lethal side effect is the syndrome of inappropriate antidiuretic hormone (3,12), particularly with fluoxetine use. This syndrome manifests as impaired water excretion leading to hyponatremia, hypo-osmolarity, and consequently, lethargy, anorexia, nausea, vomiting, muscle cramps, coma, convulsions, and death.

Serotonin syndrome (12,13) is also of significant concern. It rarely results from taking a single SSRI (unless in overdose), but rather from taking a combination of SSRIs or an SSRI with other serotonergic drugs including TCAs, monoamine oxidase inhibitors, amphetamine derivatives, L-tryptophan, dextromethorphan (13,14), and tramadol (11), all of which contribute to an increase in serotonin in the body. Serotonin syndrome occurs as the result of excess serotonin at the postsynaptic serotonin receptors. Its symptoms include agitation, confusion, mania, diaphoresis, diarrhea, fever, shivering, tremor, hyperthermia, hypotension, tachycardia, mydriasis, rigidity, hyperreflexia, myoclonus, ataxia, and sei-

Table 2 Common Side Effects of SSRIs (4)

<i>Gastrointestinal:</i>	Nausea, diarrhea, weight loss, dry mouth, dyspepsia, constipation
<i>Central Nervous System:</i>	Insomnia, anxiety/nervousness, somnolence, tremor, decreased libido, dizziness
<i>Cardiovascular:</i>	Palpitation, vasodilation
<i>Respiratory:</i>	Pharyngitis, yawning
<i>Other:</i>	Sweating, asthenia, abnormal ejaculation

zures. These symptoms are non-specific and can go unrecognized or can be misdiagnosed as neuroleptic malignant syndrome in patients also being treated with antipsychotic agents. Treatment of serotonin syndrome ranges from discontinuation of drug therapy to supportive care and treatment with agents such as chlorpromazine, cyproheptadine, and propranolol, which act as non-specific serotonin antagonists (3,13).

Potential adverse side effects of SSRI therapy also include vasoconstriction resulting from excess serotonin in platelets (3), and cardiovascular toxicity (12) in people with pre-existing heart disease. An instance of a bleeding disorder associated with sertraline (3) has also been reported.

Drug-drug interactions

Side effects result not only from pharmacodynamics but also from drug-drug interactions. Pharmacokinetic drug-drug interactions involving SSRIs are primarily the result of inhibition of hepatic CYP450 enzymes that metabolize other drugs. With their metabolism inhibited, these drugs can then accumulate and cause deleterious effects. SSRIs vary in their effects on the CYP enzymes and hence have the potential for many different drug-drug interactions (6, 9). In addition, an SSRI can inhibit the activity of an isoenzyme even if the SSRI is not a substrate of that enzyme (see Table 1). Consequently, knowledge of the metabolic pathway of the SSRI doesn't always enable one to predict its potential for drug interactions (9). The inhibition constant K_i , derived experimentally in vitro, can be a good indicator of an SSRI's enzyme inhibition potency. K_i , however, does not always accurately predict whether a pharmacokinetic drug interaction will occur in vivo or whether the inhibitory action will have clinical significance with the drugs involved (15). There are many confounding factors that lead to large interindividual variations in drug-drug interactions that must be kept in mind, but which are beyond the scope of this text (15, 16, 17).

The best-documented drug-drug interaction is between fluoxetine and desipramine, a secondary TCA (6, 9, 16, 17). Fluoxetine significantly inhibits isoenzyme CYP2D6. When fluoxetine and desipramine are taken concomitantly, the 2-hydroxylation of desipramine catalyzed by CYP2D6 (Figure 2) is inhibited, leading to an approximately fourfold increase in the desipramine, with potentially lethal con-

sequences. Similar observations were made with the co-administration of paroxetine and desipramine (9), with some increase observed with concomitant use of sertraline (9, 16). In contrast, there is no interaction seen with fluvoxamine and desipramine. However, co-administration of fluvoxamine and imipramine, a primary TCA, causes a large increase in imipramine concentration (9, 16), presumably through inhibition of isoenzymes other than CYP2D6 (Figure 2).

Paroxetine, fluoxetine, and fluvoxamine have been clinically observed to interact with methadone (18) through inhibition of CYP2D6 and CYP3A4. Tramadol and dextromethorphan are also substrates for CYP2D6 and are subject to drug-drug interactions with SSRIs.

Fluoxetine and fluvoxamine have been reported to have significant interactions with the triazolobenzodiazepines, alprazolam and triazolam, due to CYP3A4 inhibition by the SSRIs (6, 9, 16, 17). The results are variable, probably due to the high number of confounding factors that affect CYP3A4, the most prevalent CYP450 isoenzyme (15). Carbamazepine, metabolized by CYP3A4, has been reported to increase in concentration with the use of fluoxetine and fluvoxamine (6).

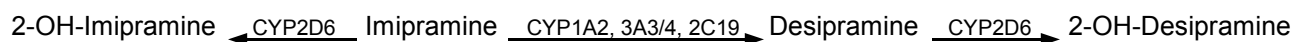
Fluvoxamine and theophylline interaction through CYP1A2 inhibition is also well-known, and it is recommended that theophylline dosing be adjusted when co-administered with fluvoxamine (17). Clozapine is also susceptible to the effects of CYP1A2 inhibition by fluvoxamine (9, 11, 16). Moreover, clozapine concentrations are increased by fluoxetine's inhibition of other isoenzymes (11, 19) and may also be increased when used simultaneously with paroxetine, and to a lesser extent, sertraline (11, 19).

Warfarin and phenytoin are substrates for CYP2C9. Fluvoxamine and fluoxetine have both been implicated in causing an increase in warfarin plasma concentrations, and fluoxetine can also elevate phenytoin (6, 9, 17, 19).

Discontinuation syndrome

In 25% of patients, abrupt cessation of SSRIs can lead to a group of symptoms known as SSRI discontinuation syndrome (8, 20). Symptoms include headache, dizziness, disequilibrium, crying, confusion, nausea, insomnia, and anxiety. The syndrome can be treated by resuming medication or gradually

Figure 2. Metabolic Pathways of Imipramine and Desipramine (9)



tapering the dose. While not dangerous, the symptoms are unpleasant and may be confused with physical illness.

Suicide increase

In March 2004, the Food and Drug Administration issued a statement that SSRIs must include a warning on their labels that all patients should be "monitored closely for worsening depression or the emergence of suicidality." This was in response to studies that found that children under 18 years of age showed a slight increase in suicidal behavior when taking SSRIs compared with placebo (3.7% vs. 2.5%) (21).

Pregnancy

While there are no apparent teratogenic effects, SSRIs have been associated with an increased rate of spontaneous abortion. Infants with lower birth weights and premature delivery may also be of concern. Recently, it was documented that newborns can suffer from SSRI withdrawal symptoms, particularly if the mother took the medication in her last trimester. In one instance, withdrawal from sertraline may have led to the death of an infant (22). Consequently, SSRIs should be used in pregnancy only if the potential benefit justifies the risks to the infant.

Geriatric population

The overall adverse effects of SSRIs in the elderly were similar to those in the younger population. Systemic illness, such as cardiac disease, and the increased chance of drug-drug interactions should be taken into consideration.

POSTMORTEM TOXICOLOGY

Lethal levels of SSRIs are difficult to define using postmortem specimens because SSRIs are rarely taken alone and the considerable potential drug-drug interactions frequently lead to SSRIs being a contributing cause of death. Other confounding factors include postmortem redistribution (23) (because not all values in the literature distinguish peripheral and central blood), the reliability of the blood source, and varying postmortem intervals. To aid with interpretation, liver concentrations should be evaluated because they are several orders of magnitude higher than blood concentrations in overdose. In addition, parent/metabolite ratios, where applicable, can help elucidate postmortem concentrations. Generally, it has been observed that fatal whole blood fluoxetine concentrations tend to be greater than 1 mg/L with a combined fluoxetine/norfluoxetine level of greater than 2 mg/L (3, 24). It has also been suggested that fluvoxamine may be lethal at whole blood concentra-

tions greater than 3 mg/L, although fluvoxamine-only deaths are rare (3). Fatal whole blood sertraline levels appear to be >1.5 mg/L (8, 25), while a peripheral whole blood concentration for a death attributed solely to paroxetine has been reported at 0.41 mg/L (3, 26). Postmortem whole blood citalopram levels greater than 1.3 mg/L in deaths attributed directly to the drug have been suggested (27), although a more conservative estimate has been given at 0.35 mg/L (28). As with any postmortem interpretation, the entire case including history, pathology, and circumstances surrounding the death must be considered.

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