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The Selective Serotonin Reuptake Inhibitor Sertraline: Its Profile and Use in Psychiatric Disorders

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ABSTRACT

The naphthylamine derivative sertraline is a potent and selective inhibitor of serotonin reuptake into presynaptic terminals. Sertraline has a linear pharmacokinetic profile and a half-life of about 26 h. Its major metabolite, desmethylsertraline does not appear to inhibit serotonin reuptake. Sertraline mildly inhibits the CYP2D6 isoform of the cytochrome P450 system but has little effect on CYP1A2, CYP3A3/4, CYP2C9, or CYP2C19. It is, however, highly protein bound and may alter blood levels of other highly protein bound agents. Sertraline is a widely used serotonin reuptake inhibitor that has been shown to have both antidepressant and antianxiety effects. Many clinical trials have demonstrated its efficacy in depression compared with both placebo and other antidepressant drugs. Its efficacy has also been demonstrated in randomized, controlled trials of patients with obsessive-compulsive disorder, panic disorder, social phobia, and premenstrual dysphoric disorder. In short-term, open-label studies it has appeared efficacious and tolerable in children and adolescents and in the elderly, and data are positive for its use in pregnant or lactating women. Typical side effects include gastrointestinal and central nervous system effects as well as treatment-emergent sexual dysfunction; withdrawal reactions may be associated with abrupt discontinuation of the agent. The safety profile of sertraline in overdose is very favorable. Sertraline's efficacy for both mood and anxiety disorders, relatively weak effect on the cytochrome P450 system, and tolerability profile and safety in overdose are factors that contribute to make it a first-line agent for treatment in both primary and tertiary care settings.

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INTRODUCTION

Sertraline is an antidepressant and antipanic agent that is a potent and selective inhibitor of serotonin reuptake into the presynaptic terminal (95,121). Selective serotonin reuptake inhibitors (SSRIs) depress the firing of neurons in the raphe nucleus, which in turn may affect norepinephrine neurons of the locus coeruleus (191). Increased firing of locus coeruleus neurons leads to desensitization of the postsynaptic β- and presynaptic α_2-receptors, and it has been demonstrated that sertraline leads to subsensitivity of β-adrenoceptors in rat brain (120). This blunted β-adrenoceptor responsivity of the noradrenergic receptor-coupled adenylate cyclase system occurs after repeated doses of many antidepressants (11,155) and has been described following electroconvulsive therapy (227). This effect may also partially account for the effectiveness of sertraline as an antipanic agent, as noradrenergic neurons of the locus coeruleus as well as the serotonergic system have been implicated in anxiety (169).

In contrast to the findings of downregulation of β-adrenoceptors, an increase in adenylate cyclase activity has been demonstrated following chronic antidepressant treatment and electroshock in rat hippocampus and cortex (40,109,174). Duman and colleagues (57) have suggested that even though there is a relative decrease in β-adrenoceptors after chronic antidepressant administration compared with acute administration, levels of cyclic adenosine monophosphate (cAMP) remain elevated compared to a no treatment state. Thus, despite downregulation of β-adrenoceptors, there is an overall increase in activity in the cAMP system because of the increased norepinephrine levels remaining in the synapse. Antidepressants, including sertraline, may ultimately exert their antidepressant effects through activation of the cAMP pathway, which in turn leads to regulation of cAMP-dependent protein kinase and subsequently to activation of the cAMP response element binding protein (CREB). CREB may mediate its effect by inducing increased expression of neuroprotective neurotrophins such as brain-derived neurotrophic factor (57) which, along with CREB, has been shown to be elevated following chronic antidepressant and electroconvulsive therapy (165,166). The effect of increased neurotrophins may be to mitigate hippocampal changes associated with exposure to stress. While largely theoretical, this model of antidepressant action provides the best current hypothesis regarding the mechanism of action of antidepressants, and it is supported by empirical studies of the pathophysiology of depression in human (186,214) and animal models (45,141,182,206).

CHEMISTRY

The structure of sertraline [(1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine], its metabolite desmethylsertraline [(1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4–tetrahydro-1-naphthalenamine], and part of the metabolic sequence are shown in Fig. 1 (96). This tetrahydronaphthylamine derivative is a white to off-white crystalline powder that is soluble in chloroform, slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

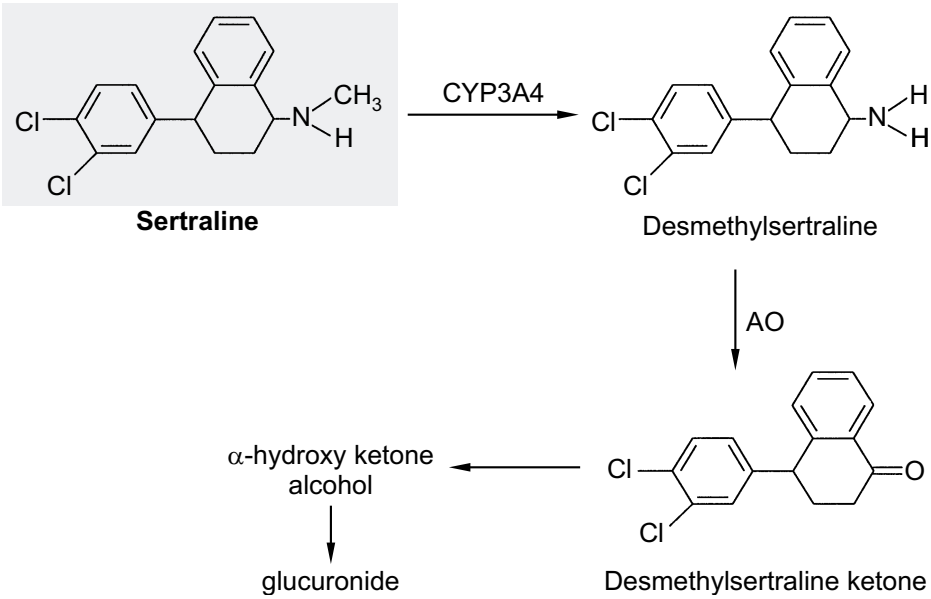

Fig. 1. The structure of sertaline and its metabolic sequence.

PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic profile of sertraline has been reviewed previously (82,161,178, 200,204,237) and we will, therefore, present only a brief overview including recent findings.

Absorption and elimination

The maximum plasma concentration has been found to be 20–55 μg/L following single 50–200 mg doses of sertraline, occurring 4–8 h after oral administration (161). The plasma elimination half-life of sertraline (about 26 h) allows for once daily dosing, and with this, a decreased likelihood of side effects due to accumulation as well as avoidance of an extended washout period after discontinuation (82). Moreover, the more rapid accumulation of sertraline to steady-state plasma levels [approximately 1 week of daily administration (243)] compared with fluoxetine, for example, suggests a concordant faster onset of therapeutic action (82).

Desmethylsertraline, the major metabolite, has a plasma half–life of about 62 to 104 h (243). The metabolite appears to lack serotonin reuptake inhibiting properties in *in vitro* and *in vivo* studies (219). A linear pharmacokinetic profile (i.e., the plasma concentration of sertraline is proportional to the dose administered) has been demonstrated at the common clinical sertraline dose range of 50 to 200 mg per day. Dose titration and multiple dosing may be less problematic with sertraline compared with other SSRIs, which have nonlinear pharmacokinetic profiles (e.g., fluoxetine or paroxetine) (82). The half-life of *N*-desmethylsertraline has been shown to be about 50% longer in elderly males and fe-

males than in young males following a single daily dose of 200 mg (200). The clinical relevance of this finding is likely to be minimal as desmethylsertraline is largely inactive (23,219).

Food increases the bioavailability of sertraline hydrochloride by at least 28% and it is recommended that it be taken with meals (201).

Cytochrome P450 enzyme system

At least five isoforms of CYP (2B6, 2C9, 2C19, 2D6, and 3A4) are involved in the metabolism of sertraline, but since the contribution of any individual isoform does not exceed 40% of the overall metabolism, concurrent administration of a drug that inhibits one of these isoforms is unlikely to cause a marked increase in the plasma concentration of sertraline (117).

Sertraline mildly inhibits the CYP2D6 isoenzyme, resulting in 10%–50% elevation in plasma levels of a co-administered CYP2D6 substrate (e.g., dextromethorphan taken with sertraline) (173,218). However, its effect on CYP1A2, CYP3A3/4, CYP2C9, and CYP2C19 appears minimal (4,82,93). There are few studies of the effect of sertraline on the 2C9/10 enzyme substrates. There is little evidence of conversion by genetically determined CYP2D6 'extensive metabolizers' to phenocopies of CYP2D6 'poor metabolizers' following treatment with daily dosages of sertraline in the range from 50–100 mg/day (187), but in general, much remains to be delineated about isoenzyme metabolism and SSRIs.

Desmethylsertraline has a mild effect on cytochrome P450 enzymes similar to that of sertraline (82). This effect is probably not meaningful at usual antidepressant doses, but may be relevant at high doses or in unusually sensitive individuals. Cytochrome P450 3A isoenzyme activity may be greater in young and postmenopausal women (185); this system is relevant to the metabolism of sertraline, and there are data describing sex- and age-related differences in plasma concentrations of sertraline (243).

Renal or hepatic impairment

Wilner and colleagues (244) demonstrated that patients with moderate to severe renal impairment do not have significantly different pharmacokinetics of sertraline. Sertraline's half-life was, however, prolonged by 42 to 92 h in patients with end-stage renal disease (207). Individuals with hepatic impairment (e.g., liver cirrhosis) have increased maximum plasma concentrations and prolonged half-lives of the drug (49).

Drug interactions

Sertraline's pharmacokinetic profile portends a favorable CYP-mediated drug–drug interaction profile, but sertraline is highly plasma protein bound and may interact with other highly protein bound drugs (178). Sertraline has been studied in combination with selected tricyclic antidepressants (TCAs), antianxiety, anticonvulsant, mood stabilizing, and antipsychotic drugs as well as with caffeine and various allergy, cold, heart, blood pressure, or anticoagulant medications (Table 1).

A number of studies have reported that the coadministration of sertraline with TCAs can increase the plasma concentrations of desipramine (2,126,189,254), imipramine (126), and nortriptyline (216). The plasma levels of a coadministered CYP2D6 substrate can be increased by an average of 19% following administration of sertraline at 50 mg/day (187).

TABLE 1. Drug–drug interaction studies with sertraline

Drug	Dose	Reference numbers	Dose of sertraline	P450 substrate	Study population	Effect of combination treatment
Tricyclics						
Desipramine	50 mg/day	189	50 mg/d	2D6	Healthy male volunteers	C_{max} DES ↑ 31%; AUC ↑ 23
Desipramine	100 mg/d	254	50–150 mg/d	2D6	Healthy male subjects	C_{max} DES ↑ up to 3-fold
Desipramine	50 mg/d	2	50 mg/d	2D6	Healthy male volunteers	C_{max} DES ↑ 44%; AUC ↑ 37%
Desipramine	50 mg/d	126	150 mg/d	2D6	Healthy male subjects	C_{max} DES ↑ 22%; AUC ↑ 54%
Imipramine	50 mg/d	126	150 mg/d	2D6	Healthy males	C_{max} IMIP ↑ 39%; AUC ↑ 88%
Nortriptyline	30–100 mg/d	216	50–150 mg/d	2D6	Elderly depressed patients	C_{max} NOR ↑ 2–50%
Anxiolytics						
Alprazolam	1 mg/d	190	50 mg/d	3A4	Healthy male volunteers	None
Alprazolam	1 mg/d	91	50–150 mg/d	3A4	Healthy male and female volunteers	C_{max} ALP + SERT (50 mg) < C_{max} ALP
Diazepam	10 mg	78	200 mg/d	2C19 3A3/4	Healthy male volunteers	Prolonged time to C_{max} N-demethyldiazepam; diazepam clearance ↓ by –0.0100 mL/min/kg
Clonazepam	1 mg/d	24	100 mg/d	3A	Healthy male and female volunteers	21% ↓ in elimination half-life of clonazepam metabolite
Mood Stabilizers/Anticonvulsants						
Lithium	1200 mg/d	8	200 mg/d	–	Healthy volunteers	↑ tremors
Carbamazepine	200–400 mg/d	195	50–200 mg/d	3A	Healthy male volunteers	None
Carbamazepine	400 mg/d	190	50–200 mg/d	3A	Healthy male volunteers	None
Phenytoin	300 mg/d	194	50–200 mg/d	2C	Healthy male volunteers	None
Antipsychotics						
Haloperidol	Unknown	131	50 mg/d	2D6	Patients with schizophrenia	None
Clozapine	175 mg/d	41	50 mg/d	1A2	Case report	2-fold CL worsening of psychotic symptoms
Clozapine	279 mg/d (mean)	38	92.5 mg/d (mean)	1A2	Psychotic outpatients	↑ CL to toxic levels

TABLE 1 (continued)

Drug	Dose	Reference numbers	Dose of sertraline	P450 substrate	Study population	Effect of combination treatment
Others						
Caffeine	100 mg	173	25–150 mg/d	1A2	Patients, healthy volunteers	None
Terfenadine	120 mg/d	190	50–200 mg/d	3A	Healthy male volunteers	None
Dextromethorphan	30 mg	173	25–150 mg/d	2D6	Patients, healthy volunteer	Modest inhibition of 2D6 activity
Dextromethorphan	30 mg	218	50–150 mg/d	2D6	Male patients with MD	Modest inhibition of 2D6 activity
Digoxin	0.25–1.0 mg/d	143	50–200 mg/d	–	Healthy male volunteers	None
Warfarin	Unknown	7	Unknown	2C8/9	Healthy male volunteers	Slight delay in prothrombin time
Atenolol	50 mg/d	252	100 mg	–	Healthy male volunteers	None
Lamotrigine	Unknown	107	25 mg +	–	2 case reports	Significantly ↑ or ↓ of lamotrigine blood levels
Methadone	Unknown	90	Unknown	3A4	Opiate addicts	↑ Methadone serum levels over 1st 6 weeks
Rifampin	600 mg/d	146	200 mg/d	3A4 inducer	Case report	↑ anxiety symptoms, dizziness; SSRI withdrawal syndrome
Ortho-TriCyclen or Ortho-Cyclen	Unknown	29	50–150 mg/d		Female patients with PMDD	↓ clearance of sertraline and desmethylsertraline in 3/8 patients

C_{max}, maximum concentration in plasma; AUC, area under the concentration–time curve; MD, major depression; PMDD, premenstrual dysphoric disorder.

The observed increases in the plasma concentration of TCAs are consistent with only weak inhibition of this system.

In controlled studies, sertraline has not been found to effect significant change in the pharmacokinetic parameters of carbamazepine (a CYP3A substrate) or its epoxide metabolite) (190,195). Similarly, no significant interaction has been found in a randomized, controlled trial of 30 healthy males who received concomitant sertraline and phenytoin (a CYP2C19 substrate) (194).

To date, there is no evidence of clinically significant interaction between sertraline and lithium (8), and sertraline does not significantly impact plasma concentration levels of haloperidol (a CYP2D6 substrate) (131). An approximately twofold increase in clozapine level (thought to be primarily a substrate of CYP1A2 [183]), associated with worsening of psychotic symptoms has been reported in a patient when sertraline 50 mg/day was added (41). Significant increases in serum concentrations of clozapine and norclozapine and significantly lower drug clearance were reported in 10 patients who received sertraline (mean dose 92.5 mg/day) in combination with clozapine (mean dose 305 mg/day) (38). Sertraline did not, however, alter caffeine clearance (a CYP1A2 substrate) in psychiatric patients and healthy volunteers, 19 to 85 years of age (173).

Sertraline, at a dose of 50 mg/day for 10 to 20 days, did not alter *in vivo* pharmacokinetics of alprazolam, a CYP3A4 substrate drug (190). A subsequent, randomized, controlled, *in vivo* study found a greater decrease in peak alprazolam concentration in patients who received sertraline 50 mg/day (but not 100 mg or 150 mg/day doses) than in those who received alprazolam only (91). Patients in the sertraline plus alprazolam group also showed a significant reduction in performance on a computerized manual tracking test (i.e., psychomotor function). Coadministration of clonazepam (1 mg), a CYP3A substrate, or sertraline (100 mg) daily for 10 days did not significantly affect the pharmacokinetics or pharmacodynamics of clonazepam, although the kinetics of its metabolite, 7-aminoclonazepam, showed a 21% reduction in its elimination half-life (24).

The *in vivo* effect of sertraline on oxidative drug metabolism mediated by CYP3A was further assessed in separate studies by coadministration with carbamazepine and terfenadine. Sertraline, at doses of 50–200 mg/day for 10–20 days, did not alter the pharmacokinetics of these CYP3A substrate drugs (190). The clearance of diazepam (metabolized by CYP2C19 and 3A3/4) and the time interval to maximum plasma concentration of its primary metabolite, *N*-demethyldiazepam, were not altered by sertraline in a clinically meaningful way (78).

In a controlled study of healthy male volunteers, sertraline administered concomitantly with digoxin did not significantly alter plasma digoxin concentrations or digoxin clearance (193). Similarly, no clinically significant interactions were reported in studies of healthy male volunteers who received sertraline concomitantly with warfarin (a CYP2C9 substrate) (7) or with atenolol (252).

There are two case reports of potent sertraline interaction with lamotrigine metabolism (107). In the first case, a dose of sertraline 25 mg/day resulted in a doubling of the lamotrigine blood level with symptoms of toxicity. In the second case, a decrease of the sertraline dose by 25 mg/day resulted in halving of the lamotrigine blood level, even with a concomitant increase in the lamotrigine dosage.

When sertraline was administered to patients maintained on methadone (a CYP3A4 substrate), a transient increase in methadone serum levels over the first 6 weeks of treatment was observed (90). With co-treatment with rifampin (a potent CYP3A4 inducer), a 34-year-old man experienced a recurrence of generalized anxiety symptoms; when the sertraline was tapered, the patient experienced symptoms synonymous with SSRI withdrawal syndrome (146).

The serotonin syndrome. The most dangerous sertraline-drug interaction is the serotonin syndrome (22,85,151,224), resulting from a toxic hyperserotonergic state, and manifesting as changes in mental status and behavior, motor system abnormalities and autonomic instability. The presence of triphasic wave activity on electroencephalography may assist in the diagnosis of serotonin syndrome (51). Accurate recognition of the syndrome is important because it can be fatal. It is thought to result from a precipitous increase in central nervous system serotonin availability (80). First described following coadministration of L-tryptophan and a monoamine oxidase inhibitor (MAOI) (170), it has been noted to occur with several serotomimetic agents, particularly when used in combination (167) (e.g., SSRI/SSRI interaction, or SSRI and TCA or MAOI interaction [80]). While most commonly described in combination with an MAOI (85) or the reversible MAOI, moclobemide (151), a possible serotonin syndrome has also been described with the coadministration of sertraline and other agents such as tramadol (148), amantadine, and carbidopa plus levodopa (Sinemet®) (51), which are thought to lead to increased central serotonin.

Two cases of suspected serotonin syndrome have been described in children following accidental overdose of only sertraline (105,175). There is a report of a manic episode emerging in a male patient who took hypericum while on testosterone replacement and sertraline following bilateral orchiectomy (12).

Pharmacodynamics

The pharmacodynamic properties of the SSRIs, including sertraline, have been previously reviewed (82,204).

Biogenic amine reuptake

In vitro studies have demonstrated that sertraline is 2–10 times more potent in inhibiting serotonin reuptake than fluvoxamine, fluoxetine, and clomipramine (100,119). In addition to animal *in vitro* and behavioral data, human blood platelet serotonin inhibition has been used as a measure of inhibitory effect (121). When healthy male volunteers took oral doses of sertraline between 50 and 200 mg/day, platelet serotonin reuptake was inhibited in a dose-dependent manner, with the compared affinity constant of serotonin also increasing in a dose-dependent manner (54). Sertraline indirectly downregulates postsynaptic β-adrenoceptors, but it has only weak effects on direct norepinephrine and dopamine reuptake. In dopamine reuptake, sertraline is more potent compared to a number of common antidepressants (bupropion, venlafaxine, nefazadone, paroxetine, norfluoxetine, nortriptyline, desipramine). It is about 60 times more potent at inhibiting serotonin than either norepinephrine or dopamine reuptake (23).

Central receptors

Sertraline has shown no significant affinity for adrenergic (α_1, α_2, or β), cholinergic, histaminergic, muscarinic, dopaminergic, serotonin$_{1(A\text{ or }B)}$, or serotonin$_2$ receptors (54,82). In animal studies, sertraline has been found to have a high affinity for the CNS σ_1 and a low affinity for the σ_2 binding sites (162,205). A role of the σ_1 site in the pharmacological action of sertraline may exist (162), but the significance of sertraline affinity for σ_1 and σ_2 receptors remains unclear (82,204).

CLINICAL STUDIES

Sertraline is one of the most widely used and studied SSRIs. In addition to the literature on the use of sertraline in the treatment of (primary) mood and anxiety disorders, there has been a surge of literature pertaining to its use for the treatment of mood symptomatology, associated with neurological and medical conditions, such as Parkinson's disease, diabetes mellitus and HIV infection-related mood disorders.

Mood Disorders

Major depression

A series of randomized, controlled studies have now demonstrated the efficacy of sertraline versus placebo in the treatment of major depression (55,63,171,198) (for a review see ref. 6).

Since 1990, a number of studies have also evaluated the use of sertraline in the treatment of major depression compared with other SSRIs, including fluoxetine (1,15,35,72,164,238) and citalopram (59); the serotonin norepinephrine reuptake inhibitor venlafaxine (153); TCAs, including clomipramine (135), amytriptyline (43,157), imipramine (110), and nortriptyline (69); the 5-HT_2 antagonist nefazodone (65); and the aminoketone antidepressant bupropion (108).

In general, sertraline has demonstrated equivalent efficacy to other antidepressant medications. The starting dose of 50 mg/day has been recommended as the usually effective, optimal dose for treating depression; the dose can be increased in patients who do not show an adequate therapeutic response within 2 to 4 weeks (188). Notably, regarding onset of action, a significant reduction in depression scores was apparent at 2 weeks in persons who received sertraline or citalopram in the course of a double-blind comparative trial with no statistically significant differences between the two drugs (59).

In the treatment of depression with melancholic features, sertraline had greater efficacy compared with fluoxetine (72,130), paroxetine (251), and mianserin (142) and equivalent efficacy to the TCAs, including amitriptyline (198) and clomipramine (135).

Patients treated for major depression who were maintained on sertraline demonstrated persistent improvement (and less frequent relapse) for up to 24 weeks following the acute treatment period compared with patients receiving placebo (111,159,177).

Equal or greater global improvement was also observed in patients taking sertraline compared with fluoxetine after 24 weeks of continued therapy (130,238). Persons in a double-blind multicenter, 24-week comparative trial demonstrated equal tolerability of citalopram and sertraline (59). The recent data that was collected by evaluating patients monthly for 48 months showed comparable preventive efficacy and safety of sertraline and fluvoxamine (4-year intent-to-treat period recurrence rates: 31.2 and 34.3%, respectively) (73).

In the treatment of major depression, Lydiard and colleagues (139) found that the patients receiving sertraline, compared with those taking amitriptyline or placebo, had earlier gains and greater overall improvement in quality-of-life outcome measures in contrast to studies examining only acute symptom reduction.

Buchsbaum and colleagues (30), compared positron emission tomography images of patients with major depression before and after 10 weeks of treatment with sertraline or placebo. Patients who received sertraline had a significant increase in the metabolic rate in frontal cortical areas and a lower metabolic rate in the medial cortical and subcortical regions; these changes were also associated with greater clinical improvement.

In exploratory studies, the β-blocker/5-HT_{1A} antagonist pindolol has been successfully added to paroxetine, fluvoxamine, and fluoxetine to potentiate the SSRI antidepressant response in patients with resistant major depression (10,21). Results of this augmentation strategy with sertraline have been less persuasive. There is a report of successful pindolol-induced (2.5 mg t.i.d.) augmentation of sertraline (150 mg/day) in a 34-year-old woman with a 2-year history of treatment-resistant depression (14), but in an open trial with five outpatients, the addition of pindolol (2.5 mg t.i.d. × 1 week) to sertraline (50–100 mg/day) did not result in significant improvement (21).

Dysthymic disorder

Sertraline (50–200 mg/day) may be effective in the treatment of dysthymic disorder (118,197,221,230), although one study (118,230) has been criticized for the relatively

small changes in depression rating scores (48). Several studies have incorporated measures of both symptom change and improvement in psychosocial outcome. The results showed that the use of sertraline (118) and sertraline in combination with interpersonal psychotherapy (221) or group cognitive therapy (197) resulted in improved psychosocial function (e.g., strategies of coping; quality of life [13]) as well as symptom reduction in both early- and late-onset dysthymia. Several studies have recently demonstrated that both major depression and dysthymia can be successfully treated with sertraline in primary care settings (221,229). It has also been suggested that sertraline may be effective in the reduction of anger attacks, which occur in some patients with atypical depression or dysthymia (64). Sertraline may be beneficial in treatment of personality disorder traits (paranoid, borderline, avoidant, dependent types) in primary care patients with comorbid major depression (58).

Anxiety Disorders

Obsessive-compulsive disorder

Randomized, controlled studies have demonstrated the efficacy of sertraline versus placebo in the treatment of obsessive-compulsive disorder (OCD) (71,86,87,124,181). In contrast to a case report of a patient with OCD whose symptoms significantly declined only at a dose of 300 mg/day (34), randomized trials that compared sertraline doses did not find clear benefit for 200 mg/day dose compared to either 50 or 100 mg/day (86). Patients with OCD who responded to sertraline within 3 months had sustained improvement over an additional 40 weeks of therapy (87), and a further study by the same group showed that benefits were sustained and perhaps enhanced, over 52 weeks of therapy (196).

In a double-blind comparative trial of sertraline versus clomipramine, significant improvement was noted with either drug. However, patients who received sertraline had greater improvement with fewer side effects than those who received clomipramine (20).

A double-blind comparison of sertraline and desipramine for concurrent OCD and major depression showed a greater treatment efficacy in favor of the serotonin reuptake inhibitor (99). More patients in the sertraline-treated group than those in the desipramine-treated group (49 vs. 35%, respectively) achieved remission of depression (HAM-D score of <7). The sertraline group also had a higher percentage of clinical responders (Y-BOCS $\geq 40\%$ reduction) than the desipramine group (48 vs. 31%, respectively) and a significantly lower discontinuation rate due to adverse events.

In addition to efficacy for OCD, a series of case reports have suggested that sertraline may be efficacious in OCD-spectrum disorders, such as trichotillomania and paraphilia (26), bulimia nervosa (199), compulsive skin picking (104), and Tourette's syndrome with attention deficit hyperactivity disorder (ADHD) (74). Sertraline also has been reported to be efficacious in the treatment of obsessive-compulsive symptoms emerging in response to risperidone treatment (52).

Social phobia

Several open studies found sertraline effective in the treatment of social phobia (47,106,147,160,235), including a series of children and adolescents with social phobia (144). A relatively small, double-blind, placebo-controlled, flexible dose, crossover study of sertraline vs. placebo reported a statistically significant decrease in the Liebowitz

Social Anxiety Scale following 10 weeks of treatment. A multisite, 20-week, double-blind, controlled study showed that sertraline is efficacious in the treatment of generalized social phobia in adults (236; for a review, see ref. 234). A 24-week follow-up randomized, controlled study of 50 patients found sertraline effective in preventing relapse of social phobia (241).

Panic disorder

There are now several randomized, double-blind controlled studies of sertraline in panic disorder, including a total of over 500 patients; these studies include fixed (137) and flexible dose (184) schedules (for a review, see ref. 84). In each study, patients who received sertraline demonstrated significantly reduced frequency of panic attacks compared with the placebo group, but a clear dose-response relation did not emerge in the fixed dose studies (212).

Post-traumatic stress disorder

Sertraline has been studied in the treatment of post-traumatic stress disorder (PTSD) with combat veterans. More than 30% of combat veterans (mostly male subjects) enrolled in two open trials, with dual diagnoses of PTSD and major depression, showed significant improvement on Clinical Global Impression scores (56,116). Kline and colleagues (116) noted reductions in symptoms of dysphoria, irritability, and anger. Open and randomized, controlled trials found sertraline effective in persons with a past experience of trauma — most frequently physical or sexual assault — and longstanding PTSD (mean duration of illness 12 years) (28,203). Sertraline was particularly efficacious in the reduction of avoidance/numbing and arousal, in improvement of occupational and social functioning as well as in overall quality of life. Sertraline has been approved by the Food and Drug Administration for the treatment of PTSD (94).

Other Psychiatric Conditions

In case reports and small series, sertraline has been shown to be effective in the treatment of depression and behavioral disturbance associated with a variety of neurological conditions, including Parkinson's disease (92); Huntington's disease (192); post-stroke pathologic crying (179); stroke-associated lability of mood (33); multiple sclerosis (208); pervasive developmental disorder in children, adolescents, and adults (68,150); ADHD and Gilles de la Tourette's syndrome (74); and poorly defined impulsive violent behavior (31).

Sertraline was also more effective in the treatment of post-psychotic depressive disorder of schizophrenia when compared with imipramine in terms of rapid onset of action; frequency, severity, and duration of side effects; and risk of schizophrenia relapse (115).

Sertraline appears to be effective and well tolerated in patients with depressive symptoms who also have such medical illnesses as diabetes mellitus (83), endometriosis (242), AIDS (66), or noncardiac chest pain (239). Sertraline also seems effective when it is given to treat major depression following acute myocardial infarction (210). However, close monitoring of thyroid indices is recommended in patients with known thyroid abnormalities (in particular, hypothyroidism) and in those who receive concomitant antidepressant medication since case reports have suggested that sertraline may suppress thyroid function (42,149).

Sertraline was not more effective than placebo in the maintenance of weight loss in obese patients (240). Furthermore, there was no significant improvement in pain or functional ability of sertraline-treated women with chronic pelvic pain compared with those treated with placebo (60).

SPECIAL POPULATIONS

Children and Adolescents

There is some evidence, including a systematic trial, suggesting that sertraline use is increasing in children and adolescents (50). There is evidence that the pharmacokinetic and safety properties of sertraline in children and adolescents are similar to those reported for adults (3), but only limited information is available about interactions of sertraline with other drugs in children or adolescents.

Sertraline appeared to be effective and well tolerated in short-term, open-label and double-blind, placebo-controlled trials for children and adolescents with OCD (with or without comorbid major depression) (3,67,145). In a case series of seven patients aged 9 to 23 years, clomipramine in combination with sertraline was found to be more effective than monotherapy — although side effects were significant (67). In case reports, sertraline was used with success in the treatment of childhood syncope (133), autism (223), nocturnal enuresis (217), and steroid-induced mood disorder and psychosis (17). A small, prospective study of aggressive behavior in hospitalized adolescents, however, reported little effect of sertraline on symptoms of physical aggression toward others or self (44).

There are several reports of children treated with sertraline developing behavioral activation or mania (79,232). Unusually, mydriasis was reported in an 11-year-old boy treated with sertraline for major depression, but the authors noted that the dose was rapidly titrated (129).

In summary, sertraline may offer advantages over the TCAs in children and adolescents, but pharmacokinetic data and systematic studies of safety and efficacy in this age group are limited (134).

Women

Premenstrual dysphoric disorder

Sertraline has proven efficacy in the treatment of premenstrual dysphoric disorder (PMDD), apparent in open-label (75) and double blind, placebo-controlled trials (76,77,89,103,248,250). Investigators have documented improvement in social and occupational role functioning, increased satisfaction in interpersonal relationships and quality of life in women who received sertraline for PMDD. Response to treatment with sertraline may occur within the first month of treatment, with 50–100 mg/day adequate for symptom relief (76,250). A decreased clearance of sertraline and desmethylsertraline was reported in three of eight women treated for PMDD who were taking oral contraceptives (29), but there was no difference in the efficacy of sertraline or adverse events among any of these eight patients.

A significant response to sertraline has been demonstrated with continuous daily dosing (76,177,248) and intermittent-dosing (luteal phase only) (76,89,103,250). Intermittent dosing offers women a less costly and more tolerable alternative to continuous treatment. The data on sertraline are thus far generally consistent with reports of efficacy and tolerability for other SSRIs (62,220,222) which, as a class, should be considered the first-line pharmacologic agents for premenstrual dysphoria (220).

Pregnancy and postpartum

A recently published report of a prospective, controlled multicenter study has suggested that when used during pregnancy in the recommended doses, the SSRIs — including sertraline — do not appear to increase teratogenic risk (125). In this cohort, 147 women used sertraline, with the majority at a dosage of 50 mg/day; pregnancy outcome did not differ between women who took medication during the first trimester only vs. those who took it throughout the pregnancy. One case of suspected neonatal sertraline dependence has been reported. In this case, the mother received 200 mg/day throughout pregnancy and the newborn baby experienced transient withdrawal symptoms (113). The risk of neonatal toxicity or neurobehavioral consequences for children exposed *in utero* to sertraline remains uncertain. The choice to prescribe antidepressants during pregnancy should be reserved for situations in which the risks of not treating appear to outweigh the potential risk of exposure (122). However, the overall body of data supporting the safety of the SSRIs in general is encouraging (39,168,176,246).

Overall, sertraline is highly efficacious and well tolerated in women with postpartum depression (225). There are several studies of sertraline and desmethylsertraline levels in infants who were breastfed during maternal treatment with sertraline (5,123,143,226,247), and one study of the platelet 5-hydroxytryptamine levels in four infants (61). The results of these studies demonstrated that plasma levels of sertraline or its metabolites in infants were very low, and that no adverse effects were detected in the observed infants. Stowe and colleagues (226) noted that concentrations of sertraline and desmethylsertraline in breast milk are influenced by the aliquot of milk sampled (higher concentrations in hind milk), time after maternal dose (highest concentrations at 7 to 10 h), and maternal daily dose. They recommended monitoring of drug levels in infants' serum (19).

Men

There is recent evidence from blinded, placebo-controlled studies to support the efficacy of sertraline in the treatment of premature ejaculation (18,114,152), but treatment trials were limited to 4 weeks.

Elderly Patients

The efficacy of sertraline in the treatment of elderly patients with major depression has been evaluated in naturalistic (231,245) and in double-blind, comparative studies (25,43,69,164). Results have shown that sertraline, 50–150 mg/day, is an effective and tolerable intervention in persons over 60 years of age. Study subjects in the sertraline-treated group showed significantly greater improvement in measures of cognitive (e.g., tasks that quantify short-term and long-term memory storage and retrieval) and psychomotor (e.g., energy and motivation factors) functioning than those in the nortriptyline- (25,69) or fluoxetine-treated groups (164). Sertraline may also be effective

for treatment of certain groups of elderly patients such as those with concomitant pathologic conditions, including cardiovascular and musculoskeletal diseases (9) or post-stroke pathologic crying (179).

The treatment of depression in patients with dementia has focused on the SSRIs — particularly sertraline and fluoxetine — that have low anticholinergic toxicity (233), but the reported results are mixed. An early investigation in elderly healthy volunteers suggested an "alerting effect" of sertraline on tests of psychomotor function (97), while a subsequent study showed no discernable effect of sertraline on psychomotor performance, memory, or attention in a similar population (98). Burke and colleagues (32) reported benefits of sertraline in the treatment of depression with psychotic symptoms in several patients with Alzheimer's disease.

Larger studies, however, have less favorable findings. A report of 97 nursing home residents (mean age, 80 years), who were observed for 10 weeks, showed that sertraline (100 mg/day) was not as effective as nortriptyline in the treatment of major or subsyndromal depression in persons with or without cognitive impairment (172). A controlled study of sertraline (100 mg/day for 8 weeks) or placebo in 17 elderly female patients with late-stage Alzheimer's disease showed equivalent improvement in behavioral and psychometric measures of depression (140); however, sertraline had no effects on agitation or feeding disturbance.

In the treatment of geriatric depression, it has been recommended to initiate pharmacotherapy at lower doses (i.e., sertraline at 25 mg/day for 4 to 7 days) with subsequent slow upward titration (163). A longer time period (i.e., 12–16 weeks) to an optimum antidepressant effect may be required (163). Older patients, in particular, may be at risk for SSRI-induced syndrome of inappropriate secretion of antiduretic hormone (SIADH) (see the following section). Close monitoring, especially within the first 4 weeks of treatment, for signs of hyponatremia is recommended (136). Sertraline has been found effective, well tolerated, and safe in elderly patients who use concurrent medications, including benzodiazepines and cardiovascular agents (e.g., antihypertensives, calcium channel blockers, cardiotonics) (9).

SIDE EFFECT AND SAFETY PROFILE

In the aggregate, the literature suggests that sertraline is a well-tolerated and safe antidepressant agent when compared with either other SSRIs or TCAs (for a comprehensive review, see ref. 80). The incidence of side effects with sertraline is related to both dose and dosage of the drug (53). In a recent review of SSRIs and anxiety disorders, Kent and colleagues (112) have suggested that, in comparison to the older medications, the SSRIs may have more favorable side effect profiles as well as greater ease of dosing, thus portending greater adherence to treatment regimens.

Side Effects

Typical adverse experiences are well outlined in the product monograph for sertraline (180) and include gastrointestinal side effects such as nausea, dyspepsia, diarrhea; and

other effects, including tremor, dry mouth, dizziness, and somnolence or insomnia. A subsequent review has elucidated SSRIs' treatment-emergent sexual dysfunction (128).

Sexual dysfunction may be noted as early as day 7 of treatment with sertraline (209). The dysfunction involves loss of sexual desire (158) and problems with orgasm (in particular, quality and delay) (127). There is a tendency for sexual function to worsen over the first month and improve over 3 months of treatment, and it is possible that sexual dysfunction may improve over longer periods of treatment. Women may experience higher rates of anorgasmia than men.

Headache is a commonly cited side effect but may not occur at rates much greater than in control patient populations, since headaches occur at a high rate in patients with depression independent of treatment (156,215). Agitation or anxiety (the 'jitteriness syndrome') may be induced by sertraline when administered at high doses (i.e., 200 mg/day) or in patients with psychomotor agitation and anxiety at the start of treatment (80). There is one case report of panic attacks precipitated by sertraline in an adult male with a history of OCD symptoms (253), and two case reports of sertraline-induced mania in a prepubertal child (79) and in an adolescent (154).

Sertraline-associated hyponatremia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is not common, and it may not be readily recognized. Symptoms can include weakness, fatigue, confusion, and disorientation as well as nausea, anorexia, muscle cramps, or seizure. However, some patients with hyponatremia may be asymptomatic. SIADH has been described most frequently in elderly patients (27,37,81,102,136). SIADH usually develops soon after the start of SSRIs therapy (i.e., within the first 4 weeks), although the time to onset of the syndrome may be as long as 4 months (136). This rare but potentially dangerous complication must be treated promptly — generally by drug discontinuation, fluid restriction, and electrolyte replacement where indicated.

Safety Profile

Sertraline alone appears relatively safe in overdose (36,53), but there has been at least one fatality associated with an overdose of a combination of sertraline with moclobemide and pimozide (151). There are reports of accidental overdose in children leading to serotonin-syndrome-like reactions (105,175). There is a report of unstable angina apparently precipitated by sertraline (228), and two reports of sudden chest pain (16,101), although the treatment with sertraline does not appear to be associated with electrocardiographic changes (70). Although its safety in patients with coronary artery disease remains to be established, the SSRIs are generally considered safer than TCAs (213), and recent data suggest that sertraline is well tolerated and effective in depressed patients following myocardial infarction (210).

Withdrawal Reactions

Withdrawal reactions can be associated with discontinuation of the SSRIs. These adverse effects include gastrointestinal complaints (nausea, vomiting, diarrhea), flu-like symptoms (muscle aches, chills, rhinorrhea, fatigue), hyperarousal or other psychological symptoms (irritability, crying spells, agitation/anxiety), sensory disturbances, and sleep disturbances (46,202,211). These reactions have been described with sertraline (138) but

appear to be more common with some of the other SSRIs (88,249). Overall, the lowest rates of withdrawal reactions appear to occur with fluoxetine (due to the very long half-life of its active metabolite norfluoxetine). The rates of withdrawal reactions with sertraline are the next lowest rates (132). Withdrawal symptoms commonly appear at 2 to 5 days after discontinuation of the therapy and are often resolved within 24 h of reintroduction of the drug.

SUMMARY

Sertraline is a potent and specific serotonin uptake inhibitor with efficacy in mood and anxiety disorders. Its therapeutic value in major depression, dysthymia, OCD, social phobia, panic disorder, and PMDD has been established. In addition, recent data support its relative safety for use in pregnant and breast-feeding women. It has relatively weak effects on the cytochrome P450 system, a tolerability profile that is positive compared with antidepressants of other classes, and it is relatively safe in overdose. These findings contribute to sertraline being the first-line agent for the treatment of several psychiatric disorders.

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