SERTRALINE

Indications

The therapeutic indications for sertraline are as follows:

1) Sertraline is recommended for the treatment of depression in adult patients, including dysthymia and forms of depression associated with Parkinson's disease in both adults and elderly patients, as well as for the prevention of recurrence (European Medicine Agency - EMEA, Food and Drug Administration - FDA).
2) Sertraline is recommended for the treatment of bipolar disorder in both adult and pediatric patients (6-12 years) and adolescents (13-17 years) (EMEA, FDA, Australia). Prolonged treatment should be carefully evaluated due to limited literature data.
3) Sertraline is recommended for the treatment of panic disorder with or without agoraphobia (EMEA, FDA). Prolonged treatment should be carefully evaluated due to limited literature data.
4) Sertraline is recommended for the treatment of post-traumatic stress disorder (PTSD) (EMEA, FDA). Prolonged treatment should be carefully evaluated due to limited literature data.
5) Sertraline is recommended for the treatment of social anxiety disorder (or social phobia) (EMEA, FDA). Prolonged treatment should be carefully evaluated due to limited literature data.
6) Sertraline is indicated for the treatment of premenstrual dysphoric disorder (FDA).

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Dosage

Monotherapy

Below we report the dosage of sertraline in the various therapeutic indications:

Depression

Oral administration.

Adults: the recommended dose of sertraline is 50 mg/day. If no or partial efficacy is observed after several weeks of treatment, gradually increase the dose by 50 mg increments. Allow sufficient time to assess the therapeutic effectiveness of the new dosage between each increment (minimum time interval: 1 week). Maximum dose: 200 mg/day.

Obsessive-compulsive disorder

Oral administration.

Adults: the recommended dose of sertraline is 50 mg/day. Therapeutic effects of sertraline become evident after 1-2 weeks from the initiation of treatment; maximum therapeutic efficacy is achieved in 4-6 weeks. If optimal therapeutic responses are not achieved, increase the dosage by 50 mg increments up to a maximum of 200 mg/day. Increases should occur at intervals of no less than one week.

Children (6-12 years): initial sertraline dose of 25 mg/day, which can be increased to 50 mg/day if necessary after 1 week.

Adolescents (13-17 years): initial sertraline dose of 50 mg/day. If there is no response or response is suboptimal, dosage can be increased by 50 mg increments up to a maximum of 200 mg as needed. Due to lower body weight in pediatric patients, carefully evaluate dosage increments (possibly resorting to increments of 25 mg at a time) to avoid the risk of overdose.

Panic disorder with or without agoraphobia

Oral administration.

Adults: initial sertraline dose of 25 mg/day, to be increased to 50 mg/day after one week. The recommended dose is indeed 50 mg/day; starting with a lower dosage helps reduce the incidence of adverse effects during the initial phase of treatment. If the recommended dose is not optimal, increase the dosage by 50 mg increments up to the maximum of 200 mg/day. Increases should occur at intervals of no less than 7 days. The pharmacological action of sertraline becomes evident after one week of therapy, but the complete therapeutic effect is achieved after 2-4 weeks.

Post-traumatic stress disorder

Oral administration.

Adults: initial sertraline dose of 25 mg/day, which can be increased to 50 mg/day after one week if necessary. If the response is suboptimal, increase the dose by 50

mg increments up to a maximum of 200 mg; make individual increases at intervals of at least 7 days.

Special populations

Patients with hepatic failure

In this patient group, use lower and less frequent sertraline dosages. Sertraline is not recommended in patients with severe hepatic failure due to limited literature data regarding efficacy and safety.

Patients with renal failure

No dosage adjustments are necessary for sertraline in this patient group.

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Contraindications

Contraindications for the use of sertraline.

1) Sertraline is contraindicated in cases of hypersensitivity;
2) Sertraline is contraindicated when used concomitantly with MAO inhibitors or pimozide;
3) Sertraline, as oral solution concentrate, is contraindicated in combination with disulfiram due to the presence of alcohol in the concentrate.

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Warnings

Discontinuation treatment/withdrawal syndrome: the cessation of sertraline treatment should occur gradually to reduce the risk of withdrawal symptoms (nausea, dizziness, headache, vomiting, muscle pain, akathisia, sleep disturbances). In most patients, withdrawal symptoms resolve within 2-3 weeks, but in a limited number of cases, they may persist for a longer period (2-3 months). Withdrawal symptoms from sertraline can occur not only upon treatment discontinuation but also with dosage changes, switching from one antidepressant to another, or missing a dose. Abruptly stopping sertraline when withdrawal symptoms appear is strongly discouraged. According to the French spontaneous adverse drug reactions database, from the introduction of selective serotonin reuptake inhibitors (SSRIs) until 2000, sertraline had the fewest reports (1 case) of withdrawal syndrome (with paroxetine being the most reported, 29 cases) (Trenque et al., 2002).

Maximum dose: do not exceed the dose of 200 mg/day of sertraline.

Duration of treatment: patients should be treated with sertraline for a sufficient period to ensure complete symptom remission. Clinical trials have demonstrated the therapeutic efficacy of sertraline for up to one year in major depressive disorder, obsessive-compulsive disorder, and panic disorder; up to 28 weeks in post-traumatic stress disorder; and up to 3 menstrual cycles for premenstrual dysphoric disorder. Therefore, it is recommended to periodically reevaluate the pharmacological therapy with sertraline for long-term treatments.

Pediatric patients: sertraline is indicated in patients under 18 years of age for the treatment of obsessive-compulsive disorder. Prescribing the drug should be based on a confirmed diagnosis by a specialist in child neuropsychiatry or a healthcare facility with expertise in child neuropsychiatry. Pediatric patients may experience behavioral disturbances (agitation, aggression), especially during dose adjustment of sertraline. In younger children (6-12 years) treated with sertraline for extended periods, weight loss can occur; thus, growth parameters should be monitored.

Suicide/suicidal ideation in pediatric patients: selective serotonin reuptake inhibitors (SSRIs) are not approved for the treatment of depression in pediatric patients. For sertraline, paroxetine, and venlafaxine, there is no evidence of efficacy in treating depression in children. The use of SSRIs in this patient population has been associated with an increased risk of suicidal behavior (suicidal ideation, suicide attempts, self-harm) compared to placebo (especially for paroxetine and venlafaxine; limited literature data for fluvoxamine). Depression is rare in children (prevalence 0.5%), increases in adolescence (prevalence 3%), and is associated with a significant suicide risk (Expertise Collective Inserm, 2003).

Suicide/suicidal ideation in adult patients: since suicidal ideation is inherent in major depressive disorder and other pathological behavior disorders, the risk of suicide remains high until clear signs of improvement related to sertraline pharmacotherapy are evident. Therefore, it is crucial to monitor signs and symptoms of suicidal ideation, especially in the initial weeks of therapy when optimal disease

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control has not yet been achieved and whenever the sertraline dosage is adjusted. According to a meta-analysis conducted by GSK in adult patients, the incidence of suicidal behaviors appears to be more frequent in the 18-30 age group compared to placebo. No difference was found when comparing selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants.

Serotonin syndrome: sertraline can cause serotonin syndrome, a rare but potentially life-threatening adverse event. Its association with serotoninergic-acting drugs increases the risk of developing this syndrome, whose symptoms may include altered mental state, fever, agitation, tremors, myoclonus, hyperreflexia, ataxia, incoordination, sweating, chills, and gastrointestinal symptoms. Rarely, increased white blood cell count, creatine phosphokinase, liver transaminases, or decreased serum bicarbonate, disseminated intravascular coagulation, myoglobinemia, and renal failure have also been observed. Clinical manifestations do not correlate with serotonin blood concentration because what matters is its concentration at the nerve ending. Treatment of serotonin syndrome involves sedation, external cooling, the administration of antiepileptic and antihypertensive drugs.

Schizophrenia: psychotic symptoms may worsen in schizophrenic patients.

Drugs with serotoninergic activity (dextromethorphan, tramadol, meperidine, venlafaxine, trazodone, nefazodone, paracetamol, doxylamine, pseudoephedrine, linezolid, tryptophan, oxitriptan, triptans, risperidone: co-administration with sertraline increases the risk of serotonin syndrome. Agitation and nausea can occur with tryptophan and sertraline. Dextromethorphan, tramadol, and meperidine inhibit serotonin reuptake. The combination of drugs with serotoninergic activity and sertraline requires caution.

MAO inhibitors: allow at least 14 days between discontinuation of monoamine oxidase inhibitors (MAO inhibitors) and initiation of sertraline and at least one week between the end of sertraline therapy and beginning of MAO inhibitors (two weeks for MAO inhibitor selegiline). The risk of serotonin syndrome is higher with non-selective or selective A-form monoamine oxidase enzyme inhibitors (moclobemide).

Atypical antipsychotics: hypertension induced by atypical antipsychotics is a known adverse event. When combined with sertraline and other selective serotonin reuptake inhibitors (SSRIs), the risk likely increases due to pharmacometabolic inhibition of SSRIs on antipsychotics. Since hypertension onset is early, closely monitor blood pressure values, especially in the initial stages of therapeutic association.

Barbiturates: co-administration of sertraline and barbiturates might lower the seizure threshold. Possible antagonism of the anticonvulsant effect.

Lithium: sertraline co-administration can lead to lithium toxicity.

Sibutramine: co-administration with sertraline is not recommended.

Pimozide, thioridazine: concomitant use with sertraline is contraindicated (risk of severe ventricular arrhythmias, including torsades de pointes).

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Neuroleptics: co-administration with sertraline requires caution as it can facilitate the development of neuroleptic malignant syndrome.

Depression and heart disease: based on available clinical studies, selective serotonin reuptake inhibitors (SSRIs) have minimal adverse cardiac effects and are a valid therapeutic option in treating depression in patients with heart disease. In these patients, an indirect risk due to SSRI use could arise from hyponatremia associated with this class of antidepressants. Among SSRIs, NICE (National Institute for Health and Clinical Excellence) recommends the use of sertraline (NICE, 2007).

Prolongation of QTc interval: given that sertraline has the potential to prolong the QTc interval, caution is advised in patients with congenital QTc interval prolongation or in cases of pharmacological combinations with drugs known to prolong the QTc interval.

Diabetes: sertraline administration can impact glycemic control in diabetic patients. Increased serotoninergic tone induced by the antidepressant appears to enhance insulin secretion and sensitivity (Gulseren et al., 2005). Literature reports a case of a patient with type 2 diabetes, treated solely with diet, experiencing glycemic decompensation after sertraline intake. Therefore, adjustment of antidiabetic medications, oral hypoglycemics, and insulin may be necessary when co-administered with sertraline (Sansone, Sansone, 2003).

Mania/hypomania: sertraline should be used cautiously in patients with a history of mania. Psychosis and a shift in mood towards a manic phase have been reported, necessitating discontinuation of the drug in patients treated for depression with bipolar disorder.

Epilepsy/seizures: sertraline should be used cautiously in epileptic patients with controlled hepatitis. Discontinue the drug if seizures occur.

Hyponatremia: selective serotonin reuptake inhibitors (SSRIs), including sertraline, can induce hyponatremia (average blood sodium level of 120 mmol/L) with a 3.5-fold increased risk (Kirby et al., 2002). This adverse effect mostly occurs within the first month of therapy and is higher in elderly women and patients taking diuretics. Hyponatremia presents with confusion, seizures, fatigue, delirium, syncope, drowsiness, restlessness, dizziness, hallucinations, and occasionally aggression, personality disorders, and depersonalization. Therefore, the appearance of neuropsychiatric symptoms during the first month of sertraline treatment should prompt measurement of serum electrolytes.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH): monitor blood sodium concentration (natremia) and urea levels in urine (uremia) before starting sertraline treatment and after 2 weeks of treatment, with further assessments if patients exhibit symptoms such as weakness, lethargy, headache, loss of appetite, confusion, constipation, and weight gain.

Electroconvulsive therapy: limited literature data are available regarding sertraline co-administration with electroconvulsive therapy, therefore caution is advised.

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Angle-closure glaucoma: sertraline may cause pupil dilation (mydriasis), so its use in patients with angle-closure glaucoma requires caution.

Sedation: Caution is advised in activities requiring constant attention, because sertraline can induce drowsiness.

Diaphoresis: diaphoresis or excessive sweating is a common adverse event with antidepressant medications. Therapy involves reducing the antidepressant dosage or discontinuing it. If discontinuation is not possible, administration of one of the following drugs has been associated with clinical benefit: benztropine (anticholinergic), cyproheptadine (acetylcholine, serotonin, histamine antagonist), labetalol (beta agonist), or clonidine (hypothalamic diaphoresis).

Non-steroidal anti-inflammatory drugs (NSAIDs): due to the increased risk of upper gastrointestinal bleeding associated with both SSRIs and NSAIDs, including acetylsalicylic acid, caution is advised when these two class of drugs are co-administered. If it is not possible to avoid the pharmacological combination, a low serotonin reuptake inhibiting antidepressant, especially in high-risk patients (age >65 years, history of peptic ulcer or gastrointestinal bleeding, debilitated patients, patients taking anticoagulants or corticosteroids), should be preferred. Consider gastroprotective treatment in these patients.

Patients with liver disease: sertraline is metabolized by the liver, so reduced liver function might alter some pharmacokinetic parameters, particularly systemic exposure to the drug. In patients with mild and non-progressive liver cirrhosis, the area under the concentration-time curve (AUC) and peak plasma concentration of sertraline are approximately three times higher compared to healthy volunteers, and the drug's half-life is prolonged. Therefore, lower and/or less frequent dosages are recommended in these patients. Sertraline is contraindicated in patients with severe liver failure.

Patients with renal disease: because the amount of sertraline excreted unchanged in urine is minimal (<0.2%), any potential renal insufficiency is not expected to clinically significantly alter the drug's pharmacokinetic profile. In patients with moderate (CLcr: 30-60 ml/min) and severe (CLcr: 10-30 ml/min) renal impairment, systemic exposure and peak plasma concentration of sertraline have not undergone significant changes compared to values observed in patients with normal renal function.

Pregnancy: carefully assess the risk-to-benefit ratio before administering sertraline to pregnant women. Depression can affect up to 20% of pregnant women and has been associated with delayed fetal growth and low birth weight. Untreated maternal depression can also affect the mother-infant relationship (impaired parenting capacity). Although clinical studies on the use of selective serotonin reuptake inhibitors (SSRIs) (as a therapeutic class) during pregnancy have shown a low risk of congenital anomalies, individual drug analysis has correlated sertraline with septal heart defects and omphalocele (failure of abdominal closure) (Louik et al., 2007). Exposure to SSRIs in the third trimester of pregnancy can lead to neonatal SSRI withdrawal syndrome and persistent pulmonary hypertension (Malm et al., 2005;

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Chambers et al., 2006). Common withdrawal symptoms include agitation, irritability, hypo/hypertonia, hyperreflexia, drowsiness, feeding problems, and persistent crying. Less frequently, hypoglycemia, respiratory difficulties, thermoregulation abnormalities, and seizures have been observed. Persistent pulmonary hypertension (PPHN) is a severe condition requiring intensive care and can lead to neurological developmental abnormalities and death. The incidence is 1/100 newborns exposed to SSRIs in the second half of pregnancy compared to an incidence of 1/1000 live births in the general population. This condition is likely related to serotonin effects on cardiovascular development (Mills, 2006). Transplacental passage of SSRIs can cause neonatal bleeding (Serebruany, 2006). The effects of SSRI exposure during pregnancy on children's neurobehavioral development are unknown. In pregnant women on sertraline therapy, fetal ultrasound monitoring is recommended at the 20th week to detect possible fetal malformations and monitoring for signs and symptoms of neonatal toxicity (respiratory distress, jaundice, seizures, persistent pulmonary hypertension).

Lactation: sertraline is excreted in minimal amounts in breast milk, but its passage to breastfeeding infants has not been associated with neonatal toxic effects (Stone et al., 1997; Weissman et al., 2004). Sertraline, along with paroxetine, is the first-line drug in the selective serotonin reuptake inhibitor (SSRI) class for treating depression during pregnancy.

Sertraline oral solution concentrate: The oral solution concentrate of sertraline contains ethanol (12%), glycerol, and butylated hydroxytoluene. The ethanol content should be considered when administering to patients with liver disease, alcoholics, epileptics patients, patients with brain trauma or brain disorders, and pediatric patients. High doses of glycerol can cause headache, abdominal pain, and diarrhea. Butylated hydroxytoluene can cause irritation to the eyes, skin, and mucous membranes.

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Interactions

Alcohol: in combination with sertraline, an increase in sedative effects may occur.

Anticoagulants, platelet antiaggregants (NSAIDs, ASA, ticlopidine): co-administration with sertraline can increase the risk of bleeding (selective serotonin reuptake inhibitors, SSRIs, are considered gastrolesive drugs). The combination of SSRIs and nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an absolute risk of gastrointestinal bleeding higher than 1 in every 80 patients treated per year. The combination of SSRIs and acetylsalicylic acid is associated with an absolute risk of 1 in every 200 patients treated per year, compared to an absolute risk of 1 in every 300 patients treated per year for SSRIs in monotherapy and 1 in 200patients treated per year for NSAIDs in monotherapy (Patron, Ferrier, 2005).

Antiepileptics: sertraline can counteract the anticonvulsant effects of antiepileptic drugs (reducing the seizure threshold).

Antivirals (darunavir, efavirenz, ritonavir): sertraline might increase plasma concentration of ritonavir. Darunavir and efavirenz decrease sertraline plasma concentration.

Atomoxetine: combined with sertraline, there might be an increased risk of seizures.

Barbiturates: sertraline can counteract the anticonvulsant effects of barbiturates due to reduced seizure threshold (a pharmacological interaction attributed to the class of selective serotonin reuptake inhibitors, SSRIs).

Bupropion: sertraline can increase bupropion plasma concentration (interaction attributed to the class of SSRIs).

Centella: when co-administered with sertraline, there might be an additive sedative effect.

Food: food in the stomach increases the area under the concentration/time curve (AUC) and peak plasma concentration of sertraline (Murdock, McTavish, 1992).

Cimetidine: increases sertraline plasma concentration due to reduced clearance (clinical significance not well-established).

Cyproheptadine: can counteract the antidepressant effect of sertraline.

Clozapine: sertraline increases its plasma concentration. A sudden death episode in a 26-year-old patient has been reported (Hoechns et al., 2001). Clozapine is associated with a 5-fold increased risk of developing cardiomyopathy compared to the general population and has antiarrhythmic properties.

Digoxin: no pharmacological interactions observed when sertraline (200 mg/day) was administered with digoxin.

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Entacapone: manufacturer of entacapone recommends caution when co-administered with selective serotonin reuptake inhibitors (SSRIs), including sertraline.

Glibenclamide: no pharmacological interactions observed when sertraline (200 mg/day) was administered with glibenclamide.

St. John's Wort (Hypericum): nausea, vomiting, lethargy, confusion, and anxiety up to serotonin syndrome can occur when combined with sertraline. This co-administration is contraindicated.

Oxycodone: co-administration with sertraline could induce serotonin syndrome.

Diazepam: intravenous administration before and after 21 days of sertraline therapy (50-200 mg/day) resulted in a 32% reduction in diazepam clearance and an increase in plasma peak of its metabolite, desmethyldiazepam. The clinical significance of these observations is unknown.

Donepezil: hepatitis has been reported in an elderly patient (>80 years) treated with sertraline (200 mg/day) and donepezil (5 mg/day). Mental confusion and jaundice appeared after 10 days of drug combination, with total bilirubin of 5.6 mg/dL, gamma-GT of 1208 U/L, ALT of 259 U/L, and alkaline phosphatase of 369 U/L. Abdominal CT scan showed cholelithiasis, and liver biopsy revealed acute hepatitis (Nace, Towers, 1999).

Duloxetine: co-administration with sertraline could be an increase in serotoninergic effects. Co-administration requires caution.

Drugs with high serum protein binding: no competition for protein binding was observed in interaction studies of sertraline with warfarin or tolbutamide. Caution is advised when co-administering sertraline with drugs with high serum protein binding due to limited clinical data.

Monoamine oxidase inhibitors (MAOIs), including linezolid and isoniazid (MAOI-activity drugs), oxitriptan, tryptophan, phenfluramine: concurrent administration with sertraline may increase the risk of serotonin syndrome. The risk is higher with non-selective and A-selective MAO inhibitors, less frequent with B-selective MAO inhibitors (selegiline, rasagiline). Allow at least 2 weeks between MAOI therapy and sertraline. Co-administration with tryptophan or phenfluramine and sertraline is contraindicated.

Drugs metabolized by the cytochrome enzyme CYP2D6: sertraline has a lower potential for interaction with drugs metabolized by CYP2D6 compared to other SSRIs. In an interaction study, sertraline (50 mg/day) moderately increased (23-37%) steady-state plasma concentration of desipramine, drug used to assess CYP2D6 enzyme activity. Caution is still recommended when sertraline is used in combination with drugs metabolized by CYP2D6 with a narrow therapeutic index such as propafenone and flecainide, some tricyclic antidepressants, and atypical antipsychotics.

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Drugs metabolized by the cytochrome enzyme CYP3A4: from pharmacokinetic interaction studies with known CYP3A4 substrates (cortisol, carbamazepine, terfenadine, alprazolam), sertraline did not exhibit clinically significant enzyme inhibition activity.

Drugs metabolized by the cytochrome enzyme CYP2C9: from pharmacokinetic interaction studies with known CYP2C9 substrates (tolbutamide, phenytoin), sertraline did not exhibit clinically significant enzyme inhibition.

Lithium: co-administration with sertraline may increase the risk of central nervous system toxicity.

Methylphenidate: it can inhibit sertraline metabolism.

Pimozide: sertraline increases plasma levels of pimozide. Increased risk of ventricular arrhythmias, including torsades de pointes. This combination is contraindicated.

Rifampicin: might reduce sertraline blood concentration due to CYP3A4-mediated pharmacometabolic induction. A case report described symptoms like disorientation, exacerbated dizziness upon movement, periods of lethargy alternating with insomnia, anxiety, restlessness, and asthenia in a patient receiving sertraline (200 mg/day) and rifampicin (600 mg/day) therapy (Markowitz, DeVane, 2000).

Sibutramine: there is an increased risk of central nervous system toxicity when sibutramine is combined with sertraline (increased risk of serotonin syndrome). Co-administration is not recommended.

Tolbutamide: sertraline reduces the clearance of tolbutamide (by 16%).

Tramadol: co-administration with sertraline increases risk of neurological toxicity (serotonin syndrome).

Triptans (almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan): concurrent use with may lead to an increased risk of hypertension and coronary vasoconstriction due to additive serotoninergic effects. Co-administration of sertraline and triptans is associated with an increased risk of serotonin syndrome. A study published in 2018 quantified this risk. The incidence of serotonin syndrome was rare, ranging from 0 to 4 cases per 10,000 person-years of exposure to SSRIs or triptans (Orlova et al., 2018).

Warfarin: sertraline increases its systemic exposure. Possible increase in anticoagulant effect: monitor International Normalized Ratio (INR).

Zolpidem: increased sedation may occur in association with sertraline.

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Side effects

The most common side effects associated with the use of sertraline and, more generally, selective serotonin reuptake inhibitors (SSRIs) in the early stages of therapy include nausea, headache, diarrhea, irritability, insomnia, and fatigue. These dose-dependent effects tend to subside within a few weeks. In long-term treatments, the most common adverse event is sexual dysfunction (reduced libido, delayed ejaculation, anorgasmia). Restlessness and insomnia observed in the initial phase of treatment can be managed with the administration of benzodiazepines.

The selective serotonin reuptake inhibitors (SSRIs) have a lower incidence of anticholinergic effects (dry mouth, constipation) compared to tricyclic antidepressants.

In pediatric and adolescent patients, the administration of selective serotonin reuptake inhibitors (SSRIs) has been associated with a significantly higher rate of adverse reactions compared to placebo. Moreover, side effects have been reported to be more frequently "severe." Some authors argue that the clinical benefit associated with the use of SSRIs in children may not outweigh the risk of serious adverse effects (Jureidini et al., 2004). In some clinical trials, the fraction of pediatric patients who discontinued treatment due to adverse drug reactions was statistically higher than placebo (9% vs. 3%) (Wagner et al., 2003). Common side effects in clinical trials with an incidence ≥2% and at least twice that of the placebo group included decreased appetite, tremor, sweating, hyperkinesia, hostile behavior, agitation, emotional lability, including crying, mood fluctuations, self-harm, suicidal ideation, especially in patients with major depression.

Discontinuation of sertraline and SSRIs, especially if done abruptly, can be associated with withdrawal syndrome characterized by gastrointestinal symptoms (nausea, vomiting, intestinal motility disorders), neurological symptoms (paresthesia, instability sensation, dizziness, headache, tremors, dystonias, decreased strength sensation, muscle pains), and psychiatric symptoms (anxiety, sleep disturbances, aggression, irritability, sadness, mood instability, fatigue, hot flashes). These symptoms commonly occur within the first 10 days after discontinuation (sleep disturbances, sensory disturbances, and dizziness have an incidence of 7%), but in most patients, these events are mild/moderate and self-limiting. Among all SSRIs, paroxetine has the highest incidence of withdrawal syndrome.

Cardiovascular: palpitations, hot flashes; tachycardia, myocardial infarction, bradycardia, postural hypotension, erythromelalgia (rare vascular syndrome). Sertraline is among the drugs potentially at risk of prolonging the QTc interval (www.torsades.org). Sertraline has been associated with erythromelalgia in the treatment of Raynaud's syndrome. Both erythromelalgia and Raynaud's syndrome are vascular syndromes affecting the extremities (hands, feet). The pathophysiology of both disorders is unknown, but serotonin is likely involved, causing vasoconstriction or vasodilation depending on the vessel involved and the integrity of the endothelium. Erythromelalgia has been observed after administration of sertraline at a dose of 50 mg/day (Rey et al., 2003). Prolongation of the QTc interval

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is associated with severe ventricular arrhythmias, including torsads de pointes (TdP). The risk increases with the concomitant use of drugs that can both modify the QT interval or when a drug that induces QT prolongation is administered in patients with congenital QT interval prolongation.

Central nervous system: (very common ≥10%) headache (21%), insomnia (19%), dizziness (11%), drowsiness (13%); (common: ≥1%, > 10%) tremors, agitation, fatigue, ataxia, difficulty concentrating, irritability, sweating, nightmares, paresthesia, depression, anxiety, hypertonia, tinnitus; (uncommon: ≥0.1%, <1%) hallucinations, seizures, mania, dystonia, ear pain, involuntary muscle contractions, ataxia, hyperkinesia, amnesia, hypoesthesia, language disturbances, postural dizziness, migraine; (rare/very rare) serotonin syndrome, suicidal behavior, coma, dyskinesia, hyperesthesia, aggression, paranoia, sleepwalking.

Excessive sweating or diaphoresis is common with antidepressant medications. The incidence of diaphoresis in patients treated with sertraline ranges from 5% to 8%. Proposed mechanisms to explain excessive sweating include sympathetic nervous system activation, hypothalamic activation, and alteration of the balance between alpha and beta adrenergic receptor systems.

Endocrine and reproductive system: (very common: ≥10%) anorgasmia; (common: ≥1%, <10%) sexual dysfunction, erectile dysfunction, reduced libido (3%); (uncommon: ≥0.001%, <1%) vaginal bleeding, female sexual dysfunction; (rare/very rare: ≥0.0001%) menorrhagia, atrophic vulvovaginitis, balanoposthitis, genital discharge, priapism, galactorrhea, dysmenorrhea, impotence, gynecomastia.

The incidence of sexual dysfunctions depends on the dose of sertraline administered.

Eye: (common: ≥1%, <10%) vision alteration; (rare/very rare: ≤ 0.01%) altered vision, ocular hypertension, glaucoma, complete or partial loss of vision in an area of the visual field (scotoma), double vision (diplopia), photophobia, accumulation of blood in the anterior part of the eye (hyphema), pupil dilation (mydriasis), abnormal tearing.

Gastrointestinal: (very common: ≥10%) nausea (24%), diarrhea (18%), dry mouth or xerostomia (up to 15% of patients); (common: >1% <10%) taste alteration or dysgeusia, constipation, abdominal pain, vomiting, dyspepsia, flatulence; (uncommon) anorexia, esophagitis, difficulty swallowing (dysphagia), hemorrhoids, excessive salivation, tongue disorders, belching; (rare/very rare) dark stools due to blood presence (melena), abnormal-colored stools usually due to blood presence (hematochezia), stomatitis, tongue ulceration, tooth disorders, tongue inflammation (glossitis), mouth ulceration, upper gastrointestinal bleeding, diverticulitis, gastroenteritis.

The administration of selective serotonin reuptake inhibitors (SSRIs) is associated with gastrointestinal symptoms (nausea and diarrhea) due to serotonin presence in the enteric nervous system. Approximately 95% of serotonin in the body is released by specific intestinal cells (enterochromaffin cells) responding to luminal pressure, acidity, and chemicals. Serotonin acts in the intestine by promoting peristalsis and secretion through stimulation of intrinsic sensory nerves (5-HT1P receptors); it

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induces nausea, vomiting, and cramps by stimulating extrinsic sensory nerves (5-HT3 receptors). Locally, serotonin is inactivated by binding to a protein (serotonin transporter protein, Sert) present on the lining cells of the intestines (serotonin reuptake). Continuous administration of selective serotonin reuptake inhibitors (SSRIs) leads to serotonin receptors desensitization due to prolonged serotonin stimulation (inhibition of serotonin transporter). Intestinal desensitization causes a shift from a condition of diarrhea (excessive stimulation of peristalsis) to constipation (peristalsis block).

Selective serotonin reuptake inhibitors (SSRIs) have been associated with upper gastrointestinal bleeding. It has been observed that the risk of bleeding increases by about a factor of 3 and is similar for all SSRIs (class effect). The adjusted relative risk for upper gastrointestinal bleeding for sertraline was 3.9 (fluoxetine, 2.5 – paroxetine, 4.3 – trazodone, 8.6) (de Abajo et al., 1999).

General: (very common: ≥10%) fatigue; (common: ≥1%, <10%) chest pain, decreased appetite; (uncommon: ≥0.1%, <1%) malaise, chills, fever, fatigue, thirst, weight loss/gain; (rare/very rare: ≥0.01%) hypersensitivity (skin rash, urticaria, angioedema, anaphylaxis, photosensitivity, vasculitis up to severe systemic reactions), facial edema, pancreatitis, hernia, fibrosis at the injection site, gait disturbances, peripheral edema.

Hematological: (rare/very rare: <0.01%) lymphadenopathy, leukopenia, thrombocytopenia.

Liver/biliary: (rare: ≥0.01%) impaired liver function, increased liver enzymes, gallbladder disorders, hepatitis, hepatocellular damage, hyperbilirubinemia, jaundice.

Metabolic disorders: low blood sodium levels (hyponatremia), syndrome of inappropriate antidiuretic hormone secretion (SIADH); low blood potassium (hypokalemia, sporadic reports) and blood glucose levels (hypoglycemia), high blood cholesterol levels (hypercholesterolemia).

Hypoglycemia is more common in elderly patients aged >70 years, receiving diuretics, or dehydrated. Onset varies from 3 days to 4 months after starting sertraline therapy. Predictive factors for the development of hyponatremia include a low plasma sodium concentration before starting sertraline therapy (<138 mEq/L) and a low body mass index.

Musculoskeletal: myalgia; (uncommon: ≥0.1%, <1%) osteoarthritis, muscle weakness, back pain, muscle cramps; (rare/very rare: ≤0.01%) bone disorders, arthralgia, muscle cramps.

Renal: (uncommon: >0.1% <1%) urinary retention, increased urine production (polyuria), increased frequency of urination associated with reduced volume urinations (pollakiuria), urinary disturbances; (rare/very rare) decreased urine production (oliguria), urinary incontinence.

Urinary incontinence risk associated with selective serotonin reuptake inhibitors (SSRIs) is almost double that of patients not taking this type of drug; among SSRIs, sertraline has the highest associated risk.

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Respiratory system: rhinitis, pharyngitis, yawning; (uncommon) upper respiratory tract infections, dyspnea, epistaxis; (rare) otitis media, laryngospasm, hyper/hypoventilation, dysphonia, hiccups.

Skin: skin rashes; (uncommon: ≥0.1%, <1%) periorbital edema, purpura, alopecia (statistically significant association), cold sweats, xeroderma, urticaria; (rare/very rare: <0.01%) dermatitis, blistering dermatitis, follicular rash, alteration of hair structure, alteration of skin odor; (sporadic reports) Stevens-Johnson syndrome, toxic epidermal necrolysis.

As serotonin is transformed into melatonin in the skin, and the latter is involved in hair growth cycles, sertraline administration might disrupt serotoninergic homeostasis in the scalp, leading to hair loss. Among SSRIs, sertraline and citalopram are the most reported molecules for alopecia.

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Toxicity

Overdose: in cases of sertraline overdose, symptoms include drowsiness, gastrointestinal disturbances, tachycardia, tremors, restlessness, and dizziness, and rarely, coma. Literature reports a fatal incident of asthma associated with sertraline overdose (900 mg). Laboratory data revealed a serum concentration of sertraline at 620 ng/ml (therapeutic range: 30-200 ng/ml) and a concentration of the metabolite desmethylsertraline at 326 ng/ml (Carson et al., 2000). Sertraline has been linked to QT interval prolongation when taken in excessive amounts (2250 mg) in association with diazepam (200 mg), and temazepam (400 mg) (Boer et al., 2005). In case of overdose, perform gastric lavage or administer activated charcoal (50 g in 12 hours). Maintain airway patency and ensure adequate oxygenation and ventilation, cardiac activity, and vital signs. Inducing vomiting is not recommended due to sertraline's extensive distribution volume; forced diuresis, dialysis, or hemoperfusion are not believed to be beneficial.

Serotonin syndrome: sertraline can induce serotonin syndrome, characterized by cognitive-behavioral alterations, anatomical and neuromuscular dysfunctions due to excessive central serotoninergic activity. Conditions leading to increased serotonin levels include:

1) administration of excessive serotonin precursors (tryptophan);
2) use of substances promoting serotonin release (ecstasy, cocaine, amphetamines);
3) use of drugs inhibiting serotonin metabolism like monoamine oxidase inhibitors (MAOIs);
4) overdose of selective serotonin reuptake inhibitors (SSRIs);
5) pharmacological combinations (sertraline with risperidone, desipramine, venlafaxine, moclobemide, dextromethorphan, linezolid);
6) alternative activation pathways (bromocriptine, activating the dopaminergic system).

Treatment involves discontinuing drugs triggering the syndrome, sedation, external cooling, administration of antiepileptic and antihypertensive drugs, and beta-blockers (propranolol) in severe cases. Literature reports a mortality rate ranging from 2-3% to 12% (Mason et al., 2000; Mills, 1997). Positive outcomes in serotonin syndrome treatment have been reported with cyproheptadine (antihistamine antagonizing serotonin receptors 5-HT1A and 5-HT2), methysergide (specific antagonist of serotonin receptor 5-HT), and chlorpromazine (antagonist of serotonin receptors 5-HT1A and 5-HT2 and dopamine D2); benzodiazepines, dantrolene, and dopamine antagonists (bromocriptine and haloperidol are not recommended due to worsening serotonin syndrome) have shown varying success and failure in treatment. SSRIs are responsible for serotonin syndrome with a higher frequency (33.5%) compared to all other classes of antidepressants. Among SSRIs, fluoxetine, sertraline, and paroxetine are most frequently associated with the syndrome. The combination of MAOIs and SSRIs results in the most severe forms of serotonin syndrome, significantly

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increasing serotonin concentrations in the brain due to blocked neurotransmitter reuptake and degradation.

Reproductive toxicity: Some clinical studies on exposure to selective serotonin reuptake inhibitors (SSRIs) during the first trimester of pregnancy have shown a slight increase in the incidence of anencephaly (partial or complete absence of the brain), craniosynostosis, (premature fusion of one or more cranial sutures) and omphalocele (failure of abdominal closure with protrusion of the viscera) (Alwan et al., 2007). Another study found no significant correlation between SSRI exposure and congenital defects. However, analysis at the molecular level within the therapeutic class revealed an association between sertraline and paroxetine and omphalocele and cardiac defects (Louik et al., 2007).

Neonatal toxicity: exposure to SSRIs during pregnancy has been associated with the following symptoms in neonates: (common) agitation, irritability, hypo/hypertonia, hyperreflexia, drowsiness, feeding problems, persistent crying; (less common) hypoglycemia, respiratory difficulties, thermoregulation abnormalities, seizures. Neonatal symptoms appear within the first week of life and tend to diminish and disappear within approximately six weeks. These symptoms are attributed to a neonatal withdrawal syndrome rather than adaptation difficulties to extrauterine life, especially when exposed to SSRIs during the third trimester. Neonatal complications have often required prolonged hospitalization, respiratory support, and tube feeding.

Exposure to SSRIs during pregnancy would also lead to delayed expulsion of the first stool (meconium) and consequent intestinal obstruction (meconium ileus) in the newborn.

Late exposure (solely after the 20th week of gestation) to SSRIs has been associated with persistent pulmonary hypertension of the newborn (PPHN), with fluoxetine being the most frequently implicated drug. PPHN has an incidence of 1-2 in 1000 newborns and is associated with high morbidity and mortality (20-30%). One hypothesized mechanism involves fetal pulmonary serotonin accumulation leading to proliferation of smooth muscle cells, a characteristic of PPHN (in addition to vasoconstrictive effects, serotonin also has proliferative effects on pulmonary smooth muscle cells). Another hypothesis considers the inhibitory effect of SSRIs on nitric oxide synthesis, a potent physiological vasodilator that seems to regulate vascular tone and reactivity in both fetus and neonate (Chambers et al., 2006; Abman, 1999).

Serotonin is present in early fetal development stages and, in addition to its role as a neurotransmitter, seems to function as a growth factor and regulator toward both serotoninergic and non-serotoninergic neurons. It has been hypothesized that exposure to SSRIs during gestation might negatively impact fetal brain development, leading to neurological and behavioral consequences in the neonate. Limited, non-uniform clinical data suggest a lower psychomotor development index in children between 6 and 40 months exposed to SSRIs in pregnancy compared to unexposed children (Oberlander et al., 2002; Morag et al., 2004; Laine et al., 2003; Zeskind, Stephens, 2004; Zeskind et al., 2005; Nulman et al., 2002; Casper et al., 2003).

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LD50: following oral administration, it is 548 mg/kg (male mouse) and 419 mg/kg (female mouse); 1591 mg/kg (male rat) and 1327 mg/kg (female rat).

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Pharmacology

Sertraline is an antidepressant drug belonging to the therapeutic class of selective serotonin reuptake inhibitors (SSRIs); chemically, derived from naphthylamine. Sertraline is indicated for the treatment of major depression and prevention of relapse, obsessive-compulsive disorder, even in pediatric patients (ages 6-17), panic disorder, post-traumatic stress disorder, social anxiety disorder, and premenstrual dysphoric disorder.

Depression is linked to alterations in the serotoninergic and/or adrenergic systems. Serotonin, through the reticular substance, is involved in the regulation of hunger and satiety, wakefulness and sleep, body temperature, sexual behavior, and aggression. Administration of drugs that inhibit neurotransmitter reuptake at the synaptic level leads, over the long term, to desensitization of receptors due to a decrease in their number and sensitivity (down-regulation mechanism). From a clinical-therapeutic standpoint, this results in the onset of antidepressant effects.

Sertraline acts by inhibiting presynaptic neuronal reuptake of serotonin, consequently increasing synaptic levels of the neurotransmitter and prolonging its activity at postsynaptic receptors. Sertraline inhibits neuronal reuptake of serotonin (in vitro) with approximately 9 times the potency of fluvoxamine, about 5 times that of fluoxetine, and about 2 times that of clomipramine (Murdock, McTavish, 1992).

Prolonged receptor stimulation induced by sertraline leads to down-regulation of serotonin receptors (5-HT2), resulting in the onset of antidepressant activity (maximum antidepressant activity occurs 2-4 weeks after the start of treatment).

Sertraline also affects dopamine reuptake. This property makes it suitable for the treatment of dysthymia (likely caused by alterations in the mesolimbic dopaminergic pathway) as an alternative to amisulpride (an effective molecule in dysthymia but associated with hyperprolactinemia after 2-3 months of therapy) and in depression associated with Parkinson's disease and in the elderly population in general, due to its action on extrapyramidal effects.

After administration of 100 mg, sertraline improves alertness and psychometric performance; after 200-400 mg, it enhances alertness but reduces psychometric performance (Murdock, McTavish, 1992).

Sertraline alters the electroencephalographic pattern: after 100 mg, it increases the frequency and intensity of alpha waves, increases the frequency, and reduces the intensity of theta waves. After 200-400 mg, it reduces the frequency of alpha and beta waves and increases the frequency of theta waves.

Sertraline improves cognitive abilities; it reduces REM sleep (both frequency and duration).

Sertraline possesses anorectic activity (in animals) by reducing food intake and inducing weight loss (Nielsen et al., 1992).

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Sertraline may increase the risk of bleeding (class effect) due to its effects on serotonin. Serotonin has vasoconstrictive and platelet anti-aggregating activity. Platelets, which cannot synthesize the neurotransmitter, absorb serotonin from the blood through a protein that acts as a serotonin transporter. Inside platelet, serotonin is stored in granules to be released back into the bloodstream when platelet is activated during hemostasis. Inhibition of serotonin reuptake induced by sertraline and other selective serotonin reuptake inhibitors (SSRIs) blocks the platelet serotonin transporter, preventing serotonin accumulation in platelets. It has been observed that SSRI treatment increases the risk of uterine bleeding, bleeding associated with orthopedic surgery in elderly patients, and upper gastrointestinal bleeding (Movig et al., 2003; van Walraven et al., 2001).

In a cohort study of patients treated with antidepressants for 3 months, the hospitalization rate for upper gastrointestinal bleeding was 3.1 episodes per 1000 treatments/year higher for patients treated with serotonin reuptake inhibiting antidepressants compared to those not inhibiting reuptake (Dalton et al., 2003). Adding non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid further increased the risk. The bleeding risk also did not appear to depend on the duration of therapy (no difference after 1 month, 2, or 6 months) (Layton et al., 2001).

In the treatment of Major Depressive Disorder (MDD), sertraline is as effective as amitriptyline; it has higher efficacy than doxepin and imipramine (Murdock, McTavish, 1992). Compared to amitriptyline, it causes fewer side effects (28% vs 35%) (Drug Ther. Bull., 1991).

In cases of bipolar disorder, sertraline is more effective than placebo in symptom improvement (56% vs 32% of patients) (Murdock, McTavish, 1992).

Depression in patients with heart disease

In the treatment of depression (HAM-D scale at 17 points: average score of 19.6) in patients with heart disease (myocardial infarction or unstable angina within the previous 30 days), sertraline did not alter the left ventricular ejection fraction compared to placebo (primary endpoint of the study), or heart rate, blood pressure, or QTc interval (secondary endpoints). Sertraline administered at a dose of 50 mg/day for 24 weeks (increases up to 200 mg/day were possible after the 12th week) was slightly more effective in reducing depressive symptoms (secondary endpoint). Subgroup analysis highlighted greater clinical benefits in patients with recurrent depression and in more severe forms of depression (Glassman et al., 2002).

Panic disorder

Panic disorder was recognized as a distinct diagnostic entity from other anxiety disorders in 1980. Panic disorder can occur with or without agoraphobia and has high morbidity: over half of the patients develop a depressive disorder. It is characterized by intense fear or discomfort accompanied by a variety of sudden-sudden physical and psychological symptoms that reach their peak within about 10 minutes: palpitations, pounding heart, rapid heart rate; sweating; trembling; shortness of breath or a feeling of choking; chest pain or discomfort; nausea or abdominal

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distress; dizziness or lightheadedness; derealization and/or depersonalization; fear of losing control or going crazy; fear of dying; paresthesia; chills or hot flushes.

In a clinical trial where patients were initially treated with open-label sertraline for panic disorder (8 weeks) and then subjected to a double-blind comparison with placebo (8 weeks), the primary endpoint, represented by the incidence of relapses, did not show significant differences between the two treatment groups (10.1% vs. 13.2% with sertraline and placebo, respectively). However, the frequency of panic attacks was significantly lower with sertraline. The percentage of patients meeting efficacy criteria (CGI-I score - Clinicians Global Impression Improvement - equal to 1 or 2) was 89.9% vs. 74.4% for sertraline and placebo, respectively (Kmijima et al., 2005).

In another study, the administration of a fixed dose of 20 mg/day of sertraline was effective in reducing the frequency of panic attacks, symptoms of agoraphobia, and anticipatory anxiety (Fisekonc', Loga-Zec, 2005).

In a comparative study of selective serotonin reuptake inhibitors (SSRIs) in the treatment of panic disorder with or without agoraphobia, sertraline and paroxetine yielded similar outcomes for both the primary endpoint ("non-inferiority" between the two treatments, measured by the PAS - Panic and Agoraphobia Scale score) and secondary endpoints (frequency of panic attacks and CGI-I score - treatment responsiveness defined as CGI-I score ≤2). Patients were treated with flexible doses of sertraline (50-150 mg/day) or paroxetine (40-60 mg/day) depending on therapeutic response for 12 weeks, followed by a dosage reduction for an additional 3 weeks. At the end of the study, patients with CGI-I ≤2 (responders) were 82% in the sertraline group and 78% in the paroxetine group. The treatment discontinuation rate due to drug-related adverse events was 12% vs. 18% with sertraline and paroxetine, respectively. Paroxetine caused a weight gain of greater than or equal to 7% in a significantly higher fraction of patients compared to the competitor (7% vs. <1%). During the last 3 weeks (drug dose reduction period), the percentage of panic-free patients increased by 4% with sertraline, while it decreased by 11% with paroxetine (Bandelow et al., 2004).

Social anxiety disorder

Sertraline has proven effective in both acute and long-term treatment of social anxiety disorder or social phobia. In patients suffering from social anxiety for over 20 years, sertraline administration elicited a positive response in 53% of patients compared to 29% in the placebo group. Among drug-responsive patients, continued treatment for another 24 weeks was associated with sustained therapeutic response in 96% of treated patients versus 64% in the placebo group.

In a clinical study comparing pharmacological therapy with sertraline (doses up to 200 mg/day) and cognitive-behavioral therapy for anxiety disorders and social phobia in children, substantial overlap between the two approaches was observed. However, the combined treatment – pharmacological therapy plus cognitive-behavioral therapy – resulted in the most significant clinical benefits. The study involved 488 patients aged between 7 and 17 years and lasted 12 weeks. The percentage of patients

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showing clear or very clear improvement according to the CGI-I scale (Clinician's Global Impression-Improvement) was 80.7% vs. 59.7% vs. 54.9% vs. 23.7%, for children treated with sertraline plus cognitive-behavioral therapy, children treated only with cognitive-behavioral therapy, children treated only with sertraline, and placebo, respectively. Therapeutic benefits were faster with sertraline compared to cognitive-behavioral therapy, although the latter was associated with a lower incidence of insomnia, fatigue, sedation, and agitation. The incidence of suicidal/homicidal ideation was not higher with the drug compared to placebo, and there were no suicide attempts (Walkup et al., 2008).

Premenstrual dysphoric disorder

Sertraline has demonstrated superior therapeutic efficacy to placebo in treating premenstrual dysphoric disorder (PMDD), improving both emotional symptoms (such as depressed mood and feelings of inadequacy) and behavioral symptoms (including anger, irritability, and interpersonal conflicts). Clinical benefits were observed both with treatment limited to the premenstrual period and with treatment extended throughout the menstrual cycle. Patients who received continuous sertraline experienced reduced breast tenderness, headache, and edema. Symptoms related to PMDD typically occur during the last week of the luteal phase, diminish in the early days of the follicular phase, and disappear in the week following menstruation.

In a double-blind clinical trial, administration of sertraline (50-150 mg/day, individualized dosage) was more effective than placebo in reducing daily total scores related to all PMDD symptoms (primary endpoint) (32% vs. 11%). The treatment response rates were 62% vs. 34% for sertraline and placebo, respectively (Yonkers et al., 1997). Generally, clinical benefits associated with SSRI therapy manifest within the first 3 weeks of treatment, but relapse occurs quite early, within 1-2 cycles after discontinuation of the medication.

Therapy with sertraline, and SSRIs in general, may induce side effects, leading to early treatment discontinuation in clinical trials at a rate 2.5 times higher than the placebo. The most frequent adverse effects included (10-20% of patients) nausea, insomnia, fatigue, xerostomia, and dizziness; (up to 10%) sweating, reduced concentration, and sexual dysfunction. The latter (reduced libido, anorgasmia) tend to persist throughout the duration of drug therapy.

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Pharmacokinetics

Following oral administration, sertraline is absorbed slowly from the gastrointestinal tract.

The peak plasma concentration is approximately 20-55 ng/ml and is achieved after 4-8 hours (Murdock, McTavish, 1992).

Peak plasma concentration and area under the concentration-time curve (AUC) increase in elderly patients (≥65 years) (Warrington, 1991) and in the presence of food in the stomach (Murdock, McTavish, 1992).

Steady state is reached approximately one week after once-daily administration of sertraline.

Serum protein binding: approximately 99%.

Volume of distribution (Vd): greater than 20 L/kg.

Sertraline is metabolized in the liver to desmethylsertraline (which has antidepressant potency approximately 8 times lower than sertraline) (Murdock, McTavish, 1992). Desmethylsertraline undergoes deamination through oxidative reactions and further metabolism. Sertraline is metabolized by cytochrome enzymes 3A4, 2D6, and 2C19.

Elimination half-life: approximately 25-26 hours (sertraline); 62-104 hours (desmethylsertraline).

In elderly patients, the elimination half-life of sertraline increases to approximately 36 hours (Warrington, 1991).

Sertraline permeates the blood-brain barrier; in animals, the drug concentration in the brain was found to be 40 times higher than in plasma.

Sertraline is excreted as metabolites, equally in feces and urine. Less than 0.2% of unchanged sertraline is excreted in urine.

Pediatric patients

The administration of sertraline (gradual doses ranging from 50 to 200 mg/day) resulted, at steady state, in serum concentrations in children aged 6-12 years that were 35% higher than in the adolescent group (aged 13-17 years) and 21% higher than in the adult reference group. Therefore, it is recommended to initiate treatment in children with lower doses than in adults and to gradually increase by 25 mg increments.

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Classification

Chemical formula

$C_{17}H_{17}Cl_2N$

Molecular weight

306.23

Atc code

N06AB06

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