

Testosterone Replacement Offers Benefits, Risks

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — Testosterone supplementation trims visceral fat, builds skeletal muscle, improves muscle strength, and promotes overall sexual function in healthy older men, according to studies presented at the annual meeting of the Endocrine Society.

The findings from small but well-controlled trials, although not definitive, add

credence to the theory that testosterone can have a positive impact on the health and vigor of older, as well as younger, men.

In a cautionary note, however, researchers found an alarming number of adverse effects—some of them severe—in men who received the highest doses of testosterone, 600 mg/wk.

For example, an institutional safety review board cut short the high-dose arm of one study when 10 subjects experi-

enced a total of 147 adverse events, including 12 serious adverse events, halfway into a 20-week trial conducted at Charles R. Drew Medical Center in Los Angeles.

The adverse events included polycythemia, leg edema, and two cases of prostate cancer that may have been indolent prior to the patients' receiving high-dose testosterone.

Despite some encouraging findings, principal investigator Thomas W. Storer, Ph.D., said, "It's very important to tell the

public that when you get up to these very high doses, clearly you're going to have problems."

Dr. Storer's study evaluated the effect of testosterone on muscle mass and strength in 60 healthy men aged 60-75 years and 61 healthy men aged 18-34 years. A long-acting GnRH agonist suppressed endogenous testosterone production in all subjects.

Participants were then randomly assigned to receive weekly testosterone enanthate in intramuscular doses of 25 mg, 50 mg, 125 mg, 300 mg, or 600 mg.

Both older and younger men significantly improved their muscle strength in a dose-dependent fashion, as measured by maximal performance on a leg press. Younger men, but not older men, also significantly increased leg power, the speed with which they were able to perform leg exercises.

In contrast to the many side effects encountered on the 600-mg dose and a substantial number of adverse events in men taking 300 mg, few side effects were seen in men assigned to the 125-mg dose. Yet the men taking the 125-mg dose had impressive gains.

"On average, they gained the equivalent of 10 pounds of lean muscle mass in 20 weeks," Dr. Storer, an exercise physiologist, said at a press briefing. "You have to train pretty hard to gain 10 pounds of lean mass in 20 weeks."

"We've gone on record as saying that we think the optimal dose, with the most improvement and the least adverse events, is 125 mg," he added.

A related Drew University study of men in the same age ranges, directed by Peter Gray, Ph.D., found improvements in overall sexual function, a category including libido, sexual activity, and erectile function. Changes in these parameters were highly correlated with testosterone dose for overall sexual function ($P = .0002$). Libido improved, but only if men were engaged in a sexual relationship at the onset of the study.

No impact was seen on mood or on performance on visuospatial cognition tests in older or younger men taking testosterone.

Meanwhile, an Australian study examined the impact of testosterone replacement on fat and muscle in 60 nonobese men aged 55 years and older with symptoms of androgen deficiency.

Testosterone replacement therapy did not decrease total body fat or abdominal subcutaneous fat during the yearlong study, reported Carolyn Allan, Ph.D., and colleagues at Prince Henry's Institute of Medical Research at Monash University, Victoria, Australia.

Abdominal visceral fat, however, increased by 16.6% in the placebo group, and decreased by 6.8% in men taking testosterone. Those results represented a significant difference between the groups, according to the investigators.

"These men were not obese, and yet we saw changes in visceral fat," suggesting that testosterone replacement may have potential for modifying cardiovascular risk, Dr. Allan said.

BRIEF SUMMARY. Consult the package insert or www.ZOLOFT.com for complete prescribing information.

Suicidality in Children and Adolescents
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZOLOFT or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZOLOFT is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD). (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

INDICATIONS: ZOLOFT is indicated for the treatment of major depressive disorder (MDD), social anxiety disorder, panic disorder, posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and obsessive-compulsive disorder (OCD), and can be used in pediatric patients (aged 6 to 17 years) with OCD. **CONTRAINDICATIONS:** Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or pimozide is contraindicated. **WARNINGS: Clinical Worsening and Suicide Risk** — Adult and pediatric patients with MDD may experience worsening of their depression and/or emergence of suicidality or unusual behavioral changes, whether or not they are taking antidepressants; this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may prompt worsening of depression and emergence of suicidality in certain patients. Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (24 trials in >4400 patients) revealed a greater risk of suicidality during the first few months of treatment in antidepressant recipients. The average risk of such events in these patients was 4%, twice the placebo risk of 2%. Risk varied considerably among drugs studied, but almost all drugs tended toward an increase. Suicidality risk was most consistently observed in MDD trials, but risk signals also arose from some trials in OCD and social anxiety disorder. **No suicides occurred in these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer term use, eg, beyond several months or to adults. **Closely observe all pediatric patients taking antidepressants for any clinical worsening, suicidality, and unusual behavioral changes, especially in the first few months of treatment, or when dose increases or decreases. This would include at least weekly face-to-face contact with patients, family members, or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks and at 12 weeks, and as clinically indicated thereafter. Additional telephone contact may also be appropriate between face-to-face visits. Adults with MDD or comorbid depression in the setting of other psychiatric illness taking antidepressants should also be observed for clinical worsening and suicidality, especially during the first few months of treatment, or at times of dose increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients taking antidepressants for MDD and other psychiatric or nonpsychiatric indications. While no causal link between the emergence of such symptoms and worsening of depression and/or emergence of suicidal impulses has been established, these symptoms may indicate emerging suicidality. Consider changing or discontinuing the therapeutic regimen in patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might indicate worsening depression and/or suicidality especially if symptoms are severe, abrupt in onset, or not part of presenting symptoms. If treatment is to be discontinued, taper medication as rapidly as possible, with attention to the association of abrupt discontinuation with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with ZOLOFT). **Alert families and caregivers of pediatric and adult patients taking antidepressants for MDD or other psychiatric or nonpsychiatric indications to monitor patients on a daily basis for unusual behavioral changes, and both the emergence of the symptoms described above and suicidality, and to report such symptoms immediately to healthcare providers.** To reduce overdose risk, write ZOLOFT prescriptions for the fewest tablets consistent with good patient management. **Screening for bipolar disorder:** An MDD episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Screen patients with depressive symptoms adequately prior to initiating antidepressant treatment to determine if they are at risk for bipolar disorder; this should include a detailed psychiatric history, including family history of suicide, bipolar disorder, and depression. ZOLOFT is not approved for use in treating bipolar depression. **Cases of serious, sometimes fatal, reactions have been reported in patients receiving ZOLOFT in combination with an MAOI. ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI. ZOLOFT is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in ZOLOFT. PRECAUTIONS: General—Activation of Mania/Hypomania** — During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT-treated patients. **Weight Loss** — Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss. **Seizure** — ZOLOFT has not been evaluated in patients with a seizure disorder. ZOLOFT should be introduced with care in patients with a seizure disorder. **Discontinuation of Treatment** — During marketing of ZOLOFT and other SSRIs, spontaneous reports of adverse events occurred upon discontinuation, particularly when abrupt. Symptoms included dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. These events are generally self-limiting, but serious discontinuation symptoms have been reported. Monitor patients for these symptoms when discontinuing treatment with ZOLOFT. Gradual dose reduction rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a dose reduction or upon discontinuation, resuming the previously prescribed dose may be considered. Subsequently, consider decreasing the dose at a more gradual rate. **Abnormal Bleeding** — Case studies have documented upper gastrointestinal bleeding episodes in patients taking serotonergic reuptake inhibitors concurrently with nonselective NSAIDs or aspirin. Bleeding at other sites may be similarly potentiated. Caution patients about bleeding risk associated with concomitant use of ZOLOFT and nonselective NSAIDs, aspirin, or other drugs that affect coagulation. **Weak Urinary Effect** — ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown. **Use in Patients with Concomitant Illness** — Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. In clinical studies, electrocardiograms of 774 patients taking ZOLOFT (excluding those with a recent history of myocardial infarction or unstable heart disease) indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. In patients with chronic mild liver impairment, sertraline clearance was reduced, thus increasing AUC, C_{max} , and elimination half-life. Effects in patients with moderate and severe hepatic impairment have not been studied. Approach the use of sertraline with caution in patients with liver disease, and use a lower or less frequent dose in patients with liver impairment. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study has indicated that renal disease does not affect sertraline pharmacokinetics and protein binding. Therefore, no dosage adjustment is needed in patients with renal impairment. **Interference with Cognitive and Motor Performance** — In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. **Hypotension** — Several cases of reversible hypotension have been reported, mostly in elderly individuals, some of whom were taking diuretics or who were otherwise volume depleted. **Platelet Function** — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. **Drug Interactions: Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** — Adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs, eg, warfarin, digoxin. Prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **Cimetidine** — When administering ZOLOFT with cimetidine, dosage adjustment after the starting dose of 50 mg should be guided by clinical effect. **CNS Active Drugs** — Concomitant use of ZOLOFT with diazepam or desmethyldiazepam may require dosage adjustment. Even though lithium levels were not altered in clinical trials, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and C_{max} of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg of this time is not known. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Caution is advised if the concomitant use of ZOLOFT and such drugs is required. There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder to ZOLOFT. Caution should be exercised when switching, particularly from long-acting agents. **Drugs Metabolized by P450 3A4** — In three separate *in vivo* interaction studies, sertraline was coadministered with the cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride, under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%). **Drugs Metabolized by P450 2D6** — Many antidepressants, eg, the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug-metabolizing enzyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. This potential interaction is of the greatest concern in those drugs metabolized primarily by 2D6 and which have a narrow therapeutic index, eg, the tricyclic antidepressants (TCAs) and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the coadministered drug. Antidepressants vary in their extent of clinically important 2D6 inhibition; sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the

other drug. Whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the coadministered drug may be required. **Sumatriptan** — Rare reports describe weakness, hyperreflexia, and incoordination following combined SSRI-sumatriptan treatment. Combined therapy warrants appropriate patient observation. **TCAs** — Caution is indicated in the coadministration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. The extent to which SSRI-TCA interactions may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the SSRI involved. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT. **Hypoglycemic Drugs** — In a placebo-controlled trial in normal volunteers, concomitant use of ZOLOFT and tolbutamide caused a decrease in the clearance of tolbutamide, which may have been due to a change in the metabolism of the drug. The clinical significance of this is unknown. **Atenolol** — ZOLOFT (100 mg) administered to 10 healthy males had no effect on the beta-adrenergic blocking ability of atenolol. **Digoxin** — In another study, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance. **Mitral Valve Prolapse** — ZOLOFT was shown to induce hepatic microsomal enzymes, as determined by a decrease in antipyrine half-life. This small change reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy (ECT)** — There are no clinical studies establishing the risks or benefits of the combined use of ECT and ZOLOFT. Alcohol — Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in clinical studies, the concomitant use of ZOLOFT and alcohol is not recommended. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies carried out in mice and rats showed a dose-related increase of liver adenomas in male mice receiving sertraline at 1040 mg/kg (0.25-1.0 times the MRRD on a mg/m² basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 1040 mg/kg, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on laboratory assays. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum human dose on a mg/m² basis). **Pregnancy—Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. ZOLOFT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy-Nonteratogenic Effects** — Neonates exposed to ZOLOFT and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertension, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In some cases, the clinical picture is consistent with serotonin syndrome. Consider carefully the potential risks and benefits when treating a pregnant woman with ZOLOFT during the third trimester. **Labor and Delivery** — The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** — It is not known whether sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use** — The efficacy and safety of ZOLOFT use in children and adolescents with OCD was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17. Safety was evaluated in a 52-week open extension study of 137 patients who had completed the initial study. In the 12-week and 52-week studies, ZOLOFT had an adverse event profile generally similar to that observed in adults. Safety and effectiveness of ZOLOFT in pediatric patients other than those with OCD have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). The results of 2 placebo-controlled trials (N=373) in pediatric patients with MDD given ZOLOFT were insufficient to support a claim for pediatric use. Use of ZOLOFT in a child or adolescent must balance the potential risks with the clinical need. The risks, if any, that may be associated with ZOLOFT's use beyond 1 year in children and adolescents with OCD have not been systematically assessed. There are no studies that directly evaluate the effects of long-term use of sertraline on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding for such effects, the potential of sertraline to have adverse effects with chronic use is not known. **Geriatric Use** — Geriatric studies of ZOLOFT in major depressive disorder in patients ≥65 years of age revealed no overall differences in pattern of efficacy or adverse reactions relative to younger patients except for urinary tract infection (incidence ≥2% and greater than placebo). As with all medications, greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients. **ADVERSE REACTIONS: Incidence in Placebo-Controlled Clinical Trials—Most Common Treatment-Emergent Adverse Events:** The most common adverse events reported in adult patients receiving ZOLOFT (N=2799; N=2394 for placebo) for the treatment of major depressive disorder, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder combined in controlled trials (incidence 2% or more for ZOLOFT and greater than placebo): **Autonomic Nervous System Disorders** — ejaculatory failure (primarily ejaculatory delay; denominator used for male patients only) 14% (n=1118) vs 1% (n=926), mouth dry (14% vs 8%), sweating increased (7% vs 2%), **Central & Peripheral Nervous System Disorders** — somnolence (13% vs 7%), dizziness (12% vs 7%), headache (25% vs 23%), paresthesia (2% vs 1%), tremor (8% vs 2%), **Disorders of Skin and Appendages** — rash (3% vs 2%), **Gastrointestinal Disorders** — anorexia (6% vs 2%), constipation (6% vs 4%), diarrhea/loose stools (20% vs 10%), dyspepsia (8% vs 4%), nausea (25% vs 11%), vomiting (4% vs 2%), **General** — fatigue (12% vs 7%), **Psychiatric Disorders** — agitation (5% vs 3%), anxiety (4% vs 3%), insomnia (21% vs 11%), libido decreased (6% vs 2%), nervousness (5% vs 4%), **Special Senses** — vision abnormal (3% vs 2%), **Adverse Events in Pediatric Patients:** In pediatric patients, the overall profile was similar to that of adults. However, the following events were also reported from controlled trials (n=281 treated with ZOLOFT) (incidence of ≥2% and at least twice that of placebo): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis, and purpura. **Associated with Discontinuation of Treatment:** The adverse events associated with discontinuation of ZOLOFT treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT) in major depressive disorder and other premarketing controlled trials are agitation, diarrhea, dry mouth, ejaculation failure (primarily ejaculatory delay), headache, insomnia, nausea, somnolence, and tremor; in OCD are diarrhea, dizziness, ejaculation failure (primarily ejaculatory delay), insomnia, nausea, and somnolence; in panic disorder are agitation, diarrhea, dyspepsia, ejaculation failure (primarily ejaculatory delay), insomnia, nausea, nervousness, and somnolence; in PTSD are headache and nausea; in PMDD (daily dosing) are diarrhea, nausea, and nervousness; in PMDD (luteal phase dosing) are hot flashes, insomnia, nausea, and palpitation, and in social anxiety disorder are abdominal pain, anxiety, ejaculation failure (primarily ejaculatory delay), fatigue, headache, insomnia, and nausea. **Sexual Dysfunction with SSRIs:** Although sexual desire, sexual performance, and sexual satisfaction may change as a manifestation of psychiatric disorders, some evidence suggests that SSRIs are cause of sexual dysfunction. Reliable estimates of such untoward experiences are difficult to obtain, due to physician and patient reluctance; accordingly, product labeling is likely to underestimate their actual incidence. There are no adequate, well-controlled studies of sexual dysfunction with sertraline. Priapism has been reported with all SSRIs. Physicians should routinely inquire about possible sexual side effects in patients taking SSRIs. **Other Events Observed During the Premarketing Evaluation of ZOLOFT:** During premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects. Events are further categorized by body system and listed in order of decreasing frequency. Note: frequent=events occurring in at least 1/100 patients; infrequent=1/1000 patients; rare=less than 1/1000 patients. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it. **Autonomic Nervous System Disorders** — Frequent: impotence; Infrequent: flushing, increased saliva, cold clammy skin, mydriasis; Rare: pallor, glaucoma, priapism, vasodilation. **Body as a Whole** — General Disorders — Rare: allergic reaction, allergy. **Cardiovascular** — Frequent: palpitations, chest pain; Infrequent: hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; Rare: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder. **Central and Peripheral Nervous System Disorders** — Frequent: hyperreflexia, hypoaesthesia; Infrequent: twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperaesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; Rare: dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyperreflexia. **Disorders of Skin and Appendages** — Frequent: pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; Rare: follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash. **Endocrine Disorders** — Rare: exophthalmos, gynecomastia. **Gastrointestinal Disorders** — Frequent: appetite increased; Infrequent: dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; Rare: melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration. **General** — Frequent: back pain, asthenia, malaise, weight increase; Infrequent: fever, rigors, generalized edema; Rare: face edema, ophthalmic stomatitis. **Hearing and Vestibular Disorders** — Rare: hyperacusis, labyrinthine disorder. **Hematopoietic and Lymphatic** — Rare: anemia, anterior chamber eye hemorrhage. **Liver and Biliary System Disorders** — Rare: abnormal hepatic function. **Metabolic and Nutritional Disorders** — Infrequent: thirst; Rare: hypoglycemia, hypoglycemia reaction. **Musculoskeletal System Disorders** — Frequent: myalgia; Infrequent: arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness. **Psychiatric Disorders** — Frequent: yawning, other male sexual dysfunction, other female sexual dysfunction; Infrequent: depression, amnesia, paranoia, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; Rare: withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion. **Reproductive** — Infrequent: menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; Rare: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis. **Respiratory System Disorders** — Frequent: rhinitis; Infrequent: coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; Rare: hyperventilation, bronchopneumonia, stridor, apnea, bronchitis, hemoptysis, hyperventilation, laryngospasm, laryngitis. **Special Senses** — Frequent: tinnitus; Infrequent: conjunctivitis, earache, eye pain, abnormal accommodation; Rare: xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect. **Urinary System Disorders** — Infrequent: micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; Rare: cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury. **Laboratory Tests:** Asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%). Hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. The safety profile observed with ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, and social anxiety disorder is similar. **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class** — ZOLOFT is not a controlled substance. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. Physicians, however, should carefully evaluate patients for history of drug abuse and observe them for signs of ZOLOFT misuse or abuse. **OVERDOSEAGE:** Reports of death attributed to overdoses of ZOLOFT alone have been extremely rare. Any overdose should be treated aggressively by ensuring an adequate airway, oxygenation, and ventilation. Gastric lavage with appropriate airway protection, may be indicated. Induction of emesis is not recommended.

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