Schizophrenia and Obsessive-Compulsive Disorder: Are They Related Disorders?

BY THOMAS H. MCGLASHAN, MD

"Older nosologic schemes in the field of neuropsychiatry regarded schizophrenia and obsessive-compulsive disorder as mutually exclusive disorders, completely separate and unrelated, with no coexistence between them. Such categorical dogmatism is curious considering that this "rule" was totally unfounded by empirical observation."

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INTRODUCTION

Older nosologic schemes in the field of neuropsychiatry regarded schizophrenia (SCZ) and obsessive-compulsive disorder (OCD) as mutually exclusive disorders, completely separate and unrelated, with no coexistence between them. Such categorical dogmatism is curious considering that this "rule" was totally unfounded by empirical observation. However, the rule was gradually ignored, and data emerged that contradicted mutual exclusivity and introduced much uncertainty and confusion to the heretofore neat and orderly picture of SCZ and OCD as separate entities.

This article reviews the papers presented in the March and April issues of *CNS Spectrums* that represent an initial look at the co-occurance and interaction between SCZ and OCD at the levels of description and treatment response. All of them prove, by the examples described herein, that these two disorders are not mutually exclusive. In fact, the data they present suggest that SCZ and OCD may be related, and they offer clues as to the nature of that linkage. The data presented in this collection of papers are very preliminary and almost entirely descriptive in nature. Yet they are compelling and provocative, suggesting that the study and treatment of comorbid SCZ and OCD will yield much in the future about the nature of these disorders, their interaction, and their treatment.

HYPOTHESIZING THE RELATIONSHIP OF SCHIZOPHRENIA AND OBSESSIVE-COMPULSIVE DISORDER

In their profile of obsessive-compulsive (OC) symptoms in schizophrenia, Porto and colleagues[1] present a comprehensive assessment of OC symptoms in a sample of 50 chronic schizophrenic outpatients. OC symptoms were present in 46% of the sample, and OCD was present in 26%, which shows considerable overlap indeed, especially if the sample was not preselected for OC features. Where overlap occurred, there appeared to be three patterns. In the first pattern, the OCD symptoms appeared unrelated to the psychotic symptoms. In the second, the OC signs and symptoms appeared related, but not restricted, to the psychotic signs and symptoms. In the third, the OC symptoms appeared to be on a continuum with psychosis in so far as obsessions would become delusions during more active phases and return to obsessions (with insight) during remissions. While the work of this group is descriptive at the symptomatic level, their phenomenologic groupings may be extrapolated into the following alternate hypotheses about the relationship between SCZ and OCD as disorders: (1) SCZ and OCD are separate entities that can co-occur; (2) SCZ and OCD are one disorder and represent different aspects of a continuum; and (3) SCZ and OCD are different disorders with shared elements of psychopathology and symptom pathophysiology.

WHAT EVIDENCE DO THE PAPERS IN THESE ISSUES PRESENT FOR OR AGAINST EACH HYPOTHESIS?

If, in their published literature, Sasson et al[2] are correct in asserting that 15% of chronic schizophrenic patients also suffer from OCD, then our first hypothesis that SCZ and OCD are separate disorders must be invalid. Schizophrenia occurs at a prevalence of 1% in the general population and OCD at a prevalence of roughly 2%. If they were independent categories, their rate of overlap would range between 1% and 2%. Fifteen percent certainly suggests some kind of linkage. These data are provocative and clearly call for more clinical epidemiologic studies to test the frequency and comorbidity with rigor and reliability. Most reports to date have counted the frequency of OC symptoms and OCD in chronic schizophrenic samples. At least two types of clinical epidemiologic studies are needed: the rate of SCZ in OCD and the rate of OCD in SCZ. Furthermore, the latter studies should involve SCZ samples that are acutely, as well as chronically, disabled.

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Could SCZ and OCD be one entity? Yaryura-Tobias and colleagues[3] address this question most directly by comparing patients with OCD and with SCZ on a variety of symptom profiles. They conclude that SCZ and OCD share symptoms and behaviors without losing nosological individuality. This suggests that the assumption of syndromal unity is incorrect. Failure to support this hypothesis probably would generate little criticism among workers in the field, especially clinicians who regard and usually treat these disorders as different. While overlap between the disorders is frequent, it is also clear that both SCZ without OCD and OCD without SCZ are common. If they were but different manifestations of the same entity, we could probably expect to see far greater comorbidity, as well as more confluence of one disorder into the other on the basis of acuteness and/or severity.

At the same time, the hypothesis of unity should not be dismissed. Many of the nonsymptomatic clinical parameters are similar between the disorders. Both tend to begin in adolescence and early adulthood, and the age of onset in both is earlier in males. The timing of onset in both can be variable, ie, gradual or acute, and the longitudinal course can fluctuate in severity depending upon ambient levels of stress. Episodic exacerbations and longitudinal deterioration can occur in both disorders. Finally, familial patterns are present in both disorders, ie, higher frequencies of disorder in first-degree relatives versus the general population, and higher frequencies in monozygotic twins versus dizygotic twins. None of these observations suggest identity, but they do imply that we should be cautious in rejecting such a possibility.

The last hypothesis is a hybrid of the first two: OCD and SCZ are different disorders that share elements of symptomatology, psychopathology, and pathophysiology. The data of Berman and colleagues[4] support this view. They assessed 30 schizophrenic patients and found 25% to have significant OC symptoms. The OC and non-OC schizophrenic patients were not different on the positive and negative symptoms of schizophrenia, suggesting independence of OC and psychosis phenomenology. On the other hand, the schizophrenic patients with OC symptoms scored deviantly on several neuropsychological subtests that are typically abnormal in nonschizophrenic OC patients. These tests involve visual-spatial skills, delayed nonverbal memory, and cognitive shifting abilities. Berman and colleagues say nothing about how schizophrenic patients without OCD score on these subtests; however, given the well-known pervasive deficits across neuropsychological profiles among schizophrenic patients, especially on tests of executive functioning such as the Wisconsin Card Sorting Test, it is unlikely the deficits recorded here are unique to OCD psychopathology. A study comparing neuropsychological profiles among three groups, ie, SCZ without OCD, OCD without SCZ, and SCZ with OCD, should be the next step. In the meantime, the study by Berman et al suggests that while there is independence between OCD and SCZ at the symptom level (OC symptoms vs positive and negative psychotic symptoms), there may be less independence at the level of cognitive functioning.

The treatment response data are mixed and confusing. Sasson and colleagues[2] found that open-label clomipramine reduced OC symptoms and psychosis in a significant subset of 18 patients with comorbid OCD and SCZ. Bermanzohn et al[5] reported cross reactivity of anti-obsessional agents on psychosis in refractory delusional states, arguing that

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these might in actuality be OCD in psychotic proportion. Cross-reactivity of neuroleptics for OC symp-toms has recently been reported in the form of risperidone augmentation of SSRI treatment of refractory OCD.[6] Overall, data suggest both specificity and cross-reactivity, but the evidence is very preliminary. The field is in need of well-designed augmentation trials that are randomized, placebo-controlled, and blinded. Also, the study of comorbid samples demands the presence of three comparison groups: the comorbid group and two control groups consisting of each disorder alone.[7]

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Perhaps the least contested finding in this burgeoning field is that comorbidity confers a poor prognosis for both SCZ on OCD course and OCD on SCZ course.[8] This finding does not support any of our three hypotheses differentially since all three might predict this finding. It does raise questions as to the degree of homogeneity versus heterogeneity of the combined pathology. From a purely descriptive, phenomenologic point of view, there may be reason to favor homogeneity. This rests upon the assumption that a cardinal feature of mental illness is repetitive mental content, in the sense of there being less variance of content, less freedom and richness of association, truncated complexity of language, more rigid coupling of thought with affective hue, and less play of will in the "choice" of mentation. These are, almost by definition, the core features of OCD. A closer look at schizophrenia, especially the hallucinations and delusions of psychosis, finds many of the same elements. Delusions are often preemptory and repetitive in theme, appear linked predictively with certain (usually primitive) affective states, and seem to empty the mind of any interest in other ideas or experiences. Hallucinations, especially auditory hallucinations, are often experienced as repeated phrases with simple sentence structure and little variation in content.[9] Unlike OCD symptoms, they are regarded as externally generated, but like OCD symptoms, they are unwillingly experienced.

Given that both SCZ and OCD bind mentation and empty it of richness and associative depth, it is no wonder that their co-occurrence can be so devastating. Whether or not this represents a confluence of similar psychopathology and pathophysiology is a highly relevant but currently unanswered question that awaits pursuit. CNS

REFERENCES

1. Porto L, Bermanzohn PC, Pollack S, Morrissey R, Siris SG. A profile of obsessive-compulsive symptoms in schizophrenia. *CNS Spectrums.* 1997;3:321-25.
2. Sasson Y, Bermanzohn PC, Zohar J. Treatment of obsessive-compulsive (OC) syndromes in schizophrenia. *CNS Spectrums.* 1997;4:34-45.
3. Yaryura-Tobias JA, Stevens KP, Neziroglu F, Grunes MS. Obsessive-compulsive disorder and schizophrenia: a phenomenological perspective of shared pathology. *CNS Spectrums.* 1997;4:21-25.
4. Berman I, Pappas D, Berman SM. Obsessive-compulsive symptoms in schizophrenia: are they manifestations of a distinct subclass of schizophrenia? *CNS Spectrums.* 1997;3:34-36.
5. Bermanzohn PC, Porto L, Arlow PB, et al. Are some neuroleptic-refractory symptoms of schizophrenia really obsessions? *CNS Spectrums.* 1997;3:50-57.
6. Saxena S, Wang D, Bystritsky A, Baxter L. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. *J Clin Psychiatry.* 1996;57:303-306.
7. McGlashan TH. Borderline personality disorder and unipolar affective disorder: long-term effects of comorbidity. *J Nerv Ment Dis.* 1987;175:467-473.
8. Fenton WS, McGlashan TH. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *Am J Psychiatry.* 1986;143:437-441.
9. Hoffman RE, Oates E, Hafner RJ, Hustig HH, McGlashan TH. Semantic organization of hallucinated "voices" in schizophrenia. *Am J Psychiatry.* 1994;151:1229-1230.

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BRIEF SUMMARY

Zoloft *(sertraline HCl)*

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. **WARNINGS: Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT in combination with an MAOI. Therefore, it is recommended that ZOLOFT 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. PRECAUTIONS: General**—During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressant and antiobsessional drugs. **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, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure –** ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for depression. However, 4 patients out of approximately 1800 exposed during the development program for obsessive compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, like other antidepressant and antiobsessional drugs, ZOLOFT should be introduced with care in patients with a seizure disorder. **Suicide –** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Weak Uricosuric 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, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness –** Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. *ZOLOFT is extensively metabolized by the* liver. A lower or less frequent dose should be used in patients with cirrhosis. Until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance –** In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. ***Hyponatremia –*** *Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when ZOLOFT* was discontinued. The majority of these occurrences have been in elderly individuals, some in patients 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. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role. ***Information for Patients:*** Patients should be told *that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and* mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed or OCD patients is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the *potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use* given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins –** Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT to a patient taking another drug which is tightly *bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect.* Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **Cimetidine –** In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown. **CNS Active Drugs –** *In a study comparing the disposition of intravenously administered diazepam before and after* 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required. There is limited controlled experience regarding the optimal timing of switching from other antidepressants to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established. **Drugs Metabolized by P450 3A4 –** In two separate in vivo interaction studies, sertraline was coadministered with the cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. **Drugs Metabolized by P450 2D6 –** Many antidepressants, e.g., the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants 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. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact 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. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the coadministered drug may be required (see Tricyclic Antidepressants under PRECAUTIONS). **Tricyclic Antidepressants (TCAs) –** The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with ZOLOFT because sertraline may inhibit TCA metabolism. Plasma concentrations of TCAs may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS). **Hypoglycemic Drugs –** In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol –** ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Digoxin –** In a placebo-controlled trial in normal volunteers, 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. **Microsomal Enzyme Induction –** Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy –** There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol –** Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed or OCD patients is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25 - 1.0 times the MRHD on a mg/m^2 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. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5 - 2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. 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/m^2 basis). ***Pregnancy*—*Pregnancy Category C:*** Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred *at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis).* The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. 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. **Labor and Delivery –** The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers –** It is not known whether, and if so in what amount, 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 –** Safety and effectiveness in children have not been established. **Geriatric Use –** Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS *Commonly Observed:*** Among patients treated with ZOLOFT in placebo-controlled premarketing studies, the most commonly observed adverse events associated with the *use of ZOLOFT and not seen at an equivalent incidence among placebo-treated patients were: gastrointestinal complaints, including* nausea (26% vs 12%), diarrhea/loose stools (18% vs 9%) and dyspepsia (6% vs 3%); tremor (11% vs 3%); dizziness (12% vs 7%); insomnia (16% vs 9%); somnolence (13% vs 6%); increased sweating (8% vs 3%); dry mouth (16% vs 9%); and male sexual dysfunction (16% vs 2%), primarily ejaculatory delay. In placebo-controlled clinical trials for OCD, adverse events observed at an incidence of at least 5% for ZOLOFT and at an incidence that was twice or more the incidence among placebo-treated patients included: *nausea (30% vs 11%), insomnia (28% vs 12%), diarrhea (24% vs 2%), decreased libido (11% vs 2%), anorexia (11% vs* 2%), dyspepsia (10% vs 4%), ejaculation failure (primarily ejaculatory delay) (17% vs 2%), tremor (8% vs 1%), and increased sweating (6% vs 1%). ***Associated with Discontinuation of Treatment:*** Fifteen percent of 2710 patients who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (*primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue. In placebo-*controlled clinical trials for OCD, 10% of patients treated with ZOLOFT discontinued treatment due to an adverse event. The more common events were nausea, insomnia, and diarrhea. ***Other Events Observed During the Premarketing Evaluation of ZOLOFT:*** During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: fre*quent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the* tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders –** *Infrequent:* flushing, mydriasis, increased saliva, cold clammy skin; *Rare:* pallor. **Cardiovascular –** *Infrequent:* postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins. **Central and Peripheral Nervous System Disorders –** *Frequent:* confusion; *Infrequent:* ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare:* local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. **Disorders of Skin and Appendages –** *Infrequent:* acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare:* bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria. **Endocrine Disorders –** *Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders –** *Infrequent:* dysphagia, eructation; *Rare:* diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration. **General –** *Frequent:* asthenia; *Infrequent:* malaise, generalized edema, rigors, weight decrease, weight increase; *Rare:* enlarged abdomen, halitosis, otitis media, aphthous stomatitis. **Hematopoietic and Lymphatic –** *Infrequent:* lymphadenopathy, purpura; *Rare:* anemia, anterior chamber eye hemorrhage. **Metabolic and Nutritional Disorders –** *Rare:* dehydration, hypercholesterolemia, hypoglycemia. **Musculoskeletal System Disorders –** *Infrequent:* arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare:* hernia. **Psychiatric Disorders**—*Infrequent:* abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare:* hysteria, somnambulism, withdrawal syndrome. **Reproductive –** *Infrequent:* dysmenorrhea (2), intermenstrual bleeding (2); *Rare:* amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).(1) - % based on male subjects only: 1005; (2) - % based on female subjects only: 1705. **Respiratory System Disorders –** *Infrequent:* bronchospasm, coughing, dyspnea, epistaxis; *Rare:* bradypnea, hyperventilation, sinusitis, stridor. **Special Senses –** *Infrequent:* abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare:* abnormal lacrimation, photophobia, visual field defect. **Urinary System Disorders –** *Infrequent:* dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention. **Laboratory Tests**: In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug 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 in OCD patients treated with ZOLOFT is similar to the safety profile in depressed patients. **DRUG ABUSE AND DEPENDENCE *Controlled Substance Class*** – ZOLOFT is not a controlled substance. ***Physical and Psychological Dependence –*** ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE *Human Experience –*** As of November, 1992, there were 79 reports of non-fatal acute overdoses involving ZOLOFT, of which 28 were overdoses of ZOLOFT alone and the remainder involved a combination of other drugs and/or alcohol in addition to ZOLOFT. In those cases of overdose involving only ZOLOFT, the reported doses ranged from 500 mg to 6000 mg. In a subset of 18 of these patients in whom ZOLOFT blood levels were determined, plasma concentrations ranged from <5 ng/mL to 554 ng/mL. Symptoms of overdose with ZOLOFT alone included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when ZOLOFT was taken alone, there were 4 deaths involving overdoses of ZOLOFT in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively. ***Management of Overdoses –*** Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for ZOLOFT. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

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