May 2004 Volume 9 -- Number 5

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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citation: *CNS Spectr*

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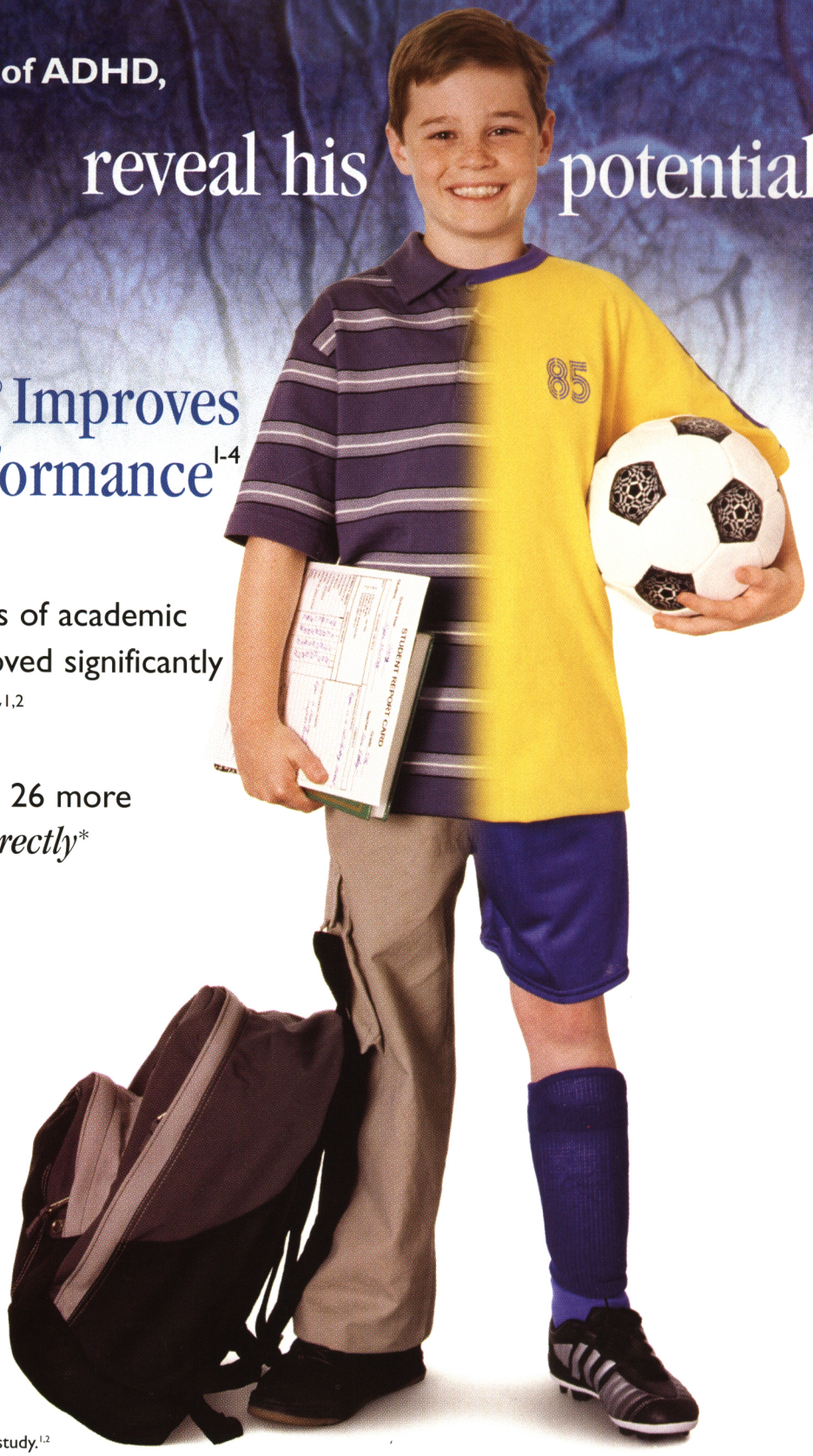
https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

In the management of ADHD,

reveal his potential



ADDERALL XR® Improves Academic Performance[1-4]

- Objective measures of academic performance improved significantly throughout the day[1,2]
- Patients completed 26 more math problems *correctly**

*Averaged throughout a 12-hour day and compared with placebo in a crossover design study.[1,2]

The most common adverse events include loss of appetite, insomnia, abdominal pain, and emotional lability.

As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Caution also should be exercised in patients with a history of psychosis.

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

References: 1. Data on file, Shire US Inc., 2003. **2.** McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2003;42:673-683. **3.** ADDERALL XR package insert, Shire US Inc., 2002. **4.** Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2002;110:258-266. **5.** Lopez FA, Ambrosini PJ, Chandler MC, Tulloch SJ, Michaels MA. ADDERALL XR® in pediatric ADHD: quality-of-life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla.

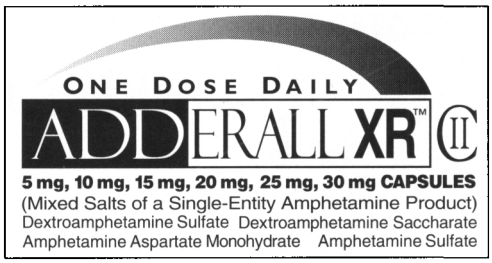
BRIEF SUMMARY: Consult the full prescribing information for complete product information.

ADDERALL XR® CAPSULES **CII Rx Only**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

INDICATIONS ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). *The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two* controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD, along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance. **CONTRAINDICATIONS** Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). **WARNINGS Psychosis:** Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. **Long-Term Suppression of Growth:** Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted. **PRECAUTIONS General:** The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. **Hypertension and other Cardiovascular Conditions:** Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension. **Tics:** Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. **Information for Patients:** Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly. **Drug Interactions:** *Acidifying agents*—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines. *Urinary acidifying agents*—These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. *Adrenergic blockers*—Adrenergic blockers are inhibited by amphetamines. *Alkalinizing agents*—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the *concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion.* Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. *Antidepressants, tricyclic*—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. *MAO inhibitors*—MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. *Antihistamines*—Amphetamines may counteract the sedative effect of antihistamines. *Antihypertensives*—Amphetamines may antagonize the hypotensive effects of antihypertensives. *Chlorpromazine*—Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. *Ethosuximide*—Amphetamines may delay intestinal absorption of ethosuximide. *Haloperidol*—Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines. *Lithium carbonate*—The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. *Meperidine*—Amphetamines potentiate the analgesic effect of meperidine. *Methenamine therapy*—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy. *Norepinephrine*—Amphetamines enhance the adrenergic effect of norepinephrine. *Phenobarbital*—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. *Phenytoin*—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Propoxyphene*—In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids*—Amphetamines inhibit the hypotensive effect of veratrum alkaloids. **Drug/Laboratory Test Interactions:** Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations. **Carcinogenesis/Mutagenesis and Impairment of Fertility:** No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis. Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative *responses in the in vitro sister chromatid exchange and chromosomal aberration assays. Amphetamine, in the* enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis). **Pregnancy:** Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the maximum recommended human dose of 30 mg/day on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity. A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function. There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **Pediatric Use:** ADDERALL XR® is indicated for use in children 6 years of age and older. **Use in Children Under Six Years of Age:** Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age. **Geriatric Use:** ADDERALL XR® has not been studied in the geriatric population. **ADVERSE EVENTS** The premarketing development program for ADDERALL XR® included exposures in a total of 685 participants in clinical trials (615 patients, 70 healthy adult subjects). These participants received ADDERALL XR® at daily doses up to 30 mg. The 615 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and one single-dose clinical pharmacology study (N=20). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. **Adverse events associated with discontinuation of treatment:** In two placebo-controlled studies of up to 5 weeks duration, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of patients discontinuing (N=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7



Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients treated with ADDERALL XR® or placebo are presented in the table below. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (N=374)	Placebo (N=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects. Allergic: Urticaria. Endocrine: Impotence, changes in libido. **DRUG ABUSE AND DEPENDENCE** ADDERALL XR® is a Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. **OVERDOSAGE** Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. Treatment: Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose. Dispense in a tight, light-resistant container as defined in the USP. Store at 25° C (77° F). Excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Manufactured by DSM Pharmaceuticals Inc., Greenville, North Carolina 27834. Distributed and marketed by Shire US Inc., Newport, KY 41071. For more information call 1-800-828-2088 or visit www.adderallxr.com. ADDERALL® is registered in the US Patent and Trademark Office.

403958 (rev. 10/2002)

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https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

May 2004 Volume 9 – Number 5

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

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BRIEF SUMMARY of PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Bipolar Mania: SEROQUEL is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 3-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness for more than 3 weeks has not been systematically evaluated in clinical trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS: Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: General: Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology in Prescribing Information). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment. Seizures:** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed

in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine: Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs: Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, *the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas* to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in PRECAUTIONS, General). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS: The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-Term, Controlled Trials: Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Acute Bipolar Mania:** Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see PRECAUTIONS): Somnolence 0.8% vs 0% for placebo and Hypotension 0.4% vs 0% for placebo. **Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials:** The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied. The following treatment-emergent adverse experiences occurred during *acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated* with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. Treatment-Emergent Adverse Experience Incidence in

SEROQUEL® (quetiapine fumarate) Tablets

3- to 12-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Schizophrenia and Acute Bipolar Mania (monotherapy): **Body as a Whole:** Headache, Pain, Asthenia, Abdominal Pain, Back Pain, Fever; **Cardiovascular:** Tachycardia, Postural Hypotension; **Digestive:** Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl, Transpeptidase Increased; **Metabolic and Nutritional:** Weight Gain, SGPT Increased, SGOT Increased; **Nervous:** Agitation, Somnolence, Dizziness, Anxiety; **Respiratory:** Pharyngitis, Rhinitis; **Skin and Appendages:** Rash; **Special Senses:** Amblyopia [1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). The following treatment-emergent adverse experiences occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Acute Bipolar Mania (Adjunct Therapy): **Body as a Whole:** Headache, Asthenia, Abdominal Pain, Back Pain; **Cardiovascular:** Postural Hypotension; **Digestive:** Dry Mouth, Constipation; **Metabolic and Nutritional:** Weight Gain; **Nervous:** Somnolence, Dizziness, Tremor, Agitation; **Respiratory:** Pharyngitis. [1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea. In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials: Dose-related Adverse Events:** Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for shizophrenia. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring 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. **Nervous System:** ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged. **Digestive System:** ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, *increased QRS duration.* **Respiratory System:** ***Frequent:*** *pharyngitis, rhinitis, cough increased, dyspnea;* ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation. **Metabolic and Nutritional System:** ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses:** ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia. **Endocrine System:** ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism. *adjusted for gender **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic dependence:** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limit*ed experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.* Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma or QTc prolongation. **Management of Overdosage:** In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Rev 01/04

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, Delaware 19850-5437

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

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EDITORIAL MISSION

CNS Spectrums' *editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.*

CNS SPECTRUMS®

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Founded in 1996, ***CNS Spectrums*** is an *Index Medicus* journal and is available on MEDLINE under the citation *CNS Spectr.* It is available online at www.cnsspectrums.com.

CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc. 333 Hudson Street, 7th Floor, New York, NY 10013.

One-year subscription rates: domestic $120; foreign $185; in-training $75. For subscriptions: Phone: 212-328-0800; Fax: 212-328-0600; Web: www.cnsspectrums.com.

Postmaster: Send address changes to ***CNS Spectrums*** c/o PPS Medical Marketing Group 264 Passaic Avenue, Fairfield, NJ 07004-2595.

For editorial inquiries, please fax us at 212-328-0600 or e-mail us at jrr@mblcommunications.com. For bulk reprint purchases, please contact: Kelly J. Staley at kjs@mblcommunications.com.

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Please see brief summary of Prescribing Information on adjacent page.

References: 1. ZONEGRAN® Prescribing Information. Elan Pharmaceuticals. 2002. 2. Brodie M, Wilson E, Smith D, et al. Steady-state drug interaction study of zonisamide and lamotrigine in epileptic patients. *Neurology*. 2001;56(3):A337 (abstract). 3. Data on file. Elan Pharmaceuticals, Inc.

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https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

CONTRAINDICATIONS

ZONEGRAN is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

WARNINGS

Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reaction to zonisamide is described below.

Serious Skin Reactions: Consideration should be given to discontinuing ZONEGRAN in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. Seven deaths from severe rash [i.e. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In post-marketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46 per million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of under-reporting. There were no confirmed cases of SJS or TEN in the US, European, or Japanese development programs.

In the US and European randomized controlled trials, 6 of 269 (2.2%) zonisamide patientsdiscontinued treatment because of rash compared to none on placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events per 1000 patient-years of exposure). During Japanese development, serious rash or rash that led to study drug discontinuation was reported in 2.0% of patients (27.8 events per 1000 patient years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the US and European studies and 90% reported within two weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

Serious Hematologic Events: Two confirmed cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and two confirmed cases of agranulocytosis in the US, European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Oligohidrosis and Hyperthermia in Pediatric Patients:

Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.

During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been one report of heat stroke in an 18-year-old patient in the US.

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with Zonegran should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

Seizures on Withdrawal: As with other AEDs, abrupt withdrawal of ZONEGRAN in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

Teratogenicity: Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of ZONEGRAN during pregnancy in humans may present a significant risk to the fetus (see **PRECAUTIONS, Pregnancy** subsection). It cannot be said with any confidence, however, that even mild seizures do not pose some hazards to the developing fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Cognitive/ Neuropsychiatric Adverse Events: Use of ZONEGRAN was frequently associated with central nervous system-related adverse events. The most significant of these can be classified into three general categories: 1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue.

In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized for depression compared to 0.4% of placebo patients, while 1.1% of ZONEGRAN and 0.4% of placebo patients attempted suicide. Among all epilepsy patients treated with ZONEGRAN, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with ZONEGRAN, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms.

Psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6–10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they at times led to withdrawal from treatment.

Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with ZONEGRAN. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300–500 mg/day. **Patients should be cautioned about this possibility and special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.**

PRECAUTIONS

General: Somnolence is commonly reported, especially at higher doses of ZONEGRAN (see **WARNINGS: Cognitive/ Neuropsychiatric Adverse Events** subsection). Zonisamide is metabolized by the liver and eliminated by the kidneys; caution should therefore be exercised when administering ZONEGRAN to patients with hepatic and renal dysfunction (see **CLINICAL PHARMACOLOGY, Special Populations** subsection of full Prescribing Information).

Kidney Stones: Among 991 patients treated during the development of ZONEGRAN, 40 patients (4.0%) with epilepsy receiving ZONEGRAN developed clinically possible or confirmed kidney stones (e.g. clinical symptomatology, sonography, etc.), a rate of 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7 per 1000 patient-years of exposure in the first six months, 62.6 per 1000 patient-years of exposure between 6 and 12 months, and 24.3 per 1000 patient-years of exposure after 12 months of use. There are no normative sonographic data available for either the general population or patients with epilepsy. The clinical significance of the sonographic finding is unknown. The analyzed stones were composed of calcium or urate salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patients treated with ZONEGRAN.

Effect on Renal Function: In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the US, Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2–3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term use. ZONEGRAN should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. ZONEGRAN should not be used in patients with renal failure (estimated GFR < 50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity.

Sudden Unexplained Death in Epilepsy: During the development of ZONEGRAN, nine sudden unexplained deaths occurred among 991 patients with epilepsy receiving ZONEGRAN for whom accurate exposure data are available. This represents an incidence of 7.7 deaths per 1000 patient years. Although this rate exceeds that expected in a healthy population, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with refractory epilepsy not receiving ZONEGRAN (ranging from 0.5 per 1000 patient-years for the general population of patients with epilepsy, to 2–5 per 1000 patient-years for patients with refractory epilepsy; higher incidences range from 9–15 per 1000 patient-years among surgical candidates and surgical failures). Some of the deaths could represent seizure-related deaths in which the seizure was not observed.

Status Epilepticus: Estimates of the incidence of treatment emergent status epilepticus in ZONEGRAN-treated patients are difficult because a standard definition was not employed. Nonetheless, in controlled trials, 1.1% of patients treated with ZONEGRAN had an event labeled as status epilepticus compared to none of the patients treated with placebo. Among patients treated with ZONEGRAN across all epilepsy studies (controlled and uncontrolled), 1.0% of patients had an event reported as status epilepticus.

Creatine Phosphokinase (CPK) Elevation and Pancreatitis: In the post-market setting, the following rare adverse events have been observed (<1:1000):

If patients taking zonisamide develop severe muscle pain and/or weakness, either in the presence or absence of a fever, markers of muscle damage should be assessed, including serum CPK and aldolase levels. If elevated, in the absence of another obvious cause such as trauma, grand mal seizures, etc., tapering and/or discontinuance of zonisamide should be considered and appropriate treatment initiated.

Patients taking zonisamide that manifest clinical signs and symptoms of pancreatitis should have pancreatic lipase and amylase levels monitored. If pancreatitis is evident, in the absence of another obvious cause, tapering and/or discontinuation of zonisamide should be considered and appropriate treatment initiated.

Information for Patients: Patients should be advised as follows:

1. **ZONEGRAN may produce drowsiness, especially at higher doses. Patients should be advised not to drive a car or operate other complex machinery until they have gained experience on ZONEGRAN sufficient to determine whether it affects their performance.**
2. Patients should contact their physician immediately if a skin rash develops or seizures worsen.
3. Patients should contact their physician immediately if they develop signs or symptoms, such as sudden back pain, abdominal pain, and/or blood in the urine, that could indicate a kidney stone. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones.
4. Patients should contact their physician immediately if a child has been taking ZONEGRAN and is not sweating as usual with or without a fever.
5. Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.
6. As with other AEDs, patients should contact their physician if they intend to become pregnant or are pregnant during ZONEGRAN therapy. Patients should notify their physician if they intend to breast-feed or are breast-feeding an infant.
7. Patients should contact their physician immediately if they develop severe muscle pain and/or weakness.

Laboratory Tests: In several clinical studies, zonisamide was associated with a mean increase in the concentration of serum creatinine and blood urea nitrogen (BUN) of approximately 8% over the baseline measurement. Consideration should be given to monitoring renal function periodically (**see PRECAUTIONS, Effect on Renal Function** subsection).

Zonisamide was associated with an increase in serum alkaline phosphatase. In the randomized, controlled trials, a mean increase of approximately 7% over baseline was associated with zonisamide compared to a 3% mean increase in placebo-treated patients. These changes were not statistically significant. The clinical relevance of these changes is unknown.

Drug Interactions: *Effects of ZONEGRAN on the pharmacokinetics of other antiepilepsy drugs (AEDs):* Zonisamide had no appreciable effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidase enzymes (cytochrome P450), as measured in human liver microsomal preparations, *in vitro*. Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes.

Effects of other drugs on ZONEGRAN pharmacokinetics: Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. The half-life of zonisamide following a 400 mg dose in patients concurrently on enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbital was between 27–38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours. Concurrent medication with drugs that either induce or inhibit CYP3A4 would be expected to alter serum concentrations of zonisamide.

Interaction with cimetidine: Zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (300 mg four times a day for 12 days).

Carcinogenicity, Mutagenesis, Impairment of Fertility: No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for two years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m^2 basis. In rats, this dose is 1–2 times the MRHD on a mg/m^2 basis.

Zonisamide increased mutation frequency in Chinese hamster lung cells in the absence of metabolic activation. Zonisamide was not mutagenic or clastogenic in the Ames test, mouse lymphoma assay, sister chromatid exchange test, and human lymphocyte cytogenetics assay *in vitro*, and the rat bone marrow cytogenetics assay *in vivo*.

Rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect of zonisamide on human fertility is unknown.

Pregnancy: Pregnancy Category C (see **WARNINGS, Teratogenicity** subsection): Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 µg/mL) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 µg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 µg/mL) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryolethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 µg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low dose in this study is approximately 1.5 times the MRHD on a mg/m^2 basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a mg/m^2 basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a mg/m^2 basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. ZONEGRAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of ZONEGRAN on labor and delivery in humans is not known.

Use in Nursing Mothers: It is not known whether zonisamide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from zonisamide, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother. ZONEGRAN should be used in nursing mothers only if the benefits outweigh the risks.

Pediatric Use: The safety and effectiveness of ZONEGRAN in children under age 16 have not been established. Cases of oligohidrosis and hyperpyrexia have been reported (see **WARNINGS, Oligohidrosis and Hyperthermia in Pediatric Patients** subsection).

Geriatric Use: Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers (see **CLINICAL PHARMACOLOGY, Special Populations** subsection in full Prescribing Information). Clinical studies of zonisamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of ZONEGRAN in controlled clinical trials that were not seen at an equivalent frequency among placebo-treated patients were somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.

In controlled clinical trials, 12% of patients receiving ZONEGRAN as adjunctive therapy discontinued due to an adverse event compared to 6% receiving placebo. Approximately 21% of the 1,336 patients with epilepsy who received ZONEGRAN in clinical studies discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse events were dose-related (see **WARNINGS and PRECAUTIONS**).

Adverse Event Incidence in Controlled Clinical Trials: Table 3 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with ZONEGRAN in controlled clinical trials that were numerically more common in the ZONEGRAN group. In these studies, either ZONEGRAN or placebo was added to the patient's current AED therapy. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when ZONEGRAN was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials (Events that occurred in at least 2% of ZONEGRAN-treated patients and occurred more frequently in ZONEGRAN-treated than placebo-treated patients)

ZONEGRAN (n=269) PLACEBO (n=230)

BODY AS A WHOLE Headache (10%/8%), Abdominal Pain (6%/3%), Flu Syndrome (4%/3%) **DIGESTIVE** Anorexia (13%/6%), Nausea (9%/6%), Diarrhea (5%/2%), Dyspepsia (3%/1%), Constipation (2%/1%), Dry Mouth (2%/1%) **HEMATOLOGIC AND LYMPHATIC** Ecchymosis (2%/1%) **METABOLIC AND NUTRITIONAL** Weight Loss (3%/2%) **NERVOUS SYSTEM** Dizziness (13%/7%), Ataxia (6%/1%), Nystagmus (4%/2%), Paresthesia (4%/1%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-ALTERED COGNITIVE FUNCTION** Confusion (6%/3%), Difficulty Concentrating (6%/2%), Difficulty with Memory (6%/2%), Mental Slowing (4%/2%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (NON-PYSCHOSIS-RELATED)** Agitation/Irritability (9%/4%), Depression (6%/3%), Insomnia (6%/3%), Anxiety (3%/2%), Nervousness (2%/1%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (PYSCHOSIS-RELATED)** Schizophrenic/Schizophreniform Behavior (2%/0%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-CNS DEPRESSION** Somnolence (17%/7%), Fatigue (8%/6%), Tiredness (7%/5%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-SPEECH AND LANGUAGE ABNORMALITIES** Speech Abnormalities (5%/2%), Difficulties in Verbal Expression (2%/<1%) **RESPIRATORY** Rhinitis (2%/1%) **SKIN AND APPENDAGES** Rash (3%/2%) **SPECIAL SENSES** Diplopia (6%/3%), Taste Perversion (2%/0%)

Other Adverse Events Observed During Clinical Trials: ZONEGRAN has been administered to 1,598 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all events were recorded by the investigators using their own terms. To provide a useful estimate of the proportion of individuals having adverse events, similar events have been grouped into a smaller number of standardized categories using a modified COSTART dictionary. The frequencies represent the proportion of the 1,598 individuals exposed to ZONEGRAN who experienced an event on at least one occasion. All events are included except those already listed in the previous table or discussed in **WARNINGS** or **PRECAUTIONS**, trivial events, those too general to be informative, and those not reasonably associated with ZONEGRAN.

Events are further classified within each category and listed in order of decreasing frequency as follows: frequent occurring in at least 1:100 patient; infrequent occurring in 1:100 to 1:1000 patients; rare occurring in fewer than 1:1000 patients.

Body as a Whole: *Frequent:* Accidental injury, asthenia. *Infrequent:* Chest pain, flank pain, malaise, allergic reaction, face edema, neck rigidity. *Rare:* Lupus erythematosus.

Cardiovascular: *Infrequent:* Palpitation, tachycardia, vascular insufficiency, hypotension, hypertension, thrombophlebitis, syncope, bradycardia. *Rare:* Atrial fibrillation, heart failure, pulmonary embolus, ventricular extrasystoles.

Digestive: *Frequent:* Vomiting. *Infrequent:* Flatulence, gingivitis, gum hyperplasia, gastritis, gastroenteritis, stomatitis, cholelithiasis, glossitis, melena, rectal hemorrhage, ulcerative stomatitis, gastro-duodenal ulcer, dysphagia, gum hemorrhage. *Rare:* Cholangitis, hematemesis, cholecystitis, cholestatic jaundice, colitis, duodenitis, esophagitis, fecal incontinence, mouth ulceration.

Hematologic and Lymphatic: *Infrequent:* Leukopenia, anemia, immunodeficiency, lymphadenopathy. *Rare:* Thrombocytopenia, microcytic anemia, petechia.

Metabolic and Nutritional: *Infrequent:* Peripheral edema, weight gain, edema, thirst, dehydration. *Rare:* Hypoglycemia, hyponatremia, lactic dehydrogenase increased, SGOT increased, SGPT increased.

Musculoskeletal: *Infrequent:* Leg cramps, myalgia, myasthenia, arthralgia, arthritis.

Nervous System: *Frequent:* Tremor, convulsion, abnormal gait, hyperesthesia, incoordination. Infrequent: Hypertonia, twitching, abnormal dreams, vertigo, libido decreased, neuropathy, hyperkinesia, movement disorder, dysarthria, cerebrovascular accident, hypotonia, peripheral neuritis, parathesia, reflexes increased. *Rare:* Circumoral paresthesia, dyskinesia, dystonia, encephalopathy, facial paralysis, hypokinesia, hyperesthesia, myoclonus, oculogyric crisis.

Behavioral Abnormalities – Non-Psychosis-Related: *Infrequent:* Euphoria.

Respiratory: *Frequent:* Pharyngitis, cough increased. Infrequent: Dyspnea. *Rare:* Apnea, hemoptysis.

Skin and Appendages: *Frequent:* Pruritus. Infrequent: Maculopapular rash, acne, alopecia, dry skin, sweating, eczema, urticaria, hirsutism, pustular rash, vesiculobullous rash.

Special Senses: *Frequent:* Amblyopia, tinnitus. *Infrequent:* Conjunctivitis, parosmia, deafness, visual field defect, glaucoma. *Rare:* Photophobia, iritis.

Urogenital: *Infrequent:* Urinary frequency, dysuria, urinary incontinence, hematuria, impotence, urinary retention, urinary urgency, amenorrhea, polyuria, nocturia. *Rare:* Albuminuria, enuresis, bladder pain, bladder calculus, gynecomastia, mastitis, menorrhagia.

élan

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6001061-BS August 27,2003 Printed in the USA

Taking Another Look at Schizophrenia

By Jack M. Gorman, MD

Until recently, paper after paper about schizophrenia always included the sentence, "the mean age of onset of schizophrenia for this group was xx." In these cases, "xx" was defined as ~21 years of age, with a range of 18–25 years of age. Consistent with what the textbooks said, schizophrenia supposedly first struck in "adolescence, early adulthood," with a slightly later age of onset for women than men.

We now know that these age of onset figures merely reflect the time when the positive symptoms of schizophrenia first become so bothersome that professional help, often in the form of a late-night trip to the emergency room, occurs. They do not by any means represent the beginning of schizophrenia. Rather, almost all experts now agree that schizophrenia is a complex mix of cognitive, positive, negative, and affective symptoms that begins as early in life as we are able to measure it and that it persists throughout life, even when hallucinations and delusions are at least temporarily quiescent.

This information has been gleaned by a number of creative studies of varied design. In the "high risk design," pioneered by, among others, my former colleague Nikki Erlenmeyer-Kimling, PhD, children of parents with schizophrenia are identified in pre-teen years and followed through the "age of risk" for developing schizophrenia, meaning until it is reasonably certain that they do not have the illness. These children are compared over time to a control group of children who do not have parents with schizophrenia. Such studies show that well before the positive symptoms of the illness emerge, children destined to develop schizophrenia manifest subtle but clearly identifiable abnormalities in cognition, social adjustment, and behavior.

In another design, used by investigators such as Robin Murray, MD, from the United Kingdom cohorts of children who underwent cognitive testing for other reasons are followed into adulthood. For example, in one study, data were available from intelligence testing done for administrative purposes on a large group of English children many years ago. By matching these data with national health registry data, it was possible to show that those in the cohort who now have confirmed diagnoses of schizophrenia had impaired intellectual functioning as children compared with those who did not develop schizophrenia. These studies are, in the aggregate, convincing that schizophrenia does not begin at 18 years of age with the onset of hallucinations, delusions, thought disorder, and odd behavior, but rather begins early in childhood (some say it is present at birth) in the form of cognitive impairment.

These findings have been used to support the widely popular "neurodevelopmental" hypothesis of schizophrenia which posits that the brain abnormalities that are at the root of the illness occur during fetal brain development and largely remain in place throughout the life of the patient. Part of this theory rests on findings that structural brain abnormalities seen in schizophrenia patients, such as enlarged ventricles, can be detected with the first episode of positive symptoms. However, the neurodevelopmental theory has engendered some dissenters, including my Mount Sinai School of Medicine colleagues Philip Harvey, MD, and Kenneth Davis, MD, who present convincing data that there is evidence of degenerative changes both in structural measures of the brain and in cognition throughout the life of patients with schizophrenia. In particular, that group and others has shown that elderly patients with schizophrenia have cognitive impairment that is often indistinguishable from that seen in Alzheimer's disease, even though in the former case at postmortem examination there is no evidence of the typical AD pathology. This raises the problem that not everything that causes schizophrenia is necessarily in place at birth and that further structural and physiological deterioration may occur during the life of the patient. Such findings are important because they encourage hope that at least some of the underlying brain pathology of schizophrenia might be amenable to reversal during the life of the patient.

The neurodevelopmental and neurodegenerative concepts are not mutually exclusive. Many brain disorders show both forms of pathology and there is no reason to believe that schizophrenia is different. What is critical, however, is the recognition that impaired cognition is one of the key elements, some would say the key element, in schizophrenia. Indeed, if we want to know how a patient in the emergency room with florid hallucinations and delusions will be doing in 5 years, the answer does not come by measuring the severity of the positive symptoms but rather by measuring the severity of impairment in functions like attention and working memory. These turn out to be the best predictors of course in schizophrenia and probably much more central to the underlying pathophysiology of the illness. In this issue of *CNS Spectrums*, we have recent research and reviews highlighting cognitive function in schizophrenia. This is cutting edge work of great interest and importance to those dedicated to helping patients with one of humankind's most devastating illnesses. CNS

Dr. Gorman is the editor of this journal and Esther and Joseph Klingenstein Professor of Psychiatry and chair of the Department of Psychiatry at Mount Sinai School of Medicine in New York City.

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

NEWS FROM THE 24TH ANNUAL CONFERENCE OF
THE ANXIETY DISORDERS ASSOCIATION OF AMERICA

RISPERIDONE FOUND EFFECTIVE FOR PATIENTS SUFFERING FROM DEPRESSION AND ANXIETY DISORDERS

Previous research has found that ~85% of depressed patient suffer various symptoms of anxiety, with 58% treated for an anxiety disorder. When anxiety presents with depression, patients have been found to have a decreased quality of life, more severe symptoms of depression, greater functional impairment, and poorer treatement outcomes. Mark H. Rapaport, MD, from Cedars-Sinai Medical Center in Los Angeles, CA, and colleagues studied 502 patients between 18 and 85 years of age with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of major depressive disorder. They also had baseline scores greater than or equal to 20 on the Hamilton Rating Scale for Depression (HAM-D) scale.

The study consisted of an open-label treatment phase and a double-blind maintenance phase. In the open-label phase, patients were treated with citalopram (Celexa) 20 mg/day monotherapy for 4–6 weeks as a means of confirming that they had no response to the medication. The patients' therapy was then augmented with risperidone (Risperdal) for 4–6 weeks. Risperidone was initiated at 0.5 mg/day and targeted to 1 mg/day for patients between 18 and 54 years of age. Patients between 55 and 85 years of age were administered medication at 0.25 mg/day titrated to 0.5 mg/day. Of the 502 patients that began the study, 393 met the criteria to enter the augmentation period. Those that did not move on to the augmentation period were considered non-responders. These were defined as patients that had <50% reduction in HAM-D scores.

Rapaport and colleagues used the Hamilton Rating Scale for Anxiety (HAM-A) and its Psychic Anxiety and Somatic Anxiety subscales to assess the patients' anxiety throughout the study. They also used the HAM-D and the Montgomery-Asberg Depression Rating Scale (MADRS) to assess the patients' depression. At baseline, the HAM-A total score was 17.8±6.9, the Psychic Anxiety subscale score was 11.2±3.9, and the Somatic Anxiety subscale score was 6.6±3.8. At endpoint, the HAM-A total scores decreased to ~13, the Psychic Anxiety subscale scores decreased to ~7, and the Somatic Anxiety subscale scores decreased to ~5.5. Only 4.6% of patients discontinued due to adverse events.

The researchers found that augmenting anxiety and depression treatment with risperidone improved the patients anxiety, as ~55% of the patients with substantial baseline anxiety had a ≥50% reduction in HAM-A total scores at endpoint. Approximately 36% of patients achieved a symptomatic remission of their anxiety symptoms while ~59% of patients were found to have an MADRS score ≥12, thus showing a symptomatic remission of depressive symptoms.

Rapaport and colleagues concluded that augmenting depression and anxiety treatment with risperidone greatly improves the patients' anxiety symptoms.–*CN*

Funding for this research was provided by Johnson & Johnson Pharmaceutical Research & Development and Janssen Pharmaceutica Products, LP. *(ADAA 2004 Poster 143)*

ANTIDEPRESSANTS EFFECTIVE FOR TREATMENT OF SAD IN UK PATIENTS

Various community studies have found social anxiety disorder (SAD) to have a lifetime prevalence rate between 2% and 16%. Previous clinical trials have found both selective serotonin reuptake inhibitors and monoamine oxidase inhibitors effective treatments for SAD. A study out of the United Kingdom details the various effects treatment of SAD with either escitalopram (Lexapro) or paroxetine (Paxil) has on a small sampling of patients.

Malcolm Lader, PhD, MD, FRCPsych, from the University of London, UK, and colleagues conducted a 24-week randomized, double-blind, placebo-controlled study of 839 men and women between 18 and 65 years of age. There was a 1-week, placebo-blind, run-in period before treatment began. The patients were then given a fixed dose of escitalopram 5, 10, or 20 mg/day, paroxetine 20 mg/day, or placebo for 24 weeks. Patients completing the double-blind phase then moved on to a 2-week, single-blind, placebo run-out period. Each patient had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of SAD; a Liebowitz Social Anxiety Scale (LSAS) of ≥70; a Sheehan Disability Score of ≥5 on one or more its subscales; and exhibited fear or avoidance in four different social situations. Lader and colleagues analyzed the change in LSAS scores from baseline to week 12 using a last observation carried forward full-set analysis and applied a general linear model for analysis of covariance adjusting for centres and baseline.

At the primary endpoint of 12 weeks, escitalopram was more effective than placebo. The researchers found an even greater improvement by week 24, which each group of escitalopram patients having significant superiority over placebo for the escitalopram 5 mg/day patients (–8.1; P=.006), the 10 mg/day patients (–7.5; P=.013); and 20 mg (–7.35; P<.001). They also found paroxetine to be significantly more effective than placebo (–9.6; P=.008).

Lader and colleagues believe that escitalopram is well-tolerated and effective for the treatment of

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SAD. They found an improvement on patients' endpoint LSAS scores when treated with escitalopram 5 and 20 mg/day, however, there was only borderline efficacy with the 20 mg/day dosage. Fewer patients discontinued treatment with escitalopram due to adverse events.–*CN*

Funding for this research was provided by H. Lundbeck A/S. *(ADAA 2004 Poster 182)*

PARENT-CHILD GROUP CBT ALLEVIATES OCD SYMPTOMS

Children and adolescents who suffer from obsessive-compulsive disorder (OCD) are likely to suffer needless anguish due to hours of lost time (ie, wasted/exhausted time, limited productivity), thus negatively impacting school performance, peer relationships, and home life. While cognitive behavioral therapy (CBT) has been shown to be effective for treating adult OCD, few studies have examined its usefulness in the pediatric OCD population and few have been designed for group therapy with long-term maintenance.

While studying 31 subjects (15 female, 16 male) ranging from 9.0 to 15.5 years of age (mean=12.01 years) involved in group treatment, Sandra L. Mendlowitz, PhD, and colleagues from the Hospital for Sick Children and University of Toronto, Canada, evaluated the effectiveness of group CBT in children and adolescents with varying degrees of OCD. There was a concurrent parental treatment component due to the enhanced treatment results of previous studies with parent participation.

"A need exists to find not only effective treatments, but in delivering these treatments, and understanding the underlying factors that contribute to successful treatment outcome," Dr. Mendlowitz stated.

Pediatric subjects participated in a 12-session program outlined by one of two treatment manuals that are geared toward specific age ranges. Patients between 8 to 12 years of age used *Step on a Crack* and patients 13 to 17 years of age used *Lucky Charms, Little Habits, Why Can't I Just Snap Out of It?*, both of which were written by Mendlowitz. Parents had a corresponding manual, *For Parents of Children with OCD*, written by Mendlowitz, Ian Shulman, PhD CPsych, and Helen Spenser, MD, FRCP, which matched the child's or adolescent's program. All three manuals are currently unpublished. All subjects and their parents were administered the semi-structured Anxiety Disorders Interview Schedule. Inclusion criteria included primary diagnosis of OCD using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria (54.8%) and secondary diagnosis of another anxiety disorder (45.2%). Exclusion criteria included psychotic disorder, developmental delay, eating disorder, interfering medical disorder, and lack of English proficiency. Subjects on psychoactive medications (55%) were included as long as the medication and the dosage was constant for three months prior to and during the study's duration.

Subjects were randomized 2 weeks prior to the initial group sessions. Assessments were made at baseline, pre-treatment, post-treatment, and 6-months post-treatment (1-year post-treatment follow-up data is currently being conducted). OCD severity was determined using Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) scores. The Family Environment Scale, a self-report inventory, was used to describe perceptions of family climates to monitor family change through a forced-choice, true-false questionnaire of 90 items. Total CY-BOCS scores (mean baseline score=18.86) measured a significant decline at post-treatment (10.95) and at 6-months post-treatment follow-up (8.46). Gender, medication, and secondary diagnosis factors did not affect symptom improvement over time. Mendlowitz and colleagues concluded that group treatment was effective in remediating OCD symptoms and that treatment gains could be extended through long-term maintenance. A higher perception of family cohesion was also found to result in greater change and improvement in OCD symptoms.

"We certainly know from several research findings that parental involvement in the treatment process is critical to treatment success. This data suggests however, that it is not just about involvement, but the degree to which the child sees the family as a unit," Dr. Mendlowitz said. "The analogy is whether or not people in the family are operating as a team (together everyone achieves more). Clearly, if the child perceives this to be true, it can positively influence the treatment process."

Further research is needed to refine aspects of family cohesion since study results bolster the critical importance of parental involvement in treating pediatric OCD. The data is a subset of a larger database which will eventually be collected to compare the benefits and disadvantages of group treatment versus individual treatment.

Dr. Mendlowitz concluded, "Group treatment is highly cost-effective and has the added benefit of providing both children and their parents with support beyond the therapy sessions whereas individual treatment can often be more intensive and tailored to individual need."–*SW (ADAA 2004 Poster 98)*

SIDE EFFECT PROFILES OF ATYPICAL ANTIPSYCHOTICS IN WOMEN IMPACT TREATMENT OPTIONS

Atypical antipsychotics have been found to cause a variety of side effects when prescribed to female schizophrenics. Two of the most detrimental adverse events caused by atypicals include hyperprolactinemia, a condition involving elevated serum prolactin levels, which can cause sexual dysfunction and galactorrhea, and weight gain, which can result in a diminished quality of life for female patients and affect their outlook of their own physicality and their overall health.

Michael T. Compton, MD, MPH, from Emory University School of Medicine in Atlanta, conducted a MEDLINE search of the entire database (both published literature and recent research) as a means of determining which treatment considerations are most relevant in women with schizophrenia.

"This literature review was meant to remind clinicians of the potential for side effects related to neuroendocrine effects of antipsychotics, including hyperprolactinemia and hyperprolactinemic hypogonadism," Dr. Compton said. "I searched the literature on this topic because of my experience with several female patients with side effects related to antipsychotic-induced hyperprolactinemia (eg, galactorrhea, amenorrhea, sexual side effects)."

Compton found one study that showed 40% to 60% of female schizophrenics treated with the atypicals reported some form of sexual dysfunction. Another study found that 66% of premenopausal women and 45% of postmenopausal women presented with hyperprolactinemia. He also found 88% of women taking risperidone (Risperdal) had a higher prevalence of hyperprolactinemia compared to 48% of women taking conventional agents. Approximately 50% of premenopausal women taking risperidone also reported menstrual irregularities.

After reviewing the cases describing weight gain, Compton found that the greatest risk of weight gain were found in women being treated with olanzapine (Zyprexa) and clozapine (Clozaril), with the least amount of weight gain in women being treated with quetiapine (Seroquel) and ziprasidone (Geodon).

Compton also presented two case studies detailing risperidone-induced hyperprolactinemia as practical, clinical examples of the issue. One case was a 44 year old woman with schizophrenia of the paranoid type. Due to treatment noncompliance, the woman's psychosis was exacerbated. Risperidone 3 mg at bedtime was initiated. After 5 weeks, her prolactin level was 141 and her paranoid symptoms did not discontinue. After initiating quetiapine and cross-tapering it with risperidone, the woman's prolatin level decreased to 45 and soon became normal and her psychotic symptoms improved.

The second case study described a 35 year old woman with schizoaffective disorder of the depressed type. The woman was taking risperidone 4 mg at bedtime, sertraline 100 mg QD, and benztropine 0.5 mg QD. She presented with galactorrhea, breast engorgement, weight gain, amenorrhea, and diminished libido. Initially, the risperidone was reduced to 2 mg at bedtime and amantadine was initiated. There was a slight reduction in the patient's galactorrhea and menstrual spotting and continued breast engorgement and diminished libido. The amantadine was discontinued and quetiapine was initiated and cross-tapered with risperidone. Risperidone was soon discontinued and the patient began taking quetiapine 300 mg at bedime. After being treatment with quetiapine, her galactorrhea and amenorrhea resolved and there was an improvement in her libido.

Compton believes that there is a need for special treatment in female schizophrenics, especially when prescribing atypical antipsychotics, especially due to hormone-related side effects. The side effects can cause the women to not adhere to their treatment regimen, thus causing relapse and there is the potential for hospitalization. Future studies are needed as a means of being aware of all of the potential side effects.

"It is very important for prescribing physicians to be aware of the potential side effects and adverse events that may occur during treatment with any medication, including psychotropic medications," Dr. Compton said.–*CN*

Funding for this research was provided by AstraZeneca Pharmaceuticals LP.

(2nd World Congress 2004 Poster 122)

PRENATAL DEPRESSION CAN POSSIBLY FORECAST POSTPARTUM DEPRESSION IN ADOLESCENT MOTHERS

Becoming a mother is a stressful experience for many women and heightened levels of depressive symptoms during pregnancy and the postpartum period are common. Maternal depression can negatively impact the relationship between the mother and baby and affect how the mother perceives her infant and herself as a mother.

Sydney L. Hans, PhD, and colleagues from the University of Chicago, performed a study of 120 African-American women between 14 and 21 years of age (mean=17.5 years). Most were unmarried and

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

giving birth for the first time. All of the patients were recruited through the prenatal clinics of the University of Chicago Hospital.

"Given the amount of research and public attention directed at postpartum depression, we were surprised to see that prenatal depression symptoms, on average, were higher than postpartum depression symptoms," Dr. Hans said.

However, postpartum depression remains a concern because it is associated with young mothers' parenting stress, characterized by worries that the child is not developing normally and unrealistic expectations about the infant's need for nurturance.

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) which was administered to the patients during the second trimester and when their infants were 4 months old. Mean CES-D scores were 16.42±8.51 prenatally and 12.29±9.29. Results indicated that 50% of the patients had CES-D scores above the clinical level (>16) during pregnancy and 28% had scores above the clinical level during the postpartum period. Prenatal and postnatal depression scores were significantly correlated (r=.43) and 73% of the patients who had levels of depression above the clinical level at four months also had clinically significant levels of prenatal depression.

Four months after giving birth, the mothers also completed subscales of the Adult-Adolescent Parenting Inventory (AAPI), the Parenting Stress Index (PSI), and the Parenting Efficacy Scale. There was a modest relation (r=.25) between postpartum depression and AAPI items assessing inappropriate developmental expectations for children. Depressed mothers were more likely to endorse items such as children having it too easy, babies being spoiled by being picked up when they cry, and children needing to be taught to obey their parents at all times.

Hans and colleagues conducted a principal components analysis of the PSI that yielded a different factor structure than the two standard subscales. The three revised factors were: worries and concerns about the child's development, perception of the child as fussy, and the mother feeling that the child does not like her or the mother feels hurt or detached. The first of these scales was the most strongly related to postpartum depression. Depressed mothers were more likely to agree with items that pointed to the child's deficiency compared to other children (eg, my child does not smile as much or perform as well) and that the child was a bigger burden than anticipated.

Although the risk of depression during pregnancy is generally emphasized during the postpartum period, the results suggest that there is considerable continuity between prenatal and postpartum depression and that symptoms may actually be lower after giving birth. The research is part of an overall study testing the effectiveness of psychosocial interventions for young pregnant women. Dr. Hans is conducting further research to examine whether maternal depression is related to mothers' actual or perceived parenting behavior.

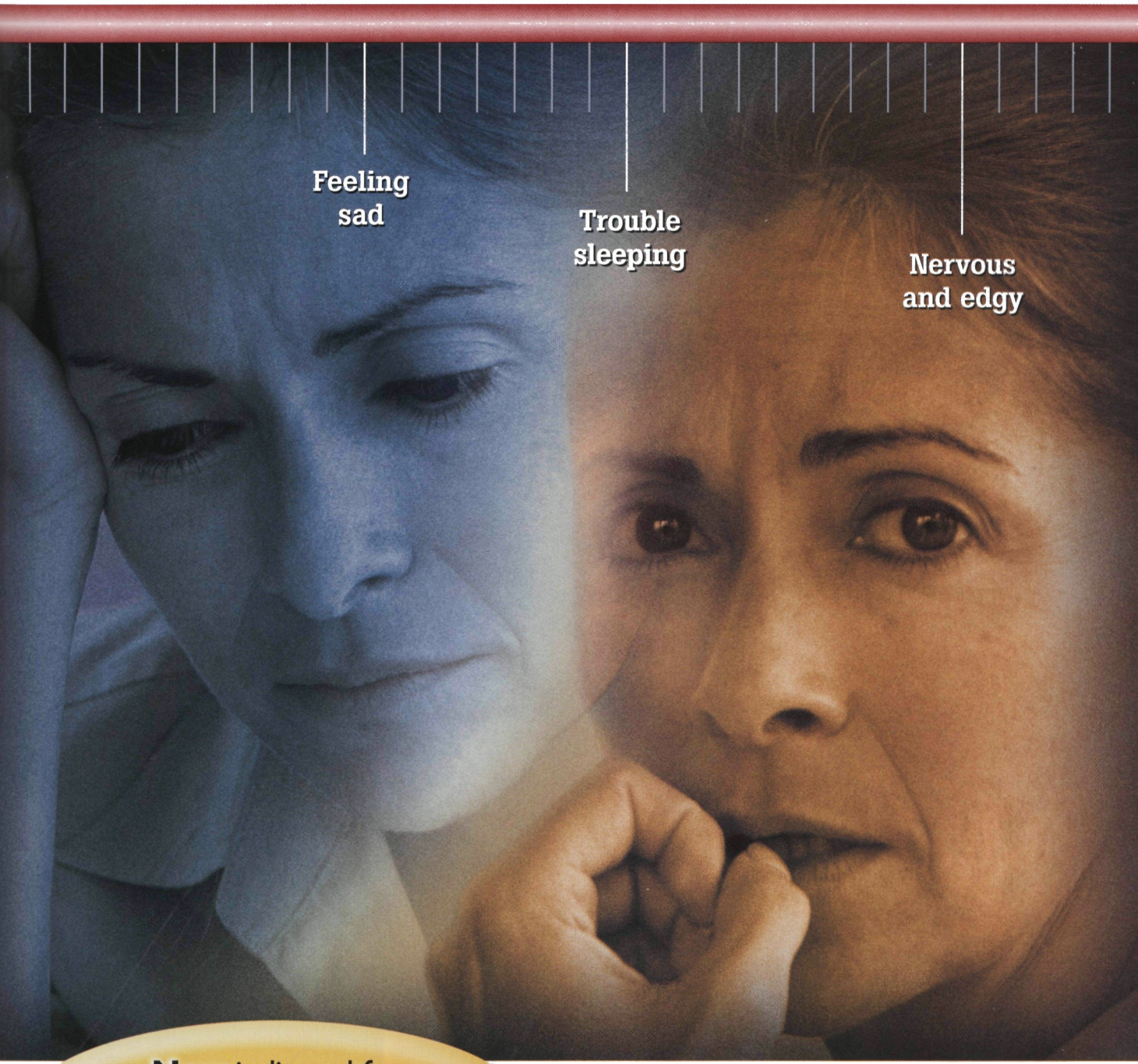
"Doctors and other medical providers working with pregnant women should be more vigilant about screening for depression during the prenatal period," Dr. Hans commented. "At least for young mothers, pregnancy appears to be a time of heightened emotional vulnerability which may forecast depression during the postpartum period as well."–*SW*

Funding for this research was provided by the United States Bureau of Maternal and Child Health.

(2nd World Congress 2004, Poster 51)

–Clinical Updates in Neuropsychiatry is compiled and written by Christopher Naccari and Shelley Wong

For depression, and now for GAD



Now indicated for
Generalized Anxiety Disorder

Lexapro
escitalopram oxalate™
Well-tolerated strength

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One effective therapy

The most common adverse events reported with LEXAPRO vs placebo (approximately 5% or greater and approximately 2X placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia. LEXAPRO is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to escitalopram oxalate or any of the ingredients in LEXAPRO. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with LEXAPRO. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of LEXAPRO with NSAIDs, aspirin, or other drugs that affect coagulation.

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for depression and anxiety

Well-tolerated therapy in a powerful SSRI

Now for GAD

LEXAPRO 10 mg/day is effective in the treatment of Depression and Generalized Anxiety Disorder[1,2,3]

LEXAPRO significantly improves depression and anxiety for many patients beginning at week 1 or 2*[1,2]

Drop-out rates due to adverse events for LEXAPRO 10 mg/day are comparable to placebo in the treatment of depression, and are low in the treatment of GAD†[3]

*Full antidepressant/anxiolytic effect may take 4 to 6 weeks.

†8% with LEXAPRO vs 4% with placebo in the comprehensive GAD safety database.

Lexapro™
escitalopram oxalate

Well-tolerated strength

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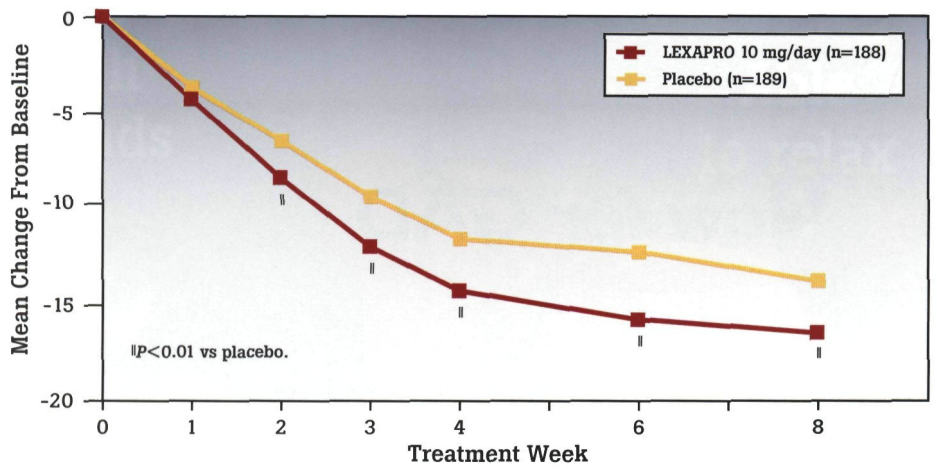
Power and tolerability in depression

In the treatment of moderate-to-severe depression

LEXAPRO 10 mg/day significantly improved depression vs placebo[4,5]

DEPRESSION

MADRS Total Score by Visit



Study design: 8-week, randomized, double-blind, placebo-controlled, fixed-dose (LEXAPRO 10 mg/day) multinational, parallel-group trial in adult patients with DSM-IV defined major depression. Overall mean MADRS=28.9 at baseline. Efficacy was assessed using last observation carried forward (LOCF) data.[5]

In 2 fixed-dose trials

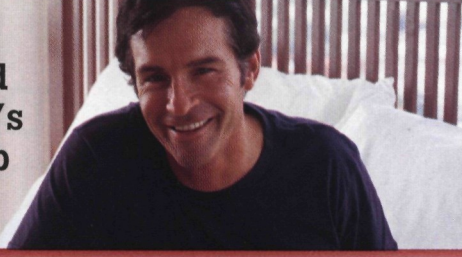
LEXAPRO 10 mg/day demonstrated no significant difference in drop-out rates due to adverse events vs placebo in the treatment of depression[3]

The most common adverse events reported with LEXAPRO vs placebo (approximately 5% or greater and approximately 2X placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

Source: Wade A, Lemming OM, Hedegaard KB. *Int Clin Psychopharmacol.* 2002.

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

and in GAD

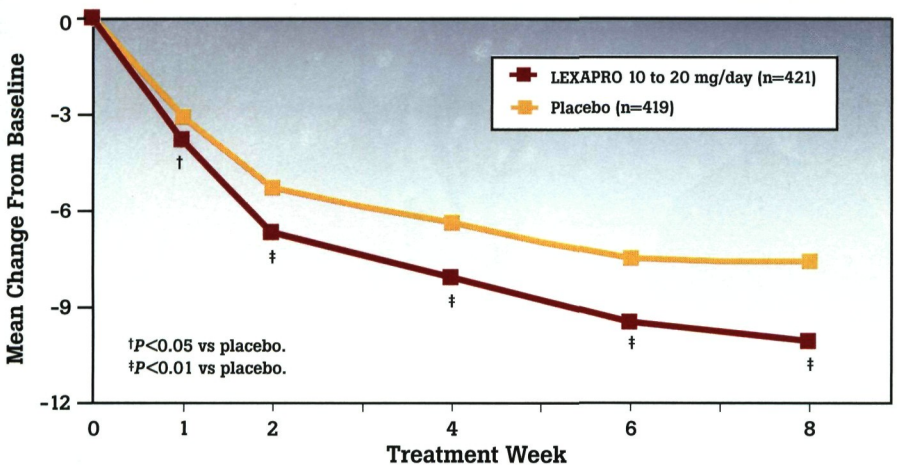


In a pooled analysis in patients with generalized anxiety disorder

LEXAPRO 10 to 20 mg/day significantly improved GAD at week 1 through week 8†[2,4]

GAD

HAMA Total Score by Visit



Study design: Pooled data from 3 randomized, 8-week, double-blind, placebo-controlled, multicenter, parallel-group, flexible-dose (LEXAPRO 10 to 20 mg/day; overall mean daily dose: 12.7 mg) trials in patients with DSM-IV defined generalized anxiety disorder (HAMA ≥18). HAMA range at baseline=18-40 (moderate-to-severe). A 1-week, single-blind, placebo lead-in was followed by an 8-week, double-blind treatment period. Efficacy was assessed using last observation carried forward (LOCF) data.[2,4]

In the comprehensive GAD safety database"

Drop-out rates due to adverse events were low in the treatment of GAD (8% vs 4% placebo)[3]

†Full anxiolytic effect may take 4 to 6 weeks.

"Includes patients treated with 10 to 20 mg/day.

Source: Goodman WK, Bose A, Wang Q. Poster presented at: 23rd Annual Conference of the Anxiety Disorders Association of America, 2003.

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escitalopram oxalate
Well-tolerated strength

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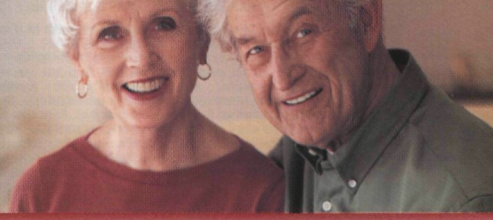
Power, tolerability, and

LEXAPRO is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to escitalopram oxalate or any of the ingredients in LEXAPRO. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with LEXAPRO. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of LEXAPRO with NSAIDs, aspirin, or other drugs that affect coagulation.

flexible dosing



In depression and in GAD, simple 10 mg/day starting dose for all patients[3]

LEXAPRO Provides Flexible Dosing

10 mg tablet (10)	Also available in oral liquid 5 mg/tsp 
20 mg tablet (20)	

New 5 mg tablet for added convenience (5)

- In depression, LEXAPRO 10 mg/day and 20 mg/day were similar in mean improvement on the MADRS score[3]
- If the dose is increased to 20 mg, this should occur after a minimum of 1 week

May be taken morning or evening once daily, with or without food[3]

No dosage adjustment necessary in special populations[3]

- 10 mg/day is the recommended dosage for elderly patients and patients with hepatic impairment[3]
- No dosage adjustment necessary for patients with mild or moderate renal impairment[3] —escitalopram should be used with caution in patients with severe renal impairment

References: 1. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry*. 2002;63:331-336. **2.** Goodman WK, Bose A, Wang Q. Escitalopram 10 mg/day is effective in the treatment of generalized anxiety disorder. Poster presented at: 23rd Annual Conference of the Anxiety Disorders Association of America; March 27-30, 2003; Toronto, Canada. **3.** LEXAPRO [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc.; 2003. **4.** Data on file, Forest Laboratories, Inc. **5.** Wade A, Lemming OM, Hedegaard KB. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. 2002;17:95-102.

Please see brief summary of prescribing information for LEXAPRO on following page.

Source: LEXAPRO Package Insert.

41-124665I8GAD 3/04

Lexapro
escitalopram oxalate™
Well-tolerated strength

https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press

LEXAPRO™ (escitalopram oxalate) TABLETS/ORAL SOLUTION

Brief Summary: For complete details, please see full prescribing information for LEXAPRO. CONTRAINDICATIONS Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). LEXAPRO is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in LEXAPRO. **WARNINGS Potential for interaction with MAOIs in patients receiving serotonin reuptake inhibitor drugs in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that LEXAPRO 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 LEXAPRO before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI. PRECAUTIONS General** Discontinuation of Treatment with LEXAPRO During marketing of Lexapro and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with LEXAPRO. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION in full prescribing information). Abnormal Bleeding Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of LEXAPRO with NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia One case of hyponatremia has been reported in association with LEXAPRO treatment. Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder. Activation of Mania/Hypomania In placebo-controlled trials of LEXAPRO in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with LEXAPRO and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with LEXAPRO treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, LEXAPRO should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, LEXAPRO has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of LEXAPRO, cases of convulsion have been reported in association with LEXAPRO treatment. Like other drugs effective in the treatment of major depressive disorder, LEXAPRO should be introduced with care in patients with a history of seizure disorder. Suicide The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. As with all drugs effective in the treatment of major depressive disorder, prescriptions for LEXAPRO should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Interference with Cognitive and Motor Performance In a study in normal volunteers, LEXAPRO 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that LEXAPRO therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with LEXAPRO in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using LEXAPRO in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. LEXAPRO has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of LEXAPRO in hepatically impaired patients is 10 mg/day (see DOSAGE AND ADMINISTRATION in full prescribing information). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with LEXAPRO, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION in full prescribing information). **Drug Interactions** CNS Drugs – Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol – Although LEXAPRO did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking LEXAPRO is not recommended. Monoamine Oxidase Inhibitors (MAOIs) – See CONTRAINDICATIONS and WARNINGS. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with LEXAPRO. Cimetidine – In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin – In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium – Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when LEXAPRO and lithium are coadministered. Sumatriptan – There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline – Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin – Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine – Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. Triazolam – Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole – Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. Ritonavir – Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. CYP3A4 and -2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. Drugs Metabolized by Cytochrome P450*2D6 – In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. Metoprolol – Administration of 20 mg/day LEXAPRO for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of LEXAPRO and metoprolol had no clinically significant effects on blood pressure or heart rate. Electroconvulsive Therapy (ECT) – There are no clinical studies of the combined use of ECT and escitalopram. **Pregnancy** Pregnancy Category C In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental, no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown. Mutagenesis Racemic citalopram was mutagenic in the in vitro bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the in vitro Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the in vitro mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled in vitro/in vivo unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the in vitro chromosomal aberration assay in human lymphocytes or in two in vivo mouse micronucleus assays. Impairment of Fertility When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **Pregnancy-Nonteratogenic Effects** Neonates exposed to LEXAPRO and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS). When treating a pregnant woman with LEXAPRO during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION in full prescribing information). **Labor and Delivery** The effect of LEXAPRO on labor and delivery in humans is unknown. **Nursing Mothers** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by the mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or LEXAPRO therapy should take into account the risks of citalopram exposure for the infant and the benefits of LEXAPRO treatment for the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of LEXAPRO in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of LEXAPRO between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of LEXAPRO cannot be ruled out. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see CLINICAL PHARMACOLOGY in full prescribing information). 10 mg/day is the recommended dose for elderly patients (see Dosage and Administration in full prescribing information). Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse event information for LEXAPRO was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for LEXAPRO in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received LEXAPRO in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day LEXAPRO was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice the placebo rate, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received LEXAPRO 10 to 20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** TABLE 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received LEXAPRO at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see TABLE 1).

TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (LEXAPRO (N=715) and Placebo (N=592)): Autonomic Nervous System Disorders: Dry Mouth (6% and 5%); Sweating Increased (5% and 2%). **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%). **Gastrointestinal Disorders:** Nausea (15% and 7%); Diarrhea (8% and 5%); Constipation (3% and 1%); Indigestion (3% and 1%); Abdominal Pain (2% and 1%). **General:** Influenza-like symptoms (5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1 %); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[12] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[2] (2% and <1%).

*Events reported by at least 2% of patients treated with LEXAPRO are listed, except for the following events which had an incidence on placebo ≥ LEXAPRO: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 LEXAPRO; N=188 placebo). §Denominator used was for females only (N=490 LEXAPRO; N=404 placebo). **Generalized Anxiety Disorder** TABLE 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 429 GAD patients who received LEXAPRO 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 2).

TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (LEXAPRO (N=429) and Placebo (N=427)): Autonomic Nervous System Disorders: Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1 %); Lethargy (3% and 1%); Yawning (2% and 1 %). **Urogenital:** Ejaculation Disorder[12] (14% and 2%); Anorgasmia[2] (6% and <1%); Menstrual Disorder (2% and 1%).

*Events reported by at least 2% of patients treated with LEXAPRO are listed, except for the following events which had an incidence on placebo ≥ LEXAPRO: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 LEXAPRO; N=195 placebo). §Denominator used was for females only (N=247 LEXAPRO; N=232 placebo).

Dose Dependency of Adverse Events The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg LEXAPRO groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg LEXAPRO-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day LEXAPRO-treated patients was greater (86%). Table 3 shows common adverse events that occurred in the 20 mg/day LEXAPRO group with an incidence that was approximately twice that of the 10 mg/day LEXAPRO group and approximately twice that of the placebo group.

TABLE 3: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day LEXAPRO (N=310), 20 mg/day LEXAPRO (N=125)]: Insomnia (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).

*Adverse events with an incidence rate of at least 5% in either of the LEXAPRO groups and with an incidence rate in the 20 mg/day LEXAPRO group that was approximately twice that of the 10 mg/day LEXAPRO group and the placebo group.

Male and Female Sexual Dysfunction with SSRIs Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. TABLE 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials.

TABLE 4: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: LEXAPRO (N=407) and Placebo (N=383)): Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); **Libido Decreased** (6% and 2%); **Impotence** (2% and <1%). **(In Females Only: LEXAPRO (N=737) and Placebo (N=636)): Libido Decreased** (3% and 1%); **Anorgasmia** (3% and <1%).

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with LEXAPRO treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving LEXAPRO indicated that LEXAPRO treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with LEXAPRO in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with LEXAPRO treatment. **ECG Changes** Electrocardiograms from LEXAPRO (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for LEXAPRO and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for LEXAPRO and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither LEXAPRO nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of LEXAPRO** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with LEXAPRO for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in TABLES 1 & 2, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with LEXAPRO, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular – *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders – *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders – *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General – *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, tall. Hemic and Lymphatic Disorders – *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders – *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders – *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders – *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* – *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N=905. Respiratory System Disorders – *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders – *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses – *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders – *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Racemic Citalopram** Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

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https://doi.org/10.1017/S1092852900009287 Published online by Cambridge University Press