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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

Index Medicus/MEDLINE
citation: *CNS Spectr*

CME Mount Sinai

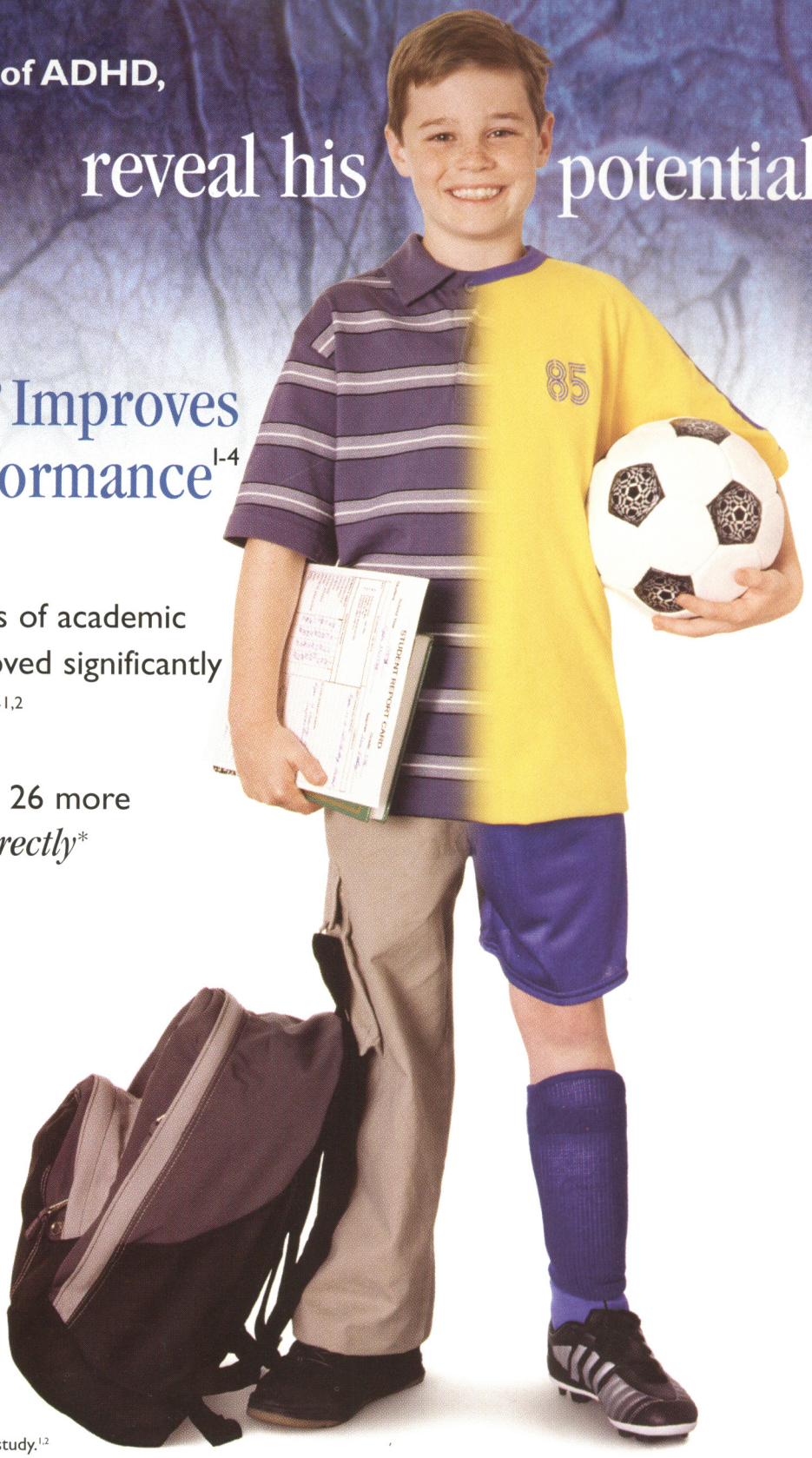
https://doi.org/10.1017/S109285290000907X Published online by Cambridge University Press

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/S109285290000907X 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.

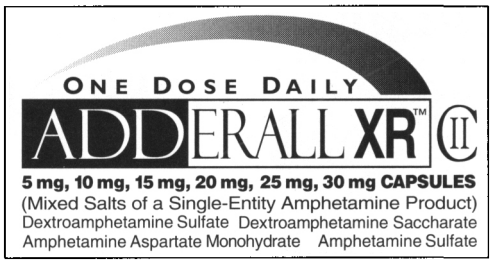
BRIEF SUMMARY: Consult the full prescribing information for complete product information.

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.

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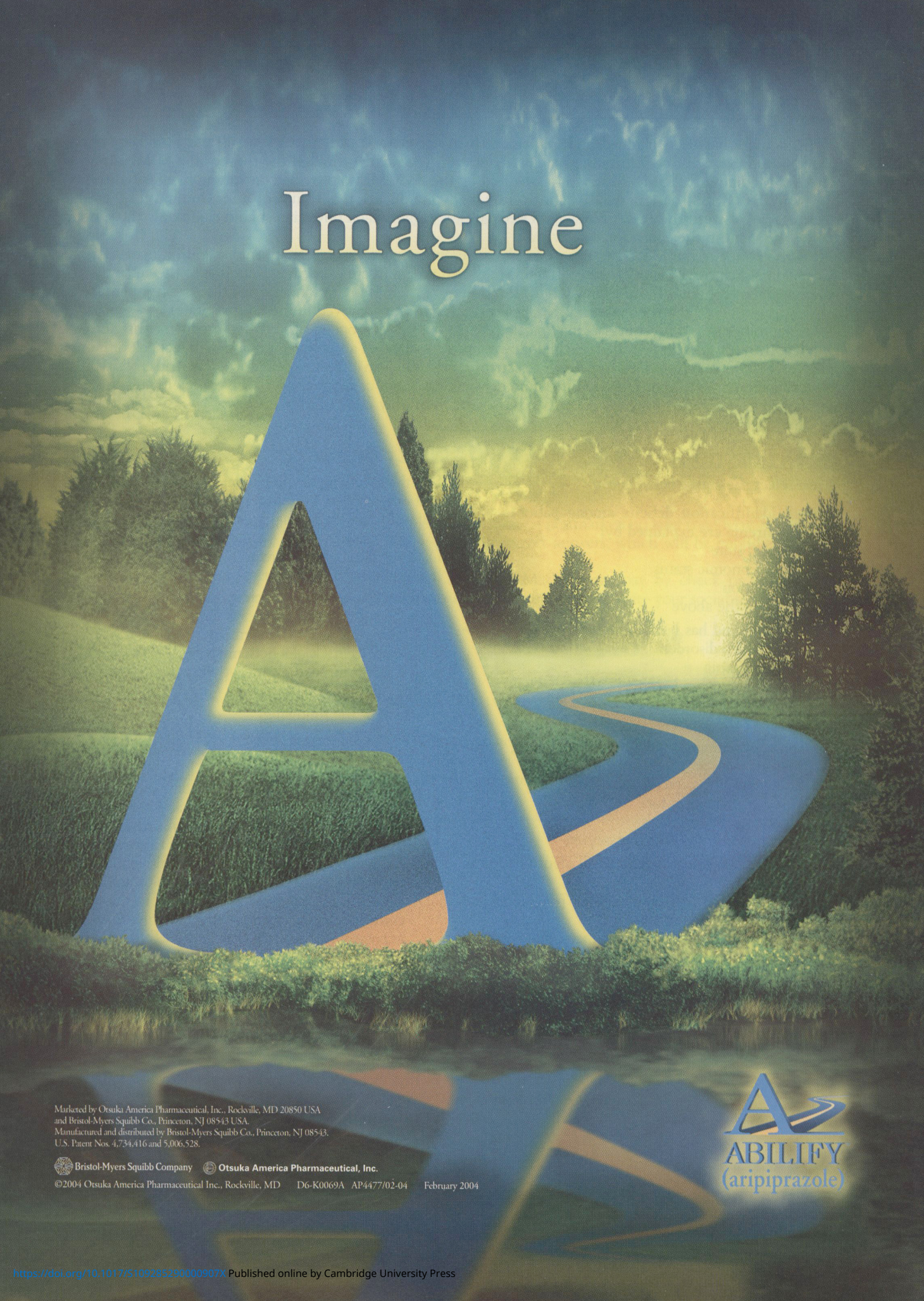

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Feature Articles

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®

The International Journal of Neuropsychiatric Medicine

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GO BEYOND THE MAX

Introducing NEW 25 mg and 50 mg capsules of ZONEGRAN® (zonisamide)

MORE dosing flexibility has arrived!

More dosing options for meeting patients' needs

- Increase your dosing flexibility
- Choose from 3 dosage strengths: 25 mg, 50 mg, and 100 mg capsules
- Tailor therapy to the individual patient

Proven efficacy with confidence-building benefits[1-3]

- Few drug-to-drug interactions
- Minimal cognitive impairment
- 63-hour half-life—the longest of any newer AED
- Convenient QD dosing*

ZONEGRAN is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

In clinical trials, the most common adverse events that occurred with ZONEGRAN were somnolence, dizziness, anorexia, headache, nausea, and agitation/irritability.

*Can also be dosed twice daily.

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.

zonegran™
zonisamide capsules

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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

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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%
HEMATOLOGIS 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.

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Going in Reverse to Go Forward

By Jack M. Gorman, MD

In most medical specialties, detailed knowledge of the normal anatomy, physiology, and histology of the organs of interest were known before the specifics of disease states were revealed. Long before it was understood that tiny plaques clogging coronary arteries is the proximate cause of myocardial infarction, the fact that a heart has four chambers that work in concert to pump blood throughout the circulatory system was well-known.

In psychiatry, and to some extent neurology, we have tried to do things in the opposite direction. We want to know what a brain is like in someone with depression, schizophrenia, panic disorder, or multiple sclerosis. However, what do we really know about the normal function of the central nervous system? We really do not know what the brain actually does that is associated with someone feeling happy or sad, calm or anxious. Many of the details of how the brain lays down myelin, the target for multiple sclerosis, are still unknown. In essence, we have tried to skip over an understanding of normal brain function and jump right into wanting to know what causes serious and complex brain diseases. The result has not been a whopping success.

This month's *CNS Spectrums*, guest edited by Israel Liberzon, MD, features articles on what neuroscientist Joseph E. LeDoux, PhD,[1] has called "the emotional brain." LeDoux has spent a lifetime trying to understand what happens in the brain during one typical and normal emotion, fear. Thanks to him and other scientists like Michael Davis, PhD, and Trevor W. Robbins, PhD, we now know in great detail the neuroanatomy, physiology, and cellular and molecular biology of at least one type of fear, conditioned fear. From this basic knowledge, gained only by years of painstaking work at the laboratory bench and later by neuroimaging studies of normal human volunteers, the field has now moved toward understanding what happens when normally expressed fear becomes pathological, resulting in anxiety disorders.

This is clearly a strategy that we need to follow more extensively in our search for causes and cures of psychiatric and neurologic disease. Studies are now underway, for example, to better understand the normal aging process in animals and humans as a basis for learning more about Alzheimer's disease. A group led by Daniel Weinberger, MD,[2] at the National Institute of Mental Health recently showed that naturally occurring polymorphisms in the gene encoding the enzyme catechol-O-methyltranferase affect memory and prefrontal cortical activation in normal individuals.

A study recently published by Tor D. Wager, PhD, and colleagues[3] showed brain regions that are activated in normal individuals by pain and by the belief that they had been given an analgesic medication, which was actually a placebo. All of this research helps us understand how the normal human brain operates, even when it performs operations and experiences emotions for which we either have no viable animal models or know for sure that animals are not capable of performing or experiencing.

It is a cliché, of course, to state that the brain is the organ of interest for psychiatrists and neurologists. It is surprising, however, how very little we know about its basic operations in normal, daily activity. For those reasons, we should welcome the kind of work represented by the articles in this month's *CNS Spectrums* and hope that it helps encourage much more work in this area. CNS

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NEWS FROM THE 17TH ANNUAL MEETING OF
THE AMERICAN ACADEMY OF GERIATRIC PSYCHIATRY

CHART REVIEW FINDS ZIPRASIDONE SAFE AND EFFECTIVE IN THE TREATMENT OF DEMENTIA IN THE ELDERLY

As baby boomers age, the incidences of dementia increase, and with it the need for better treatment options for dementia-related disorders (eg, Alzheimer's disease, bipolar disorder, and major depression). Some of the medications that are currently used to treat this family of disorders have side effects that often prove intolerable for patients. Ziprasidone (Geodon), an atypical antipsychotic agent, was the focus of a recent chart review by Alan Berkowitz, MD, of the Psychiatric Centers at San Diego in California.

Berkowitz conducted a chart review of 62 geriatric patients between 64 and 92 years of age that were previously admitted to an inpatient psychiatric facility with diagnoses of mood and behavior disturbances secondary to multi-infarct dementia, AD, and schizoaffective disorder, among other mental illnesses. Inclusion in the review meant patients had to have failed to respond to an agent other than ziprasidone or failed to report severe adverse effects to an agent other than ziprasidone. Patients also had to have been administered ziprasidone prior to discharge.

Ziprasidone was given as either monotherapy or along with other psychotropics and medications for comorbid conditions, such as congestive heart failure. The mean dose, 100 mg/day, was administered for ~8 days. Extensive admission and discharge workups were analyzed retrospectively using the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) subscales. The CGI-S was performed at baseline prior to ziprasidone administration and at endpoint (endpoint equaled discharge or cessation of drug treatment) and the CGI-I was performed at endpoint. Berkowitz reported that documentation was only available for 46 individuals for CGI analysis. Electrocardiograms were given to all of the patients at admission and at a post-discharge follow-up in the first 14 patients. Berkowitz noted that no further electrocardiograms were performed because ziprasidone's safety was already ascertained.

After analysis, the results showed that the mean CGI-S decreased from 5.7±0.7 points (6 points indicated severe illness) at baseline to 3.5±0.9 points, where 3 points indicated only mildly ill ($P<.0001$). Thirty-three patients had a decrease of ≥2 points from baseline to endpoint on severity scores. At endpoint, 37 (80.4%) patients had a CGI-I score of 1 (very much improved) or 2 (much improved). Four patients at baseline had a CGI-S score of 7. Two of these patients had a score of 2 and had an endpoint CGI-I score of 1 or 2, while the other two showed no change (CGI-I score: 4). Berkowitz noted that there was no baseline-to-endpoint CGI-S score change in 2 (4.3%) patients and a CGI-S score decrease of 1 in 11 subjects.

The most common adverse effect reported was sedation. However, a dose reduction of 20 mg for 2–3 days eliminated the sedation and this generally did not occur after resuming the original dose. Mild-to-moderate extrapyramidal symptoms were observed in only three patients.

These findings suggest that ziprasidone may assist improvement in psychotic symptoms and behavioral disturbances in elderly individuals with dementia, whether used as monotherapy or in conjunction with other medications.–*JRR*

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(AAGP 2004 Poster P083)

RESEARCHERS FIND DIFFERENCES IN TREATMENT OF ALZHEIMER'S DISEASE WITH CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors are considered an effective treatment in the fight against mild-to-moderate Alzheimer's disease, with numerous medications available to both treat the various symptoms of AD and to improve the quality of life of AD patients.

Sharon B. Dybicz, PharmD, from Omnicare Senior Health Outcomes in Pennsylvania, and colleagues evaluated the dosing of donepezil (Aricept), galantamine (Reminyl), and rivastigmine (Exelon) in 2,873 resident nursing home patients receiving a new prescription of any of these three cholinesterase inhibitors. Of these patients, 1,906 were treated with donepezil, 460 were treated with galantamine, and 507 were treated with rivastigmine. The patients received an average dose of donepezil 7.7 mg, galantamine 12.9 mg, and rivastigmine 5.7 mg.

Dybicz and colleagues studied these nursing home residents for 3 months and used the following methods to determine the efficacy of the medications:

Method 1: Number of tablets X Strength per tablet X Daily dosing frequency X Proportion of days scheduled per week

Method 2: Metric quantity/Days supply X Strength per tablet

Method 1 was used 70% of the time while Method 2 was used the remaining 30%. Dybicz and colleagues

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used the results of Method 1 when both values could be calculated and they used Method 2 when only Method 2 was available (due to missing prescribing information). To compare the efficacy of the medications, the researchers used Chi-Square tests and pairwise comparisons.

Dybicz and colleagues found that by the third month of receiving any of the cholinesterase inhibitors, 99.1% of donepezil patients were receiving an effective dose, compared to ~64% of rivastigmine patients and ~56% of galantamine patients ($P<.001$). Overall, ~80% of donepezil patients, ~79% of galantamine patients, and 75% of rivastigmine patients were treated for three months.

Dybicz and colleagues believe that the doses of galantamine and rivastigmine in some AD patients is ineffective, causing patients to receive suboptimal therapy. Their study found that ~79% of donepezil patients, ~48% of rivastigmine patients, and 44% of galantamine patients were receiving an effective dose of the medication to properly treat their symptoms of AD ($P<.001$). *–CN*

(AAGP 2004, Poster 015)

GALANTAMINE MAY LIKELY DELAY BEHAVIORAL IMPAIRMENT IN ALZHEIMER'S DISEASE

Although the decline of cognitive function is one of the key symptoms of Alzheimer's disease, the decline of behavioral areas is a significant part of the disease's progression. While galantamine (Reminyl) has demonstrated sustained cognitive benefits for patients with mild to moderate AD, its noncognitive benefits have not been clearly established. This motivated Daniel I. Kaufer, MD, from the University of North Carolina School of Medicine, in Chapel Hill, and colleagues to conducted a long-term evaluation of behavioral benefits of an approved therapy for mild to moderate AD.

With galantamine therapy, patients experienced a delayed emergence of behavioral disturbances, indicating the potential effectiveness of galantamine over time. Results of the study revealed that galantamine was found to be well-tolerated over the course of an 18.5-month trial. Control of behavioral symptoms will likely improve quality of life, reduce caregiver burden, and delay patient institutionalization.

"Medications are often used for only 3–6 months and discontinued if no improvement is seen, before long-term benefits begin to accrue," Kaufer said. "Stabilization of symptoms over time is the primary goal."

Subjects with mild-to-moderate AD participated in a multi-phase trial for up to 18.5 months. A 5-month, double-blind, placebo-controlled trial was followed by a 6-week withdrawal trial (or the double-blind study only, with sponsor approval) and patients were further eligible to participate in a 12-month, open-label extension phase. The latter phase enrolled 699 patients, including 18 patients who participated in the double-blind study but did not participate in the withdrawal study. Regardless of the treatments administered in the first two phases, all extension subjects received 24 mg/day for 50 weeks (following a 2-week dose escalation period of galantamine 8 mg/day for 1 week and galantamine 16 mg/day for 1 week).

The patient population consisted of 204 patients who had received placebo during both previous phases, followed by 12 months exposure to galantamine in the open-label extension; 288 who received galantamine during all three phases, for a full 18.5 months; and 189 who received placebo only during the 6-week withdrawal phase. Of the 681 subjects who participated in all three phases, 457 (67.1%) completed the open-label extension (11 of the 18 [61.1%] who participated only in the double-blind study completed the open-label extension).

Behavioral effects were measured using the Neuropsychiatric Inventory (NPI) scale which calculated the total NPI score from the sum of frequency and severity products in the 10 domains measured by the scale. The maximum score is 120 and a higher score indicates more severe behavioral impairment.

Although all three subject groups had small increases in mean total NPI, researchers found that patients treated continuously with galantamine for the full 18.5 months experienced the least decline at study end. Patients initially treated with placebo during the first 5 months (double-blind phase) experienced deterioration in mean total NPI scores, but scores stabilized after galantamine was introduced in the open-label extension phase. A 6-week withdrawal of galantamine showed a deterioration that would not be recoverable after reinitiating therapy.

Adverse side effects were primarily mild or moderate, and included nausea, agitation, falling, and diarrhea in the open-label phase. The most common severe injuries were syncope, pneumonia, and falling. Ninety-six subjects (13.7%) discontinued treatment due to adverse side effects, most commonly nausea and vomiting. Nausea appeared to be more common in patients who first received the drug in the open-label extension phase than those who had received it in previous phases.

Further research is warranted to investigate the long-term benefits of galantamine in controlling

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behavioral impairment in AD patients. Kaufer hopes to continue following the research over several years.

"[The study indicates that there is a] need to develop a broader appreciation of symptomatic treatment for behavioral symptoms in AD," Kaufer said. "Slowing the typical worsening of behavioral symptoms over time in a progressive degenerative disorder with galantamine is an important therapeutic benefit."

Funding for this research was provided by Janssen Pharmaceutica.–*SW*

(AAGP 2004 Poster P018)

LOW CONCENTRATIONS OF QUETIAPINE SHOWN TO HAVE NEUROPROTECTIVE PROPERTIES IN TREATING LEWY BODY DEMENTIA

Quetiapine (Seroquel) is an atypical antipsychotic that has been found to be effective in the treatment of hallucinations and nighttime agitation associated with Lewy body dementia (LBD). LBD is a neurodegenerative disorder characterized by hallucinations, fluctuations in cognition, parkinsonism, falls, and nighttime agitation. Neuropathological studies of the disorder have shown nonapoptotic neuronal death in several brain structures, including the hippocampus.

Andrius Baskys, MD, PhD, and colleagues at University of California, Irvine, examined whether quetiapine was efficacious as a neuroprotective agent on *N*-methyl-D-aspartate (NMDA) receptor stimulation-induced cell death in rat organotypic hippocampal cultures in vitro.

All of the experiments used organotypic hippocampal cultures from 7-day-old Wistar rats. To induce cell death, cultures were transferred into a medium containing 50 μM NMDA for 30 minutes or a medium lacking glucose and bubbled with CO_2/N_2 mixture (5%/95%) for 1 hour. The propidium iodide method was used to quantify cell death 24 and 72 hours later.

The researchers found that prolonged treatment with quetiapine (1–7 days) reduced NMDA-induced cell death. They also found that quetiapine neuroprotection was concentration-dependent and it was efficacious at low concentrations of 1–100 μM. Significantly less cell death occurred with quetiapine 100 μM followed by NMDA compared to NMDA alone. There was no effect at doses higher than 100 μM ($P>0.05$).

Short-term treatment with quetiapine (2 hours) was not found to reduce NMDA-induced cell death. In addition, quetiapine applied after or with NMDA treatment did not alter NMDA-induced cell death. Oxygen-glucose deprivation-induced cell death was reduced by quetiapine (10 μM) treatment. All experiments were conducted on 5–6 cultures simultaneously and were repeated 2–4 times.

Unlike NMDA receptor antagonist MK801, quetiapine was not effective in blocking NMDA receptor-mediated effects. Therefore, Baskys and colleagues reasoned that quetiapine's neuroprotective effectiveness in the NMDA model is not related to induced changes in NMDA receptor/channel properties. Quetiapine was found to reduce nonapoptotic neuronal death at low concentrations.

"[This study] suggests that neuroprotection may be the mechanism of the drug's action in treating hallucinations," Baskys said. "If proven, this may open new opportunities for clinical trials to test if using quetiapine at low doses could altogether prevent development of hallucinations and other psychiatric problems in patients with dementia with Lewy bodies and perhaps other dementias. This would be a big achievement because behavioral symptoms are the most difficult part of dementing illness both for the patient and the caregiver."

Funding for this research was provided by investigator-initiated research grants from AstraZeneca and VISN22 MIRECC to Dr. Baskys.–*SW*

(AAGP 2004, Poster P031)

ESCITALOPRAM FOUND EFFECTIVE FOR DEPRESSION IN GERIATRIC PATIENTS

Depression has been found to affect ~6 million Americans ≥65 years of age, with only ~10% of those affected receiving treatment for depression. There are a variety of risk factors that can lead to depression in the elderly, including stroke, isolation/loneliness, loss of a long-time loved one or of a child, and an overall feeling of death. Current research has found the majority of antidepressants to be as effective in the elderly as they are in younger patients, however, the risk of side effects is greater and the time the medication takes to reach efficacy is longer.

A. John Rush, Jr., MD, from the University of Texas Southwestern Medical Center in Dallas, and colleagues conducted an 8-week, Phase IV, open-label, naturalistic trial of 1,436 depressed patients. They studied the effects of escitalopram (Lexapro) on 784 patients ≥60 years of age. The patients began taking escitalopram 10 mg/day, which was titrated to 20 mg/day in some patients four weeks later. The researchers assessed the efficacy of escitalopram using the Clinical Global Impression of Improvement (CG-I) scale and the Patient Global Evaluation (PGE) Scale, with a response defined as a score of 1 (very much improved)

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or 2 (much improved) on either scale. These scales were given at week 4 and week 8 and were used because they are easy-to-use and the standard scales in the field.

"Older patients often have trouble tolerating medications," Dr. Rush said, "and their depression can be quite disabling."

Approximately 75% of the patients completed the study. Of the completers, there was a 71% response rate to the CGI-I and a 69% response rate to the PGE. Approximately 13% of patients dropped out due to adverse events, such as nausea, headache, and ejaculation disorder.

"These older patients were part of a larger study that included all adults (at least 18 years old). The older patients did as well as the younger ones," Dr. Rush said. "The mean dose of escitalopram was just over 11 mg/day, which means that 9 out of 10 patients were found to do well on 10 mg/day and did not need a dosage increase."

Rush and colleagues believe that escitalopram is just as effective as other SSRIs in treating depressed patients ≥60 years of age and is well-tolerated in patients in this age group.

Funding for this research was provided by Forest Pharmaceuticals.–*CN*

(AAGP 2004 Poster P053)

BRAIN TUMOR PATIENT FOUND TO HAVE NEUROLOGICAL DEFICITS

Previous research has found that patients with brain tumors often present with psychiatric disturbances and they have also proven to be somewhat unresponsive to pharmacotherapy. Subramoniam Madhusoodanan, MD, from St. John's Episcopal Hospital in New York, NY, and colleagues presented a case study of a 79-year old caucasian women that presented to the emergency room (ER) with complaints of depression. At the time of her admission, her depression had lasted 4–5 months in duration and she had previously been prescribed paroxetine (Paxil) 20 mg QD by her primary care physician and she had been taking it for a few weeks. The patient had no history of psychiatric illness and there was no family history of mental disorders. She was unwilling to be discharged when the attending physicians concluded their examinations.

While in the ER, the physicians ordered a complete blood count, serum chemistry, thyroid function tests, B12, folate, and a serological test for syphilis. All of which showed no significant abnormalities. After administering a Mini Mental Status Examination, the patient's mood was found to be depressed, angry, and irritable, and she knew places and people but not the time. Her memory was impaired when it came to remote events. Her insight and judgment were poor and she was unable to make decisions regarding her care. After her trip to the ER, she was given a prescription for venlafaxine (Effexor).

A computed topography scan found a 5 cm left parietal mass which caused the patient to undergo a resection of the mass and followed by chemotherapy and radiotherapy. Venlafaxine was discontinued after surgery. The patient's mood was found to improve after surgery.

Madhusoodanan and colleagues found some neurological deficits through clinical examinations. They believe that brain imaging is essential to determining a specific patient's diagnosis, regardless of neurological signs or symptoms and that neuroimaging is essential to those patients without a psychiatric history and those that have been unresponsive to pharmacotherapy.–*CN*

(AAGP 2004 Poster P03)

–Clinical Updates in Neuropsychiatry is compiled and written by Christopher Naccari, José R. Ralat, and Shelley Wong

CORRECTION

In volume 9, number 2, "The Goal of Epilepsy Therapy: No Seizures, No Side Effects, as Soon as Possible," Jerome Engel, Jr., MD, PhD, the phone number for the University of California, Los Angeles should be 310-267-2880 and the contact e-mail for the Swedish Medical Center is erin.lystad@swedish.org

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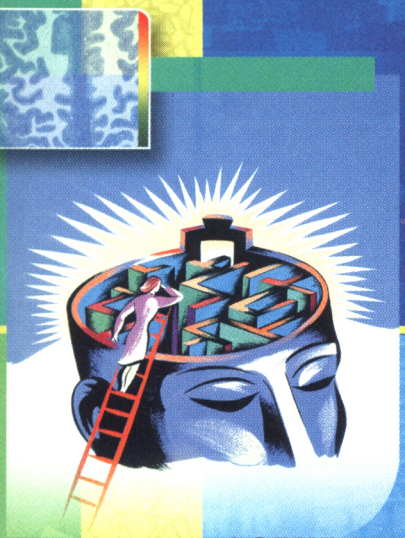
Don't miss this symposium

Are All Atypical Antipsychotics Equal for the TREATMENT OF COGNITION AND AFFECT in Schizophrenia?



APA 157TH ANNUAL MEETING

AGENDA

1:00 PM **Lunch**

1:30 **Welcome and Introduction**
Stephen M. Stahl, MD, PhD
Program Chairperson
Chairman and CEO
Neuroscience Education Institute
Carlsbad, California
Adjunct Professor of Psychiatry
University of California, San Diego
La Jolla, California

1:40 **Schizophrenia: *From Circuits to Symptoms***
Stephen M. Stahl, MD, PhD

2:10 **Effects of Atypical Antipsychotic Drugs on Cognition and Negative Symptoms**
Herbert Y. Meltzer, MD
Bixler Professor of Psychiatry and Pharmacology
Director, Division of Psychopharmacology
Department of Psychiatry
Vanderbilt University Medical Center
Nashville, Tennessee

2:40 **Optimal Health Outcomes in Schizophrenia**
Jonathan M. Meyer, MD
Staff Psychiatrist, VA San Diego Healthcare System
Assistant Adjunct Professor of Psychiatry
University of California, San Diego
La Jolla, California

3:10 **Maximizing Function from a First Episode of Psychosis**
Lili C. Kopala, MD, FRCPC
Clinical Professor of Psychiatry
Centre for Complex Disorders
University of British Columbia
Department of Psychiatry
Powell River, British Columbia, Canada

3:40 **Panel Discussion/Question and Answer Session**

4:30 **Adjournment**

OBJECTIVES

At the conclusion of this program, participants should be able to:

- Describe the scientific rationale for the mechanistic distinctions among atypical antipsychotics and the related effects in cognition and affect for patients with schizophrenia;
- Recognize multiple dimensions that contribute to overall functional outcomes of persons with schizophrenia, including health considerations, medication tolerability, and adherence.

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award and for the CME requirement of the APA. Each physician should only claim those credits that he/she actually spent in the activity.

Attendees must be registered for the APA 2004 Annual Meeting to attend this symposium. Seating is limited and will be on a first-come, first-served basis. For more information about the meeting, please visit the APA Web site at www.psych.org or contact the APA toll free at 1-888-357-7924 (within the United States or Canada) or 703-907-7300.

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