February 2004 Volume 9 — Number 2

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

The Goal of Epilepsy Therapy: No Seizures, No Side Effects, as Soon as Possible
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The Consequences of Uncontrolled Epilepsy
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Barriers to the Management of Patients with Surgically Remediable Intractable Epilepsy
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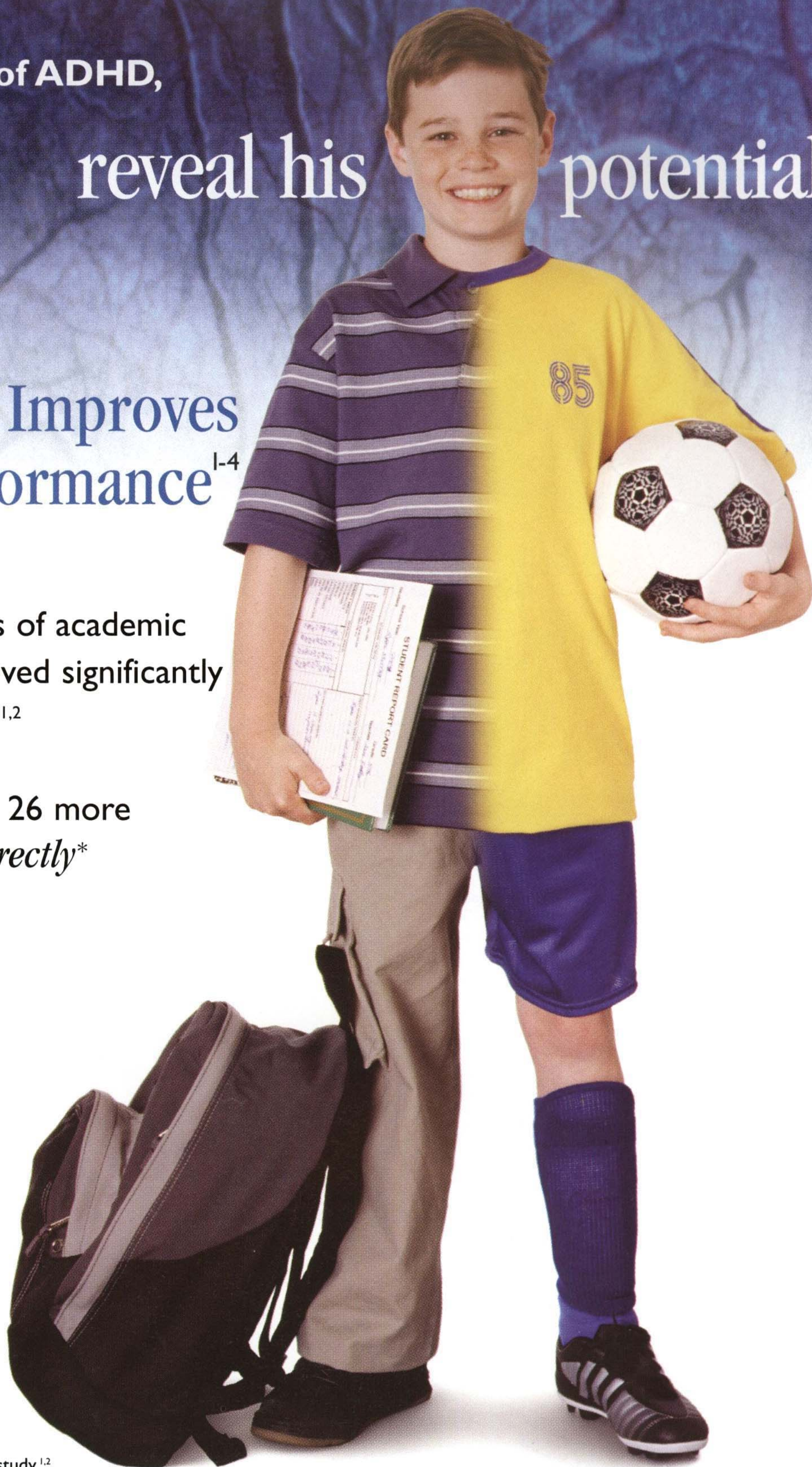
Index Medicus/MEDLINE
citation: *CNS Spectr*

CME 3 Mount Sinai

https://doi.org/10.1017/S1092852900008415 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.

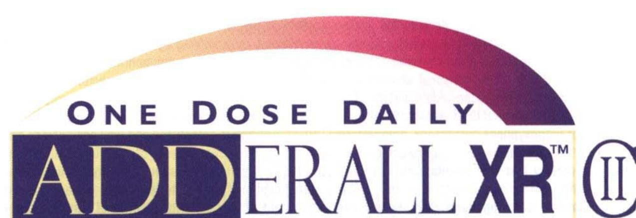
As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Caution also should be exercised in patients with a history of psychosis.

https://doi.org/10.1017/S1092852900008415 Published online by Cambridge University Press

with two-sided improvement

ADDERALL XR Enhances Social Functioning[5]

- Helps provide *efficacy* that lasts through school and other *social activities*[1-4]
- Significantly improves *attention* and *behavior* throughout the school day and into the early evening[1-4]



5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg CAPSULES
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Dextroamphetamine Saccharate
Amphetamine Aspartate Monohydrate Amphetamine Sulfate

Removing obstacles in ADHD™

Please see references and brief summary of prescribing information on adjacent page.

www.ADDERALLXR.com

Shire US Inc.
...your ADHD support company™
1-800-828-2088

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Abuse of amphetamines may lead to dependence. ADDERALL XR is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism and glaucoma, known hypersensitivity to this class of compounds, agitated states, history of drug abuse, or current or recent use of MAO inhibitors. ADDERALL XR should be prescribed with close physician supervision.

https://doi.org/10.1017/S1092852900008415 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

ONE DOSE DAILY

ADDERALL XR™ CII

5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg CAPSULES

(Mixed Salts of a Single-Entity Amphetamine Product)

Dextroamphetamine Sulfate Dextroamphetamine Saccharate

Amphetamine Aspartate Monohydrate Amphetamine Sulfate

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)

Shire

https://doi.org/10.1017/S1092852900008415 Published online by Cambridge University Press

February 2004 Volume 9 - Number 2

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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https://doi.org/10.1017/S1092852900008415 Published online by Cambridge University Press

Introduction

CNS Spectrums is an *Index Medicus* journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician on a monthly basis. Our mission is to provide physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues between neurology and psychiatry will be given immediate priority.

Scope of Manuscripts

CNS Spectrums will consider and encourages the following types of articles for publication:

Original Research presents methodologically sound original data.

Reviews are comprehensive articles summarizing and synthesizing the literature on various neuropsychiatric topics and presented in a scholarly and clinically relevant fashion. Diagnostic and treatment algorithms should be designed to aid the clinician in diagnosis and treatment.

Case Reports, single or multiple, are encouraged for publication.

Letters to the Editor will be considered and are encouraged for publication. All letters will be edited for style, clarity, and length.

Manuscript Submission

General Information Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, MD, Editor (or, in Europe, to Joseph Zohar, MD, International Editor), c/o MBL Communications, 333 Hudson Street, 7th Floor, New York, NY 10013. Authors are also required to submit their manuscripts on computer disk in Microsoft Word format. Disks should be labeled with the word processing program, title of paper, and lead author's name. Accepted manuscripts will be edited for clarity and style.

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Peer Review Authors must provide three to five names of qualified potential reviewers with no conflict of interest in reviewing the work. Contact information with affiliations and e-mail address should be included. -eReview is anonymous.

Manuscript Preparation

Length Reviews and Original Research should not exceed 5,000 words *(excluding References)*. Diagnostic and treatment algorithms should contain an introduction, flowcharts or a series of graphs, and a concise summary. Letters should not exceed 1,500 words. Single Case Reports should not exceed 3,750 words and may be submitted with a photograph, if applicable.

Please note: If your article is Original Research, it should be formatted as: Abstract (100–200 words); Introduction, Methods; Findings; Discussion; Conclusion; References (numbered and comprehensive list).

Spacing and Pagination One space should be left after commas and periods. Manuscripts should be double-spaced and numbered.

Abstract Authors must provide a brief abstract of 100–200 words.

Focus Points Please provide three to six points that dictate the main focus of the manuscript and clearly illustrates what you are trying to convey in the article.

Figures/Tables Please provide figures and/or tables if content is amenable to it.

References Please use American Medical Association style. References should be superscripted in text, then numbered, and comprehensive in list. See the following examples:

1. Jones J. Necrotizing Candida esophagitis. *JAMA*. 1980;244:2190-2191.
2. Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.
3. Alzheimer's Disease Cooperative Study. Valproate protocal. Available at: http://adcs.ucsd.edu/VP_Protocol.htm. Accessed October 15, 2003.

Continuing Medical Education Authors must submit six multiple-choice questions (three Type A and three Type K), with answers.

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Submission Checklist

- ☐ Original manuscript plus one copy, with cover letter on author's letterhead
- ☐ Copies of permission letters to reproduce previously published and unpublished material
- ☐ A brief abstract of the article
- ☐ Six CME multiple-choice questions with answers
- ☐ Three to six focus points
- ☐ Disk labeled with the word processing program, title of paper, and lead author's name
- ☐ Names and affiliations of three to five potential peer reviewers

https://doi.org/10.1017/S1092852900008415 Published online by Cambridge University Press

Vivactil® (Protriptyline HCl, USP) 5-mg and 10-mg Tablets

Brief Summary: See package insert for full prescribing information

INDICATIONS AND USAGE: Protriptyline hydrochloride tablets are indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients.

CONTRAINDICATIONS: Protriptyline hydrochloride tablets are contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to substitute protriptyline for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. Protriptyline should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Protriptyline is contraindicated in patients taking cisapride because of the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac arrhythmias and conduction system disturbances.

This drug should not be used during the acute recovery phase following myocardial infarction.

WARNINGS: Protriptyline may block the antihypertensive effect of guanethidine or similarly acting compounds.

Protriptyline should be used with caution in patients with a history of seizures, and, because of its autonomic activity, in patients with a tendency to urinary retention, or increased intraocular tension.

Tachycardia and postural hypotension may occur more frequently with protriptyline than with other antidepressant drugs. Protriptyline should be used with caution in elderly patients and patients with cardiovascular disorders; such patients should be observed closely because of the tendency of the drug to produce tachycardia, hypotension, arrhythmias, and prolongation of the conduction time. Myocardial infarction and stroke have occurred with drugs of this class.

On rare occasions, hyperthyroid patients or those receiving thyroid medication may develop arrhythmias when this drug is given.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

Pediatric Use: The safety and effectiveness of protriptyline in pediatric patients have not been established.

Usage in Pregnancy: Safe use in pregnancy and lactation has not been established; therefore, use in pregnant women, nursing mothers or women who may become pregnant requires that possible benefits be weighed against possible hazards to mother and child.

In mice, rats, and rabbits, doses about ten times greater than the recommended human doses had no apparent adverse effects on reproduction.

PRECAUTIONS: General - When protriptyline HCl is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant drug. Paranoid delusions, with or without associated hostility, may be exaggerated. In any of these circumstances, it may be advisable to reduce the dose of protriptyline or to use a major tranquilizing drug concurrently.

Symptoms, such as anxiety or agitation, may be aggravated in overactive or agitated patients.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. This type of patient should not have access to large quantities of the drug.

Concurrent administration of protriptyline and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Discontinue the drug several days before elective surgery, if possible.

Both elevation and lowering of blood sugar levels have been reported.

Information for Patients: *While on therapy with protriptyline, patients should be advised as to* the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions: When protriptyline is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

*Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepres*sants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side-effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Tricyclic antidepressants may enhance the seizure risk in patients taking ULTRAM (tramadol hydrochloride).

Protriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Drugs Metabolized by Cytochrome P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C anti-arrhythmics, propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic anti-depressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Pediatric Use: *The safety and effectiveness of protriptyline in pediatric patients have not been established.*

Geriatric Use: Clinical studies of protriptyline 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. (see WARNINGS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when protriptyline is administered. Protriptyline is more likely to aggravate agitation and anxiety and produce cardiovascular reactions such as tachycardia and hypotension.

Cardiovascular: Myocardial infarction; stroke; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; hypertension; tachycardia; palpitation.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; hypomania; exacerbation of psychosis; insomnia, panic, and nightmares.

Neurological: Seizures; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of extremities; extrapyramidal symptoms; drowsiness; dizziness; weakness and fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, delayed micturition, dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis; dry mouth and rarely associated sublingual adenitis.

Allergic: Drug fever; petechiae, skin rash, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general, or of face and tongue).

Hematologic: Agranulocytosis; bone marrow depression; leukopenia; thrombocytopenia; purpura; eosinophilia.

Gastrointestinal: Nausea and vomiting; anorexia; epigastric distress; diarrhea; peculiar taste; stomatitis; abdominal cramps; black tongue.

Endocrine: Impotence, increased or decreased libido; gynecomastia in the male; breast enlargement and galactorrhea in the female; testicular swelling; elevation or depression of blood sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; parotid swelling; alopecia; flushing; weight gain or loss; urinary frequency, nocturia; perspiration.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE:

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS:

Critical manifestations of overdosage include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under **ADVERSE REACTIONS**.

MANAGEMENT:

General:

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose. These patients had *clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination.* Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination:

All patients suspected of a tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular:

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS:

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP:

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT:

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION:

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Usual Adult Dosage – Fifteen to 40 mg a day divided into 3 or 4 doses. If necessary, dosage may be increased to 60 mg a day. Dosages above this amount are not recommended. Increases should be made in the morning dose.

Adolescent and Elderly Patients – In general, lower dosages are recommended for these patients. Five mg 3 times a day may be given initially, and increased gradually if necessary. In elderly patients, the cardiovascular system must be monitored closely if the daily dose exceeds 20 mg.

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

The safety and effectiveness of protriptyline in pediatric patients have not been established.

METABOLISM:

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and only a small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver. It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8 to 12 hours, then declining gradually.

Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

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Vivactil®
(Protriptyline HCl, USP)

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1. Vivactil [package insert]. East Hanover, NJ:Odyssey Pharmaceuticals, Inc. 2000.

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PIOPV-603 04/03

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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.

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Reference: 1. Jibson MD, Tandon R. New atypical antipsychotic medications. *J Psychiatr Res.* 1998;32:215-228.

210737 3/03

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