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12

Investigating Neuropsychiatric Disorders

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MEETINGS

60-Day Planner

January

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1 (–31) Baylor College of Medicine Evaluation of the Child With the First Seizure Houston *Contact:* Tel: 713-798-8237 cme@bcm.tmc.edu	*2*	*3*	*4*
5	*6*	*7*	*8*	*9*	*10*	*11 (–12)*
12	*13*	*14* Southern Illinois University Medical School Neuroradiology Conference Springfield, IL *Contact:* Tel: 217-545-4413 bshelow@siumed.edu	*15*	*16 (–17)* L'Institut Pasteur Depression: Emerging Research and Treatment Approach Paris *Contact:* Tel: 33-0-140-613-405 euroconf@pasteur.fr	*17 (–19)* Annual Meeting of the California Association of Neurological Surgeons Newport Beach, CA *Contact:* Tel: 916-457-2267 jt4ns@aol.com	*18*
19	*20*	*21*	*22*	*23*	*24*	*25*
26	*27*	*28 (–31)* Annual Meeting of the Australian Neuroscience Society Adelaide, Australia *Contact:* Tel: 61-882-044-263 judy.morris@flinders.edu.au	*29 (–Feb 1)* Congress of the Neurological Association of South Africa Cape Town, South Africa *Contact:* sellliott@cure.uct.ac.za	*30*	*31 (–Feb 7)* University of Utah Health Sciences Center Winter Neurosurgical Conference Snowbird, UT *Contact:* Tel: 801-581-6554 lanette.dunbar@hsc.utah.edu	

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60-Day Planner

MEETINGS

February

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1 (–28) Baylor College of Medicine Evaluation of the Child With the First Seizure Houston *Contact:* Tel: 713-798-8237 cme@bcm.tmc.edu
2	*3 (–7)* Harvard Medical School Mini-Fellowship in Transcranial Magnetic Stimulation Boston *Contact:* Tel: 617-384-8600 hms-cme@hms.harvard.edu	*4*	*5 (–8)* Annual Meeting of the International Neuropsychological Society Honolulu *Contact:* Tel: 614-263-4200 osu_ins@postbox.acs.ohio-state.edu	*6*	*7*	*8* Johns Hopkins Medical Institutions Parkinson's Disease and Related Movement Disorders in Primary Care Baltimore *Contact:* Tel: 410-955-2959 cmenet@jhmi.edu
9	*10*	*11*	*12 (–14)* 8th International Conference on Mental Retardation and Other Developmental Disabilitites: Research to Practice Kauai, HI *Contact:* Tel: 905-890-1010 cperras@cgocablle.net	*13* 28th International Stroke Conference Phoenix *Contact:* Tel: 214-706-1100 Fax: 214-706-5262	*14*	*15*
16	*17*	*18 (–22)* Inaugural Meeting of the European Chapter of the International Society for Neuronal Regulation Undine, Italy *Contact:* Tel: 351-916-305-575 belling@clix.pt	*19*	*20*	*21*	*22 (–26)* 2nd International Meeting on Steroids and Nervous System Torino, Italy *Contact:* Tel: 39-0-116-707-732 giancarlo.panzica@unito.it
23	*24*	*25*	*26 (–28)* 4th Latinamerican Congress of Neuropsychopharmacology Cartagena, Colombia *Contact:* Tel: 571-215-0010 clanp2003@yahoo.com	*27*	*28*	

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DNmA™ 1-4*

- (Dopamine/Norepinephrine
- Modulating Agent)

the science behind ADHD and

3 *NEW* Strengths

5 mg, 15 mg, and 25 mg Capsules

Provide Even More Flexibility

ADDERALL XR was generally well tolerated in clinical trials of pediatric patients. 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. Administration of amphetamine may exacerbate symptoms of behavior disturbances and thought disorder in psychotic patients.

ADDERALL XR is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism and glaucoma, known hypersensitivity or idiosyncrasy to sympathomimetic amines, agitated states, history of drug abuse, or within 14 days of administration of a MAO inhibitor. The possibility of growth suppression warrants monitoring of patients receiving long-term therapy. **Prolonged use of amphetamines may lead to drug dependence**. ADDERALL XR should be prescribed with close physician supervision as part of a multimodal treatment program for ADHD.

References: 1. Kuczenski R, Segal DS. Neurochemistry of amphetamine. In: Cho AK, Segal DS, eds. *Amphetamine and Its Analogs: Psychopharmacology, Toxicology, and Abuse*. San Diego, Calif: Academic Press; 1994:81-113. **2.** Wilens TE, Spencer TJ. Pharmacology of amphetamines. In: Tarter RE, Ammerman RT, Ott PJ, eds. *Handbook of Substance Abuse: Neurobehavioral Pharmacology*. New York, NY: Plenum Press; 1998:501-513. **3.** Grace AA. Psychostimulant actions on dopamine and limbic system function: relevance to the pathophysiology and treatment of ADHD. In: Solanto MV, Arnsten AFT, Castellanos FX, eds. *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. New York, NY: Oxford University Press; 2001: 134-157. **4.** Pliszka SR. Comparing the effects of stimulant and non-stimulant agents on catecholamine function: implications for theories of ADHD. In: Solanto MV, Arnsten AFT, Castellanos FX, eds. *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. New York, NY: Oxford University Press; 2001:332-352. **5.** Frankel F, Cantwell DP, Myatt R, Feinberg DT. Do stimulants improve self-esteem in children with ADHD and peer problems? *J Child Adolesc Psychopharmacol*. 1999;9:185-194. **6.** Alston CY, Romney DM. A comparison of medicated and nonmedicated attention-deficit disordered hyperactive boys. *Acta Paedopsychiatr*. 1992;55:65-70. **7.** Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*. 1996;35:409-432. **8.** ADDERALL package insert, Shire US Inc., 2000. **9.** Data on file, Shire US Inc., 2002. **10.** ADDERALL XR package insert, Shire US Inc., 2002. **11.** 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*. In press. **12.** McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of SLI381 for the treatment of ADHD. Poster presented at: 47th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 26, 2000; New York, NY. **13.** Ambrosini PJ, Lopez FA, Chandler MC, Tulloch SJ, Michaels MA. An open-label community assessment trial of Adderall XR in pediatric ADHD. Poster presented at: 155th Annual Meeting of the American Psychiatric Association; May 22, 2002; Philadelphia, Pa.

*Mechanism not proven but supported by current scientific hypotheses.

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ONE DOSE DAILY

ADDERALL XR™ II

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

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/m^2 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/m^2 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/m^2 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/m^2 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 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

Manufactured by DSM Pharmaceuticals Inc., Greenville, North Carolina 27834. Distributed and marketed by Shire US Inc., Florence, KY 41042

For more information call 1-800-536-7878 or visit www.adderallxr.com

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CNS SPECTRUMS®

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

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COGNITIVE DECLINE AND QUALITY OF LIFE IN PATIENTS WITH HIV: WHAT IS THE BEST TREATMENT?

page 860

"HIV has evolved into a chronic condition that is complicated by neurocognitive factors. Cognitive difficulties associated with HIV are characterized by a subcortical pattern with primary deficits in information processing speed and psychomotor speed. These deficits interfere with the ability of patients to complete important instrumental activities of daily living even in the absence of dementia. Treatment of HIV improves neurocognitive functioning, but the regimens are complex and adherence is critical. Cognitive factors can negatively impact treatment adherence, which in turn results in poorer immunological, cognitive, and psychiatric outcome. This cycle emphasizes the important interrelationships between symptom expression and treatment outcome in patients with HIV. The nature of these relationships will change with further developments in treatment regimens such as once-daily dosing. Less complex treatment approaches should improve health outcome as well as provide additional opportunities to further understand the impact of HIV on brain function."

SUBSTANCE P SPREADS HIV

page 867

"Neuropeptides, such as SP, may play a central role in stressed HIV-infected patients by affecting immune cell functions, which may trigger further HIV disease progression and immune deficiency. In AIDS patients, abnormal neuropeptide levels may be related to severe psychological disturbances. Since SP enhances inflammatory cytokine production by immune cells, such as macrophages, and these cytokines modulate HIV infection of human immune cells that also are the targets for HIV infection, it is postulated that SP promotes HIV infection of these immune cells."

LITERARY CHARACTERS LEAP TO LIFE IN NEUROPSYCHIATRY

page 875

"von Münchhausen's quiet life was cut short by Rudolf Eric Raspe. Raspe was a curator for Frederick II in a museum located about 50 miles south of Bodenwerder at the same time the von Münchhausen was entertaining guests with his mendacious stories. Raspe, caught embezzling from the museum, fled to England. There he anonymously published *Baron Munchausen's Narrative of His Marvelous Travels and Campaigns in Russia in 1785*. The book was translated into German, and made von Münchhausen an immediate celebrity. Curious tourists flocked to the von Münchhausen's estate and harassed the old man.

When von Münchhausen sued Raspe for damages, he lost the case because the title of the book had only one "h" instead of two and there was no author listed. von Münchhausen became even more depressed and withdrawn in 1790, when his wife died. He sought solace, at 74 years of age, by marrying 17-year-old Bernahardine von Brunn in 1794. Soon after, the young lady gave birth to an illegitimate daughter. von Münchhausen eventually divorced her. The proceedings involved alimony that kept von Münchhausen unhappy until he died in 1797."

TICS, OBSESSIVENESS, COMPULSIONS, AND BEHÇET'S SYNDROME PRESENTED IN ONE PATIENT

page 878

"During immunosuppressive therapy for presumed re-exacerbation of NBS, AC experienced an explosive onset of severe OCS, including contamination fears that he would become ill from certain foods, such as red meat and pork, accompanied by compulsive hand-washing, up to 20 times daily until the skin on his hands was severely abraded, compulsions that required him check the stove and sink faucet, and to arrange/rearrange piles of papers on his desk for hours. These symptoms were accompanied by nearly constant repetitive involuntary eye-blinking, grimacing, head-shaking, shoulder-shrugging, and complex vocalizations (eg, barking, echolalia)."

ARE SELECTIVE SEROTONIN REUPTAKE INHIBITORS MORE EFFECTIVE THAN VENLAFAXINE?

page 882

"Venlafaxine was consistently superior to SSRIs and placebo in every category observed, with roughly twice the benefit over placebo and 1.5 times the benefit over SSRIs. In this figure, the α-values represent a weighted proportion of patients obtaining remission with mild AEs (category II) to patients obtaining pure remission (category I). As the α-value decreases, the drug benefit increases and as the α-value increases, drug benefit decreases (the more weight attributed to AEs, the greater potential negative impact on overall efficacy). So, this graphic depicts how the efficacy obtained by venlafaxine, even when associated mild AEs are considered, still has a higher relative gain over the efficacy obtained by SSRIs, when their associated AEs are considered." CNS

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BRIEF SUMMARY. See package insert for full prescribing information. **CONTRAINDICATIONS**: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. **WARNINGS**: ***Potential for Interaction with Monoamine Oxidase Inhibitors*—Adverse reactions, some serious, have been reported in patients who were recently discontinued from an MAOI and started on venlafaxine, or who recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. It is recommended that Effexor XR not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Experience with immediate release venlafaxine showed that sustained hypertension was dose related. It is recommended that patients receiving Effexor XR have regular monitoring of BP. For patients who experience a sustained increase in BP either dose reduction or discontinuation should be considered. **PRECAUTIONS**: **General**—***Insomnia and Nervousness:*** Treatment-emergent insomnia and nervousness have been reported. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients in Phase 3 depression studies. In Phase 3 Generalized Anxiety Disorder (GAD) trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of patients. ***Changes in Appetite/Weight:*** Treatment-emergent anorexia has been reported. A loss of 5% or more of body weight occurred in 7% of patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of patients in placebo-controlled GAD trials. The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Activation of Mania/Hypomania:*** Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia:*** Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics. ***Mydriasis:*** Mydriasis has been reported; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma should be monitored. ***Seizures:*** In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine-treated patients. Use Effexor XR cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding:*** There have been reports of abnormal bleeding (most commonly ecchymosis). ***Suicide:*** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same precautions should be observed when treating patients with GAD. ***Use in Patients With Concomitant Illness:*** Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. In short-term depression studies electrocardiographic changes in corrected QT interval (QTc) showed a mean increase of 4.7 msec, and the mean change from baseline heart rate was 4 beats per minute. In GAD studies, mean changes in QTc did not differ significantly from placebo and the mean change from baseline heart rate was 3 beats per minute. In a flexible-dose study with immediate release Effexor (mean dose >300 mg/day), patients had a mean increase in heart rate of 8.5 beats per minute. Caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent MI). In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—There are no specific laboratory tests recommended. **Drug Interactions**—***Alcohol:*** A single dose of ethanol had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine:*** Use with caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam:*** A single dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV. Venlafaxine did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol:*** Venlafaxine decreased total oral-dose clearance of haloperidol which resulted in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged. ***Lithium:*** A single dose of lithium did not appear to affect the pharmacokinetics of either venlafaxine or ODV. Venlafaxine had no effect on the pharmacokinetics of lithium. ***Drugs Inhibiting Cytochrome P4502D6 Metabolism:*** Venlafaxine is metabolized to its active metabolite, ODV, via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. Since the composite plasma levels of venlafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. The concomitant use of venlafaxine with a drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes:*** Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine:*** Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by 2.5-4.5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. ***Risperidone:*** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxy-risperidone, resulting in an approximate 32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). ***Indinavir:*** In a study of 9 healthy volunteers, venlafaxine resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. ***MAOIs:*** See "Contraindications" and "Warnings." ***CNS-Active Drugs:*** Caution is advised if the concomitant administration of venlafaxine and CNS-active drugs is required. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis:*** There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. ***Mutagenesis:*** Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility:*** No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy**—***Teratogenic Effects—Pregnancy Category C.*** Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects.*** If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in pediatric patients have not been established. **Geriatric Use**—Approximately 4% and 6% of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. Several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in depression and GAD trials included: nausea, anorexia, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for Depression and GAD***—Body as a Whole: asthenia. Cardiovascular: vasodilatation, hypertension. Digestive: nausea, constipation, anorexia, vomiting, flatulence. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation. Respiratory System: pharyngitis, yawn. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, anorgasmia (female). ***Vital Sign Changes:*** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the "Sustained Hypertension" section of "Warnings.") ***Laboratory Changes:*** Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled depression trials was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively. Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL. This increase was duration dependent over the 12-month study period and tended to be greater with higher doses. An increase in serum cholesterol from baseline by >50 mg/dL and to values >260 mg/dL, at any time after baseline, has been recorded in 8.1% of patients. ***ECG Changes:*** See the "Use in Patients with Concomitant Illnesses" section of PRECAUTIONS. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=5079. "Frequent"= events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor. **Digestive system** - Frequent: eructation, increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, proctitis, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, emotional lability, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, twitching; Rare: akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, libido increased, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: rash, pruritus; Infrequent: acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; Rare: erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, petechial rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: dysuria, metrorrhagia,* prostatic disorder (prostatitis and enlarged prostate),* urination impaired, vaginitis*; Infrequent: albuminuria, amenorrhea,* cystitis, hematuria, leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; Rare: abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.* (*Based on the number of men and women as appropriate). **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly). There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION:** Please consult full prescribing information for detailed dosing instructions. **Discontinuing Effexor XR**—When discontinuing Effexor XR, the dose should be tapered gradually, based upon the dose, duration of therapy and the individual patient. Discontinuation symptoms reported include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo and vomiting. **Switching Patients To or From a Monoamine Oxidase Inhibitor**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see "Contraindications" and "Warnings"). This brief summary is based on the circular CI 7509-4, revised April 11, 2002.

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In a pooled analysis of over 2,000 patients, against leading SSRIs (fluoxetine, paroxetine, fluvoxamine), EFFEXOR XR/EFFEXOR offered something extra—**remission* of depression in 1/3 more patients.**[1] Remission of symptoms is a first step on the road to recovery.[2]

***Remission is defined as minimal or no symptoms (HAM-D ≤ 7).**[1]

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.

Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. Less than 1% discontinued treatment because of elevated BP. Regular BP monitoring is recommended.

Patients should not be abruptly discontinued from antidepressant medication, including EFFEXOR XR. See the Dosage and Administration section of the Prescribing Information.

References: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241. **2.** Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(5, suppl):28-34.

Please see brief summary of Prescribing Information on adjacent page.

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