

Wide Variation Seen in Hepatitis A Vaccination

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Immunization rates for hepatitis A in children aged 24-35 months vary widely across areas and populations in the United States, the Centers for Disease Control and Prevention said.

In 1999, the CDC recommended routine immunization against hepatitis A for children residing in 11 states in which the average annual incidence during 1987-

1997 was at least 20 per 100,000 population, or twice the national average. Those states are Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah, and Washington.

They also advised that hepatitis A vaccination be considered in another six states (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) where the average incidence was 10-20/100,000 population (MMWR 2005; 54:141-5).

Later this year, the CDC's Advisory Committee on Immunization Practices is expected to discuss broadening these recommendations for the two currently-licensed hepatitis A vaccines, GlaxoSmithKline's Havrix and Merck's VAQTA. Both are inactivated vaccines, given in two doses at least 6 months apart to children aged 24 months and above.

In the first national analysis of hepatitis A vaccination coverage among children, data were collected from provider immunization records for 13,731 children during 2003. In the 11 states in which routine hepatitis A vaccination is recommended, the proportion of children aged 24-35 months who had received at least one dose of vaccine varied from a low of 6.4% (South Dakota) to a high of 72.7% (Alaska).

The overall rate, 50.9%, is below that of other vaccines recommended for routine use in children, the CDC said.

In the six states where hepatitis A vaccination should be considered, 25.0% of children aged 24-35 months had been vaccinated, compared with just 1.4% in the other 33 states with no recommendation.

Only two states (Alaska and Arizona) and four urban areas (Maricopa County, Ariz., Los Angeles County, Calif., and Bexar and El Paso Counties, Tex.) had coverage estimates over 60%.

The wide variation in coverage is likely due to targeted programs in some areas. For example, vaccination requirements in Texas border counties for all children attending day care programs probably account for the higher coverage in El Paso County (71%), compared with the rest of the state, the CDC said.

Within the areas where routine hepatitis A vaccine is recommended or should be considered, Hispanic and Native American/Alaska Native children had higher coverage rates that either non-Hispanic white or black children. This finding may be related to greater recognition of the disease among groups that have been identified as high risk.

Flu Vaccine Maker Back on Track for 2005

Chiron's license to manufacture influenza vaccine, which was suspended in October as a result of contamination at the company's Liverpool, England, facility, has been reinstated, and vaccine manufacturing for the coming season will proceed.

The British Medicines and Healthcare Products Regulatory Agency (MHRA), working closely with the U.S. Food and Drug Administration, has been monitoring Chiron's progress in correcting the manufacturing problems that reduced the doses of vaccine slated for the U.S. market for the 2004-2005 flu season by nearly 50 million.

The MHRA made the decision to lift the suspension, but the FDA will conduct a comprehensive inspection of the facility once manufacturing resumes and the corrective action can be evaluated to ensure production of a safe and effective vaccine, according to a statement by Jesse Goodman, M.D., director of the FDA's Center for Biologics Evaluation and Research.

The vaccine shortages that resulted from Chiron's license suspension brought the FDA under fire from government officials, who said the crisis was in part a result of the agency's lax oversight of the facility after previous findings of bacterial contamination and poor sanitary procedures.

—Sharon Worcester

References: 1. Ambrosini PJ, Lopez FA, Chandler MC, et al. Safety and efficacy of ADDERALL XR in pediatric ADHD: results of an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. 2. Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*. 1996;35:409-432. 3. Lopez FA, Ambrosini PJ, Chandler MC, et al. 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. 4. Lopez FA, Chandler MC, Biederman J, et al. Long-term Adderall XR treatment improves quality of life in ADHD children. Poster presented at: 156th Annual Meeting of the American Psychiatric Association; May 21, 2003; San Francisco, Calif.

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

ADDERALL XR® CAPSULES

CI 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 GIVEN TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

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 in children aged 6 to 12, and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), 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.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. ADDERALL XR® generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose.

Hypertension: 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 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. Mepredine—Amphetamines potentiate the analgesic effect of mepredine. Methamphetamine—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine 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 overdose, 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-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 (child) 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-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 (child) 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 that of a human dose of 30 mg/day [child] 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 965 participants in clinical trials (635 pediatric patients, 248 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). 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 among children with ADHD, 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 of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

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

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.8% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence, and, 0.5% (n=1) each for ALL increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adults treated with ADDERALL XR® or placebo are presented in the tables below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events 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 Pediatric 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% |
| Nervous System | Vomiting | 7% | 4% |
| | Dizziness | 2% | 0% |
| | Emotional Liability | 9% | 2% |
| Metabolic/Nutritional | Insomnia | 17% | 2% |
| | Nervousness | 6% | 2% |
| | Weight Loss | 4% | 0% |

Table 2 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

| Body System | Preferred Term | ADDERALL XR® (n=191) | Placebo (n=64) |
|-----------------------|-------------------------|----------------------|----------------|
| General | Asthenia | 6% | 5% |
| | Headache | 26% | 13% |
| Digestive System | Loss of Appetite | 33% | 3% |
| | Diarrhea | 6% | 0% |
| | Dry Mouth | 3% | 5% |
| | Nausea | 8% | 3% |
| Nervous System | Agitation | 8% | 5% |
| | Anxiety | 8% | 5% |
| | Dizziness | 7% | 0% |
| Cardiovascular System | Insomnia | 27% | 13% |
| | Tachycardia | 6% | 3% |
| Metabolic/Nutritional | Weight Loss | 11% | 0% |
| | Urinary Tract Infection | 5% | 0% |

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, tachycardia, dyspnea, sweating, dysmenorrhea, and impotence.

*Included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. 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, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke. 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 dose 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 overdose 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 overdose, 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 light, 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: Shire US Inc., Newport, KY 41071 Made in USA For more information call 1-800-828-2088, or visit www.adderallxr.com. ADDERALL® and ADDERALL XR® are registered in the US Patent and Trademark Office. Copyright ©2004 Shire US Inc.

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