

Explore Emotions of Atopic Dermatitis Patients

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ROME — A pediatric atopic dermatitis treatment plan is not complete without a psychological element, Dr. Caroline Koblenzer said at the 10th World Congress of Pediatric Dermatology.

"Without adding a psychological component to treatment, patients with atopic dermatitis can stay in a chronic course of remission and exacerbation," said Dr.

Koblenzer of the University of Pennsylvania, Philadelphia.

"Most patients do respond well to treatment, but in recalcitrant patients, you need to explore the experience of early infancy."

Studies have shown that up to 60% of dermatology patients have at least one co-existing psychiatric condition, she said.

Atopic children tend to be more emotionally and behaviorally immature than do controls.

Often, these children use their scratching behavior as a tool to manipulate their parents, define weak boundaries, or express anger and aggression.

The foundation for these behaviors is laid in infancy, when the atopic infant, itchy and restless, fails to perceive empathic touch while absorbing negative psychic energy from an anxious, guilt-ridden mother.

This initiates a self-renewing cycle of emotionally and physically related events

that trigger more atopic flares for the infant.

In infancy, Dr. Koblenzer said, empathic touch, usually from the mother, helps develop the infant's capacity to release and regulate tension.

This release is modulated by nonverbal two-way communication with the mother: The infant uses the mother as a mirror of his/her feelings until he/she develops emotional self-regulation.

"The relaxed mother will have a soothing effect, while the anxious, unhappy mother will increase the infant's distress," Dr. Koblenzer said.

"Failure to internalize this emotional control can lead to continued tension discharge through physical pathways.

"This stress may cause physical symptoms."

In addition to promoting the atopic cycle, this dance between the mother and infant has the ability to blunt the child's behavioral and emotional growth. "The itchy, restless infant whose anxiety continues to rise and who is difficult to soothe results in a mother who feels anxious and frustrated," Dr. Koblenzer said.

These feelings of anxiety and frustration can raise the mother's anxiety even more, leading to a corresponding increase in the infant's anxiety, she said.

The mother may feel inadequate and then guilty about her perceived inadequacy. As a result, the mother may fail to set boundaries, thereby retarding the child's emotional development and perpetuating the negative emotional cycle.

Other family members also feel the impact of this problematic relationship, she said.

"The emotional and financial costs of atopic dermatitis are actually greater for the family than if the child has insulin-dependent diabetes," Dr. Koblenzer said. "And because the mother's time is monopolized, siblings may act out with attention-seeking behavior."

Additionally, she said, atopic children, whose sense of body integrity is poorly developed, may interpret treatments as assaults. That is particularly the case when treatments, involve the face, neck, and genital areas.

It is crucial that physicians recognize and bring to the surface the emotional aspects that influence atopic dermatitis, particularly with patients who don't readily respond to conventional therapy, Dr. Koblenzer said.

The value of the doctor-patient relationship with these families can't be understated, she stressed.

"It's really important for us to empathize and understand the burdens on the parents, the patient, and the family."

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

ADDERALL XR[®] CAPSULES

Cl 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. 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[®] for the treatment of ADHD was established in the course 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 atherosclerosis, 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 delirium 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 weight monitored.

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 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 amphetamine molecules, 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[®] with other 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 effects of amphetamines. **Antidepressants**—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. **Serotonins** 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. **Meprobamate**—Amphetamines potentiate the anorectic effect of meprobamate. **Methamphetamine**—Urinary excretion of amphetamines is increased, and efficacy is reduced by administering methamphetamine. **Morphine**—Amphetamines enhance the adrenergic effect of morphine. **Phenobarbital**—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. **Phenylethylamine**—Amphetamines may delay intestinal absorption of phenylethylamine; co-administration of phenylethylamine may produce a synergistic anticonvulsant action. **Propoxyphene**—Amphetamines enhance the CNS stimulation and potentiate and local 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 1.5, 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 XR[®] (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 vivo* sister chromatid exchange and chromosomal aberration assays. Amphetamine, in the enantiomer ratio present in ADDERALL XR[®] (immediate-release) (d- to l-ratio of 3:1), did not adversely affect fertility or 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 XR[®] (d- to l-ratio of 3:1), had no apparent effects on embryofetal development or survival when orally administered to pregnant rats and rabbits at oral doses of up to 10 and 16 mg/kg/day, respectively. These doses are approximately 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. Fetal malformations and death have been reported in mice following parental administration of d-amphetamine doses of 50 mg/kg/day (approximately 1.5 times that of a human dose of 30 mg/day [child] on a mg/m² body surface area 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 dl-), 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 motor 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 body deformity, tracheo-esophageal fistula, and anal atresia (water association) in a baby born to a woman who took dextroamphetamine sulfate with levoratan 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.

Use 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 5 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 adult subjects). Of these 965 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 choice. 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% (7/255) 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=131) were 3.1% (n=9) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) for headache, palpitation, and somnolence; and, 0.6% (n=1) each for ALT 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 frequencies 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, users, and investigators. They do not, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence 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%
	Headache	2%	2%
	Intercourse	4%	2%
	Urinary Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	3%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional lability	2%	0%
	Insomnia	2%	2%
	Nervousness	6%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	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%
	Nausea	8%	3%
	Vomiting	8%	3%
Digestive System	Loss of Appetite	33%	0%
	Diarrhea	3%	0%
	Dry Mouth	3%	0%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urinary System	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[®]. There are reports of patients who have experienced the following: anorexia, decreased reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, tachycardia, vasodilation, dysmenorrhea, and impotence.

Incidence does not add to 60%.

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 become physically dependent on amphetamine. 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 somnolence, marked irritability, myoclonus, hyperreflexia, and psychomotor changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSEAGE

Individual patient responses 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, hyperreflexia 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.

Use in Pregnancy: Use in pregnancy is contraindicated. **Use in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

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 5 years of age.

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