

# Gene Therapy Helps Parkinson's in Phase I Trial

BY JONATHAN GARDNER  
London Bureau

Gene therapy for Parkinson's disease was safe and well tolerated by 11 patients, who also showed significant improvement in motor function at 1-year follow-up in an open-label phase I trial.

The 11 patients were treated at New York–Presbyterian Hospital, New York, with a therapy aimed at inhibiting the neu-

rologic stimulation that causes motor dysfunction in Parkinson's disease patients. To accomplish this goal, surgeons delivered the glutamic acid decarboxylase gene to the neurons of the subthalamic nucleus using adeno-associated virus (AAV); no adverse events occurred.

At 1 year after treatment, the researchers found a statistically significant improvement in scores on the 56-point motor component of the Unified Parkinson's Disease Rating Scale (UPDRS)—by

24% when patients were tested 12 hours after withdrawal of medication, and by 27% an hour after patients had taken medication. Statistically significant improvements in scores were also recorded at 3 and 6 months (Lancet 2007;369:2097-105).

"Our results show that AAV-mediated gene transfer can be done safely in the human brain, with no evidence of substantial toxic effects or adverse events in the perioperative period" and for at least 1 year after treatment, wrote the researchers, led

by Dr. Michael G. Kaplitt of Cornell University, New York. This open label, non-randomized phase I study "was not designed to assess the effectiveness of the intervention. Nonetheless, the clinical outcomes were encouraging."

Should further research support this treatment for Parkinson's, it would have an advantage over deep-brain stimulation, which is being used to improve motor function, the researchers wrote.

"The absence of indwelling hardware reduces the risk of infection, and some patients with Parkinson's disease simply prefer not to have an implanted device," they wrote. "Additionally, frequent visits for deep brain stimulation adjustments are not needed" with the investigational approach.

In an accompanying commentary, Dr. A. Jon Stoessl, of the Pacific Parkinson's Research Centre at the University of British Columbia, Vancouver, questioned whether the development of a gene therapy approach would be superior to deep-brain stimulation.

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"Apart from the avoidance of stimulator

adjustments and potential hardware problems, what is the real advantage of this approach?" Dr. Stoessl wrote. He cautioned that the research did not study the long-term effect of changing the neurologic pathways. But he praised the study and wrote that the approach should be subjected to further randomized, double-blind evaluation.

Because of ethical concerns, the researchers were restricted to using the treatment in only the more symptomatic hemisphere of the brain. They recorded greater improvements in motor function in the contralateral side of the body, compared with the untreated side, on the UPDRS.

In addition, although they did not record any improvements in the activities of daily living scores during the course of the study, at 12 months they measured a trend toward improvement in the off-medication state.

The researchers performed PET scans on the patients at 12 months, and found substantial reductions in glucose metabolism in the thalamus and overall in the operated hemisphere, a change that they did not detect on the untreated side.

## NEXT ISSUE

### Palliative Medicine

With subspecialty certification on the way, Practical Psychopharmacology examines the role of pharmacotherapy.

**BRIEF SUMMARY:** Consult the Full Prescribing Information for complete product information.

**ADDERALL XR<sup>®</sup> CAPSULES** CR/Pi 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<sup>®</sup> is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of ADDERALL XR<sup>®</sup> in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV<sup>®</sup> criteria for ADHD, along with extrapolation from the known efficacy of ADDERALL<sup>®</sup>, the immediate-release formulation of this stimulant.

**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 crisis may result).

**WARNINGS**  
**Serious Cardiovascular Events**  
Sudden Death and/or Existing Structural Cardiac Abnormalities or Other Serious Heart Problems  
Children and Adolescents  
Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

**Adults**  
Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see CONTRAINDICATIONS).

**Hypertension and other Cardiovascular Conditions**  
Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) (see ADVERSE EVENTS), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmias (see CONTRAINDICATIONS).

**According to Cardiovascular Data in Patients Being Treated with Stimulant Medications**  
Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmias) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

**Psychiatric Adverse Events**  
Pre-existing Psychosis  
Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder.

**Bipolar Illness**  
Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of manic episodes in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; careful monitoring should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

**Emergence of New Psychotic or Manic Symptoms**  
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychiatric illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 3.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

**Aggression**  
Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical studies of stimulant treatment. The risk of aggression or hostility may be increased in patients with ADHD. There is no systematic evidence that stimulants cause aggressive behavior or hostility; patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

**Long-Term Suppression of Growth**  
Careful follow-up of weight and height in children aged 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in retrospective studies of newly methylphenidate-treated and non-medication treated children over 30 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during the initial 4 weeks of therapy was -1.1 lbs. and -3.8 lbs., respectively, for patients receiving 10 mg and 20 mg ADDERALL XR<sup>®</sup>. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth. However, it is anticipated that they will have similar effects on growth. Therefore, growth should be monitored in patients with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

**Seizures**  
There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

**Visual Disturbances**  
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

**PRECAUTIONS**  
The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. ADDERALL XR<sup>®</sup> should be used with caution in patients who use other sympathomimetic drugs.

**Toxicity:** Amphetamines have been reported to exacerbate motor and phoric tics and Tourette's syndrome. Therefore, clinical evaluation for tic and tics/tourette's syndrome in the patient and their families should precede use of stimulant medication.

**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:** Acetylcholinesterase inhibitors, anticholinergic agents (antihistamines, tricyclic antidepressants, antiparkinsonian agents, antispasmodics, etc.) may increase the concentration 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. 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.

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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 (VACTEROL association) in a baby born to a woman who took dextroamphetamine sulfate with levodopa during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Neonatology:** 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 droopiness, including agitation, and significant irritability.

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

**Pediatric Use:** ADDERALL XR<sup>®</sup> is indicated for use in children 6 years of age and older.

**Use in Children Under Six Years of Age:** Effects of ADDERALL XR<sup>®</sup> 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<sup>®</sup> has not been studied in the geriatric population.

**ADVERSE EVENTS**  
Hypertension (See WARNINGS section) In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations  $\geq 15$  mmHg were observed in 754 (11%) placebo-treated patients and 7130 (7%) patients receiving ADDERALL XR<sup>®</sup> 10 or 20 mg. Isolated elevations in diastolic blood pressure  $\geq 8$  mmHg were observed in 1064 (25%) placebo-treated patients and 20700 (22%) ADDERALL XR<sup>®</sup>-treated patients. Similar results were observed at higher doses.

In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%) subjects administered 10 mg and 20 mg ADDERALL XR<sup>®</sup>, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared within 2 to 4 hours post-dose and not associated with symptoms.

The pre-treatment development program for ADDERALL XR<sup>®</sup> included exposures in a total of 1315 participants in clinical trials (835 pediatric patients, 356 adolescent patients, 240 adult patients, 52 healthy adult subjects). Of these, 835 patients (ages 6 to 12) were evaluated in two controlled clinical studies, an open-label clinical study, and two single-dose clinical pharmacology studies (N=46).

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 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% (70/425) of ADDERALL XR<sup>®</sup>-treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.1% (7/258) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR<sup>®</sup> 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<sup>®</sup> for 12 weeks or more.

Adverse event	% of pediatric patients discontinuing (N=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Conduct disorder	1.0
Depression	0.7

Insomnia, 7% (n=2) each for headache, palpitation, and somnolence; and, 8.5% (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 adolescents and adults, respectively, treated with ADDERALL XR<sup>®</sup> or placebo are presented in the tables below. Physicians 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 investigations. 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.

The following adverse reactions have been associated with the use of amphetamine, ADDERALL XR<sup>®</sup>, or ADDERALL<sup>®</sup>: Cardiovascular: Palpitation, 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, dysphoria, dysphoria, depression, anxiety, headache, exacerbation of motor and phoric 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, rash, hypersensitivity reactions (including angioedema and anaphylaxis). Serious skin reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported.

**Endocrine:** Impotence, changes in libido.

**DRUG ABUSE AND DEPENDENCE**  
ADDERALL XR<sup>®</sup> 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 levels many times higher than recommended. Abrupt cessation following prolonged use of amphetamines may result 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 with amphetamines, often directly indistinguishable from schizophrenia.

**OVERDOSE**  
Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

**Symptoms:** Manifestations of acute overdose include anorexia, hyperreflexia or hyporeflexia, tachycardia, hypertension, 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 guidelines 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 recommendations in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if hyperosmolarity is present. If acute severe hyperreflexia 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. Sympathomimetic antagonists are the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

If prodromal symptoms of hypotension and circulatory collapse, gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

**Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR<sup>®</sup> with Higher Incidence Than on Placebo in a 524 Patient Clinical Study**

Body System	Preferred Term	ADDERALL XR <sup>®</sup> (n=214)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Anorexia (hunger)	2%	0%
	Fever	3%	2%
	Weight loss	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
Nervous System	Dizziness	2%	0%
	Emotional Lability	3%	2%
	Insomnia	17%	2%
Metabolic/Nutritional	Nervousness	8%	2%
	Weight Loss	4%	0%

**Table 2 Adverse Events Reported by 5% or more of Adolescents (weighing  $\geq 75$  kg) Receiving ADDERALL XR<sup>®</sup> with Higher Incidence Than Placebo in a 267 Patient Clinical Forced-Washout Study\***

Body System	Preferred Term	ADDERALL XR <sup>®</sup> (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
	Weight loss	5%	0%
Digestive System	Loss of Appetite <sup>†</sup>	36%	2%
	Diarrhea	6%	0%
Nervous System	Insomnia <sup>†</sup>	12%	4%
	Nervousness	6%	0%
Metabolic/Nutritional	Weight Loss <sup>†</sup>	8%	0%