

Genome Scan Reveals Areas Linked to Alcoholism

BY JEFF EVANS
Senior Writer

The most extensive analysis of genetic variations more common in people with alcohol dependence than in healthy controls has identified 51 small chromosomal regions spread across the genome that hold genes with various important functions, reported Catherine Johnson of the National Institute on Drug Abuse and her associates.

"This identification provides the first genome-wide, association-based assessment for genomic loci likely to contain variants that contribute to dependence on alcohol," wrote Ms. Johnson of the intramural research program in the molecular neurobiology branch at the institute in Baltimore, and her associates.

Previous research has shown that a substantial portion of the regions where these genes are located have been associated with alcoholic and other addictive

phenotypes, according to Ms. Johnson and her colleagues.

The researchers identified and pooled together samples from 120 unrelated alcohol-dependent individuals and then pooled a separate group of samples from 160 unrelated, unaffected controls who self-reported European American ethnicities. Most of the healthy control participants had married into the pedigrees, which were collected as part of the Collaborative Study on the Genetics of Al-

coholism (Am. J. Med. Genet. B Neuropsychiatr. Genet. Epub ahead of print 2006;DOI:10.1002/ajmg.b.30346).

Instead of conducting association and linkage studies with whole family pedigrees, the investigators performed association genome scanning to assess the location and significance of the relationships among many more single nucleotide polymorphisms (SNPs) than would be possible with these other techniques, the investigators said.

Using a new kind of SNP microarray chip, the investigators assessed a set of 104,268 SNPs that were localized to the autosomal chromosomes. In each of the sample pools, alleles with frequencies of 2% or higher could be identified, allowing the study of many more SNP markers for

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more unrelated individuals than were previously available.

From these 104,268 SNPs, the investigators narrowed their analysis down to 188 SNPs that lay in 51 clusters in people with alcohol dependency. These clusters had to

contain at least 3 SNPs that were close to one another and have an allele frequency that was significantly different from that of the controls.

Of the 26 candidate genes that were identified within these clusters, 10 also had been identified in the results of other association and linkage studies of addictions in European American, African American, and Japanese individuals who were dependent on at least one substance.

"This level of replication is especially remarkable, since these convergences were sought for samples from different ethnic backgrounds and different addictions," Ms. Johnson and her associates said.

The candidate genes that were identified in the study involve a potassium channel, intra- and intercell-signaling molecules, enzymes that convert propeptides to biologically active peptides, phospholipid-signaling pathways, regulatory and developmental genes that could alter brain development and/or adult form and function, cell adhesion molecules and their possible ligands, as well as those that encode proteins with unknown function, they noted.

"While these data nominate interesting genes, it is only confirmation in multiple data sets in ongoing and future studies that will link each of them securely to addiction vulnerability," the researchers cautioned.

However, this investigation represents a step forward in the area of identifying genetic pathways to addiction. "As we identify more and more of the allelic variants that contribute to vulnerability to abuse of alcohol and other substances, we will be better able to understand addictions themselves," they said.

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules

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 a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode 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; such screening 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 a prior history of psychotic 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 0.1% (4 patients) with events out of 3,482 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 trials and the post marketing experience of some medications indicated for the treatment of ADHD. Although 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 ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 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 this period of development. In the 7-week double-blind placebo-controlled study of Focalin® XR (dexmethylphenidate extended-release capsules), the mean weight gain was greater for patients receiving placebo (+0.4 kg) than for patients receiving Focalin XR (-0.5 kg). Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment 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 abnormality, 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 Disturbance

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

Use in Children Under Six Years of Age

Focalin XR should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

Drug Dependence

Focalin XR should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parental abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients

Patient information is provided at the end of this insert. To assure safe and effective use of Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules, the patient information should be discussed with patients.

Drug Interactions

Focalin XR should not be used in patients being treated (currently or within the preceding two weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Because of possible effects on blood pressure, Focalin XR should be used cautiously with pressor agents. Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Dexmethylphenidate is metabolized primarily to *D*-ritalinic acid by de-esterification and not through oxidative pathways. The effects of gastrointestinal pH alterations on the absorption of dexmethylphenidate from Focalin XR have not been studied. Since the modified release characteristics of Focalin XR are pH dependent, the coadministration of antacids or acid suppressants could alter the release of dexmethylphenidate.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally-acting alpha-2-agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week study of racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed doses of the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60-74 mg/kg/day of racemic methylphenidate.

Dexmethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, or the *in vivo* mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day.

Pregnancy

Pregnancy Category C

In studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed.

At the highest doses tested, plasma levels (AUCs) of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with 20 mg/kg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. Focalin XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Focalin XR is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Focalin XR in children under 6 years old have not been established. Long-term effects of Focalin XR in children have not been well established (see WARNINGS).

In a study conducted in young rats, racemic methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of racemic methylphenidate on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the racemic MRHD on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules was administered to 46 children and 7 adolescents with ADHD for up to 7 weeks and 206 adults with ADHD in clinical studies. During the clinical studies, 101 adult patients were treated for at least 6 months.

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, MedDRA 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. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Continued brief summary of prescribing information from previous page.

Adverse Events in Acute Clinical Studies with Focalin® XR – Children

Adverse Events Associated with Discontinuation of Treatment

Overall, 50 of 684 children treated with Focalin immediate-release formulation (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each). None of the 53 Focalin XR-treated pediatric patients discontinued treatment due to adverse events in the 7-week placebo-controlled study.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin® XR-Treated Patients

Table 1 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible Focalin XR doses of 5-30 mg/day. The table includes only those events that occurred in 5% or more of patients treated with Focalin XR and for which the incidence in patients treated with Focalin XR was at least twice the incidence in placebo-treated patients. 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.

	Focalin® XR N=53	Placebo N=47
No. of Patients with AEs		
Total	76%	57%
Primary System Organ Class/ Adverse Event Preferred Term		
Gastrointestinal Disorders	38%	19%
Dyspepsia	8%	4%
Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	20%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

¹Events, regardless of causality, for which the incidence for patients treated with Focalin XR was at least 5% and twice the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events in Clinical Studies with Focalin® XR – Adults

Adverse Events Associated with Discontinuation of Treatment

In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin® XR-Treated Patients

Table 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. 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.

	Focalin® XR 20 mg N=57	Focalin® XR 30 mg N=54	Focalin® XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	6%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

¹Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

	Focalin® XR 20 mg N=57	Focalin® XR 30 mg N=54	Focalin® XR 40 mg N=54	Placebo N=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Adverse Events with Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

- Cardiac:** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia
 - Gastrointestinal:** abdominal pain, nausea
 - Immune:** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura
 - Metabolism/Nutrition:** anorexia, weight loss during prolonged therapy
 - Nervous System:** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis
 - Vascular:** blood pressure increased or decreased, cerebral arteritis and/or occlusion
- Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:
- Blood/Lymphatic:** leukopenia and/or anemia
 - Hepatobiliary:** abnormal liver function, ranging from transaminase elevation to hepatic coma
 - Psychiatric:** transient depressed mood, aggressive behavior
 - Skin/Subcutaneous:** scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG USE AND DEPENDENCE

Controlled Substance Class

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

Store at 25°C (77°F), excursions permitted 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] Dispense in tight container (USP).

Focalin® XR is a trademark of Novartis AG. This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders, 4th ed. Washington DC: American Psychiatric Association 1994.

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