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Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules

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.

Table 2
Treatment-Emergent Adverse Events¹ Occurring During Double-Blind Treatment – Adults

	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	5%	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.

Table 3
Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	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; **Hepatic/Biliary:** 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 ABUSE 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.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center

The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdose with methylphenidate.

Recommended Treatment

As with the management of all overdose, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdose has not been established.

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

SODAS® is a trademark of Elan Corporation, plc.

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.

Gene Expression May Be 'Therapeutic Target' for Stroke

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — Characteristic patterns of gene expression in blood samples can now identify patients with migraine, Tourette's syndrome, neurofibromatosis type 1, tuberous sclerosis type 2, Down syndrome, and early ischemic stroke, among other diseases, Dr. Frank Sharp said at the annual meeting of the American Neurological Association.

The notion that genomic expression can provide a fingerprint of a disease is increasingly proving to be true, although the patterns in blood are not as robust as those found in tissue and are sometimes seen in complex combinations, said Dr. Sharp, who is professor of neurology at the M.I.N.D. Institute, University of California, Davis.

The findings in stroke are particularly intriguing, however, with profound implications for better understanding the timing and nature of inflammatory responses to acute stroke, which in turn could aid in early diagnosis, prognosis, and treatment. Dr. Sharp and his associates have identified shifting alterations in the gene expression in blood cells in response to stroke, reflecting the release of proteins, changes in neurotransmitters, and immunologic responses.

Early results of a University of Cincinnati trial found that a set of 18 genes involved in leukocyte activation and inflammation correctly identified ischemic stroke in 10 of 15 patients at 3 hours, 13 of 15 patients at 5 hours, and all 15 patients at 24 hours post stroke.

Patients who had been taking aspirin

prior to their strokes had a significantly different genomic expression of 143 genes when their blood samples were compared with samples from patients who were not taking aspirin prior to enrollment in the Combined Approach to Lysis Utilizing Eptifibatid and rt-PA in Acute Ischemic Stroke (CLEAR) trial.

"This is, in fact, a biologic response to dying tissue ... white [blood] cells sensing dead brain or unhappy brain. It's [valuable for] much more than just diagnosis. In my mind, every single one of these genes ... is a potential therapeutic target for stroke."

Polymorphonuclear leukocytes and monocytes drive the distinguishing genetic profile of ischemic stroke. But genetic expression of CD8 and natural killer cells are more pronounced in the fingerprint for Tourette's syndrome. For migraine, monocyte platelet genes are the ones to watch. "It turns out that for autism, lupus, and rheumatoid arthritis ... we can map these genes onto these cell types and they're all different.

"You can see a profile in every muscular disease. What we don't know is how specific these profiles are," he said. Not every disease will be equally amenable to categorization. Five genes in the blood differentiate neurofibromatosis type 1 and tuberous sclerosis type 2, for example.

The profile of Down syndrome involves 200 genes, and the genetic fingerprint looks different still in Down syndrome patients with congenital heart disease.

Dr. Sharp acknowledged the contributions of many colleagues in his pursuit of an understanding of blood genomics, including Dr. Yang Tang, who is also at the University of California, Davis. ■

Physicians, Others Face Greater Risk of Developing Parkinson's

BY MARY ELLEN SCHNEIDER

Senior Writer

Physicians and individuals with 9 or more years of education are at an increased risk of developing Parkinson's disease, according to a study by Dr. Roberta Frigerio of the Mayo Clinic in Rochester, Minn., and her colleagues.

Individuals such as construction and extractive workers, production workers, metal workers, and engineers who have more physically demanding jobs are at a reduced risk for the disease, the researchers found (*Neurology* 2005;65:1575-83).

The researchers examined the education levels and occupations of 202 individuals in Olmsted County, Minn., who developed Parkinson's disease from 1976 through 1995. Each case was matched by age and sex to a general population control who was free of Parkinson's disease and living in the same county. Of those individuals, they were able to obtain medical records for 196 cases and 196 controls. In addition, they obtained data from telephone interviews available for 149 cases

and 129 controls. But the findings should not be a cause for alarm among physicians or those with higher levels of education, Dr. Demetrius Maraganore, a professor of neurology at the Mayo Clinic and one of the study authors, said in an interview.

The number of physicians in the study was small and therefore the effect size is unstable. "Parkinson's disease is a thousand-piece puzzle," Dr. Maraganore said.

More research is needed to figure out what these findings mean. For example, the findings could mean that being a physician is an indirect marker for other environmental factors. Or it could be that being a physician or having more education are not risk factors at all, Dr. Maraganore said. Instead, additional years of schooling and becoming a physician could be early manifestations of the disease, which affects personality and behavior.

Parkinson's disease is marked by a deficiency of dopamine, which is important to personality. A deficiency of dopamine could shape personality in a way that makes a person more inclined to sit at a desk and study, he said. ■