Continued brief summary of prescribing information from previous page.

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 Events[1] 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%

[1]Events, 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; ***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 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 overdosage, 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 overdosage with methylphenidate.

Recommended Treatment

As with the management of all overdosage, 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 overdosage 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.

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Use of Racially Targeted Drug Therapy Questioned

BY JOYCE FRIEDEN
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WASHINGTON — Drugs like BiDil that target a particular racial or ethnic group do not represent the best approach for looking at health disparities, Dr. Francis S. Collins said at a meeting sponsored by the Department of Health and Human Services and the Office of Minority Health.

"It is a good thing that we have a drug that treats individuals with congestive heart failure and clearly improves their survival," said Dr. Collins, director of the National Human Genome Research Institute, in Bethesda, Md. "But are we sure that this came about in a way that actually makes the most sense? Are we sure this drug would not have benefited other groups?"

Although the original clinical trial for BiDil (fixed-dose isosorbide dinitrate and hydralazine) appeared to show that only African Americans clearly benefited from the drug, "it was a relatively modest-sized study, and there could very well have been some benefit in others," Dr. Collins said. "Are we sure that this has anything to do with being African American, or could it be that since African Americans tend to have heart failure on the basis of hypertension, that this [study] says this drug works for hypertensive heart failure and not as well for heart failure from coronary artery disease, which is perhaps more common in other groups?"

Separating people into races is problematic, partly because the makeup of all humans is quite similar. People are 99.9% the same, genetically speaking.

With the responders lumped into the category of a racial group, "there's a real risk that this will be interpreted as, 'Oh, well, that means black people really are biologically different. After all, there is this drug that only works for them,'" said Dr. Collins. "That is unjustified by the science that's been done here."

More drugs like BiDil may be coming, but "I don't think this is where we want to go," he said. "I think we want to go in the direction of figuring out, 'Okay, if this drug works for some people and not others, why is that? What specific DNA variants are responsible for the variation in response?' Let's check the individuals and find out whether they're likely to respond to the drug or not, and not use this very murky and potentially misleading and damaging proxy called race, and pretend that we're practicing really upscale medicine. We can do better than that."

Part of the problem with using racial groups to explain health disparities is that race is hard to define, Dr. Collins noted. "First you have to decide exactly what you mean by race. Race has so much baggage; it carries with it connotations of history and discrimination, culture and society, and dietary practices. It carries a little bit of ancestral geography, of course, but that is probably in the minority of what most people are actually thinking of when the term race appears in the census," he said.

Another problem with separating people into races is that the genetic makeup of all humans is actually quite similar, said Dr. Collins, who leads the Human Genome Project. He noted that people are 99.9% the same, genetically speaking.

"We are much more alike … than most other species on the planet. There's more diversity in a small group of chimpanzees living on one hillside than there is in the entire human race, because we're so new on the scene."

Most of the variation in the human genome over the last 100,000 years "relates to the ways in which those genes were spread as those people migrated out of Africa to other parts of the world," he said. And while genomics may play a role in the reasons for health disparities, "it is almost always in concert with environmental factors." When new mutations have occurred, for the most part they appear and then disappear, according to Dr. Collins. One exception to that, however, is any mutation that gave people a selective advantage. Skin color is an example.

"If you're dark-skinned in a northern climate where there's not as much sun exposure, you're likely to get rickets, and someone with rickets will have a difficult time in childbirth," he said. "Whereas, if you have light skin at the equator, you're going to end up with a very high risk of skin cancer."

The way that lighter-skinned people evolved from their starting point as black Africans just proves the fact that "we white people are actually mutants," he added.

Now that the Human Genome Project and other private groups have decoded the human genome, researchers are focusing on the 0.1% of the genome that varies among individuals. Dr. Collins is currently managing the International HapMap Project, a cooperative effort among researchers in six countries to build a catalog of human genetic variation.

"In the space of just 3 years, the HapMap has delivered this remarkable picture of how DNA variation has occurred across all chromosomes," he said. "This has been a gold mine of information for people trying to unravel the genetic contributions of diabetes, heart disease, mental illness, blindness, and a whole host of conditions that fill up our hospitals and our clinics."

If medical researchers really want to know how genetic variation affects predisposition to illness, "we're going to need more data, and the good news is, in another 2 or 3 years, we're going to have a lot more data on this subject and will be much more poised to do something about it," he said. ■

International HapMap Project information can be found online at www.hapmap.org.