

Fluoxetine Offers No Benefit for Anorexia Patients

BY TIMOTHY F. KIRN
Sacramento Bureau

TORONTO — Fluoxetine failed to prevent relapse of anorexia nervosa in the largest controlled medication trial to date exploring the issue, Dr. B. Timothy Walsh reported at the annual meeting of the American Psychiatric Association.

"Antidepressants don't offer patients with anorexia nervosa very much," said Dr. Walsh, director of the eating disorders

research unit of the New York State Psychiatric Institute, New York City. "We can't say for sure that an antidepressant other than fluoxetine wouldn't have an effect, but it would surprise me."

The study represents yet another failure to find an efficacious medical treatment for anorexia. These failures imply that anorexia is unlike any other psychiatric condition, Dr. Walsh said.

"Interventions that are useful for other sorts of possibly related disorders don't

work terribly well for anorexia nervosa," he said. The only evidence-based treatment for anorexia is cognitive-behavioral therapy (CBT), which helps, but "not a lot," he added.

The investigators, whose results were later published, compared fluoxetine with placebo in a clinical trial involving 93 patients who had completed intensive treatment and maintained a body mass index (BMI) of at least 19 kg/m² for at least 2 weeks. The patients, all female, were aged

16-45 years and were treated at two medical centers that had extensive experience treating the disorder. The mean age of the patients was 23 years, and the average BMI of the subjects at the start of the trial was 20 (JAMA 2006;295:2605-12).

Subjects were randomly assigned to receive 20 mg daily of fluoxetine (49 patients), with a goal of increasing to 60 mg, or placebo (44 patients). They were monitored by a psychiatrist for dosing, adverse effects, and general medical status. They also received CBT.

The subjects underwent assessments of depression, anxiety, self-esteem, and quality of life every month. They were followed for 50 weeks, or until they either relapsed,



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DR. WALSH

defined as falling back to a BMI of 16.5 for 2 weeks, or dropped out of the study.

At 25 weeks, 48% of the 49 fluoxetine-treated subjects had either dropped out or relapsed, versus 39% of the placebo controls. At 50 weeks, 58% of the fluoxetine-treated subjects and 55% of the controls had either dropped out or relapsed.

To pick up on any possible benefit of the drug, Dr. Walsh and his colleagues also considered just those who relapsed, and those who relapsed plus those who clinically appeared to be in trouble when they dropped out—either because their BMI had dropped to 17 or because they had begun bingeing and purging again, at least twice a week.

At 50 weeks, 27% of the fluoxetine-treated patients and 29% of the placebo controls were documented relapsers.

Considering as failures both those with documented relapse and those who clinically appeared to be not doing well when they dropped out, the percentages were 49% fluoxetine and 51% placebo.

Dr. Walsh said he also looked only at those with depression, and at those who purged or restricted food only, and treatment still made no difference in those particular patients. "However we cut it, we can find no evidence that fluoxetine prolongs time to relapse following successful initial treatment, and we've looked pretty hard," Dr. Walsh said.

In an editorial comment accompanying the published report, Dr. Scott J. Crow of the University of Minnesota, Minneapolis, said, "While the results of previous relapse prevention trials have been mixed, the report by Walsh and colleagues has many strengths and appears convincingly negative" (JAMA 2006;295:2659-60).

The study amply demonstrates that antidepressant therapy, "a fairly common treatment practice for this illness," provides no benefit, Dr. Crow noted.

Additional reporting was done by contributing writer Mary Ann Moon.

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules

for the presence of cardiac 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 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 hydrochloride) 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 height or 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 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 parenteral 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 diets containing 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 impact 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/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 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.

Continued brief summary of prescribing information from previous page.

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.

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.

Table 1
Treatment-Emergent Adverse Events¹ Occurring During Double-Blind Treatment – Pediatric Patients

	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		
Dyspepsia	38%	19%
Metabolism and Nutrition Disorders		
Decreased Appetite	8%	4%
Nervous System Disorders		
Headache	34%	11%
Psychiatric Disorders		
Anxiety	30%	9%
Insomnia	25%	13%
Tachycardia	26%	11%
Weight loss	8%	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 incidence 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				
Dry Mouth	28%	32%	44%	19%
Dyspepsia	7%	20%	20%	4%
Nervous System Disorders				
Headache	5%	9%	9%	2%
Psychiatric Disorders				
Anxiety	37%	39%	50%	28%
Insomnia	26%	30%	39%	19%
Weight loss	40%	43%	46%	30%
Respiratory, Thoracic and Mediastinal Disorders				
Pharyngolaryngeal Pain	5%	11%	11%	2%
Tachycardia	16%	9%	15%	8%
Weight gain	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; **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 16-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.

REFERENCE

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

You can also call 1-888-NOW-NOVA (1-888-669-6682).

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