



RADIOLOGICAL SOCIETY OF NORTH AMERICA

Violent Videos Alter Brain Functioning, Study Shows

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CHICAGO — Adolescents who play violent video games demonstrate distinct alterations in brain activation on functional magnetic resonance imaging, investigators have shown for the first time.

In a study of 44 healthy adolescents, the

teens who played violent video games demonstrated less activation in the frontal lobes associated with inhibition, concentration, and self-control, and more activation in the amygdala, which governs emotional arousal, Dr. Vincent Mathews reported at the annual meeting of the Radiological Society of North America.

Additional research is needed to determine if this combination of effects could make these individuals more likely to engage in violent behavior. But for now, the study provides parents, physicians, and scientists with data proving that differences in brain function exist in teens who play violent video games, compared with those who don't.

"The fact [that] we are seeing something should at least alert people to the fact [that] something is going on, and that they should be concerned with the types and amount of media they and their children are exposed to," Dr. Mathews said in an interview.

He and his colleagues at Indiana University, Indianapolis, randomly assigned the adolescents to play either "Medal of Honor," a violent video game, or "Need for Speed," an equally exciting but nonviolent game, for 30 minutes immediately before imaging. Functional MRI data were acquired on a 3-Tesla scanner using a 2D gradient echo-planar imaging sequence during two modified Stroop paradigms.

In the emotional Stroop task, participants pressed different buttons according to the color of the visually presented words. Words indicating violent actions such as "hit" or "harm" were interspersed with nonviolent action words such as "run" or "walk." In the counting Stroop task, participants were required to press buttons to indicate the number of displayed objects, with X's used as control events and numerals presented as activation stimulation.

There was no difference between groups in age, gender, IQ, video playing expertise, or overall violent media exposure. Their mean age was 15 years, and the average IQ was 110 in the nonviolent game group and 108 in the violent game group. There was no significant difference between groups in accuracy or reaction time during the tasks.

The group that played the nonviolent game showed more activation in the frontal lobes, including the anterior cingulate and dorsolateral prefrontal cortex, during both Stroop tasks, reported Dr. Mathews, a professor of radiology at the university.

The group that played the violent game demonstrated less activation in prefrontal lobes during both tasks and increased activation in the right amygdala during the emotional Stroop task. These differences remained after controlling for previous violent media exposure and gender, he said.

"There is a little bit more credence to [physicians] recommending limiting this activity," he said, adding that further study is needed to examine behavior and duration of effect in adolescents who watch violent videos.

Functional MRI findings show less brain activation in the frontal lobes and more activation in the amygdala in teens playing violent versus nonviolent video games.

Focalin XR (dexamethylphenidate 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 (dexamethylphenidate) 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 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 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 (dexamethylphenidate 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.

Dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate.

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 dexamethylphenidate. 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 increased tumor incidence. 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.

Dexamethylphenidate 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 Category C
In studies conducted in rats and rabbits, dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate 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 dexamethylphenidate 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 (dexamethylphenidate 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%
Dysphagia	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

*Events, 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	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

*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.

	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 (dexamethylphenidate 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.