Study of Anxiety, Physical Conditions Is a First

BY MARY ANN MOON Contributing Writer

nxiety disorders are associated with a broad range of physical conditions, including respiratory diseases, gastrointestinal diseases, arthritic conditions, allergic conditions, thyroid diseases, and migraines, reported Dr. Jitender Sareen of the University of Manitoba, Winnipeg, and his associates.

The researchers conducted what they

Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules

electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syn-cope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation. Psychiatric Adverse Events Pre-Existing Psychesis Administration of stimulants may eveneted crusts f stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a hotic disorder.

Iness care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of r possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a situation with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar dis-th screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder,

d depression. **hergence of New Psychotic or Manic Symptoms** atment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and ado-cents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms cur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be propriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about % (4 patients with events out of 3.482 exposed to methyphenidate or amphetamine for several weeks at usual doses) stimulant-treated patients compared to 0 in placebo-treated patients.

But by (1) patients who would be compared to 0 in placebo-threated platients. 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. Long-Term Suppression of Growth. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methydhenidate or non-medication treatment for ADHD. Although there is a no systematic evidence that stimulants cause 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 methydhenidate treated and non-medication treatment for ADHD. Shows and the set of the ages of 10 to 13 years), suggests that consistently medicated or hidren (lags and the obstown of evidence of growth reated on the set of development. In the 7-week double-bind placebo-controlled study of Focalin® XR (development). In the 7-week double-bind placebo-controlled study of Focalin® XR (dexmethydhenidate freese capsules, the mean weight gain was greater for platients receiving placebo (14 kg) than for platests receiving Focalin XR (Foc Ng). Published to data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; situate to determine whether there well. Therefore, growth should be monifored during in greater that by likely have a rest. **Seizures** There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of eizures, **Seizures**

Sources Secures Secures Secures Secures in patients with prior history of seizures in patients with prior EEG automatilies 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.

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. hydrochloride) extended-release capsures, the patient monimation should be detected at the patient monimation should be detected at the patient 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. Deximethylphenidate is metabolized primarity to d-ritalinic acid by decesterification and not through oxidative pathways.

Dexmethylphenidate is metabolized primarily to d-ritalinic acid by de-esterification and not through oxidative pathways. The effects of apactonicestinal 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 anti-coagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., impiramine, clomipramine, desipramine). Downward does 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 Impirment of Fertility**

Serious adverse events have been reported in concomment use with obstance, the centrally-acting alpha-2-agonists has not been systematically evaluated. Carcinogeneists, and Impairment of Fertility Lifetime carcinogeneist, Mutageness, and Impairment of Fertility Lifetime carcinogeneist, subtageness, and Impairment of Fertility arried out in BGG3F1 mice, rearemic methylphenidate cause of an increase in hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant thepatocellular 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 thepatocellular 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 thepatocellular adenomas, and in males only, an increase in hepatoblastomas at a daily dose of approximately 45 mg/kg/day. In a 24-week study of racenim emblylphenidate in the transgenic mouse strain p53+/, which is sensitive to genotoxic carcinogenicity the high-dose group was exposed to 60-74 mg/kg/day of racenic methylphenidate. Dexmethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivio* nithe mouse byom parrow micronucleus sasay. Recenic methylphenidate in cultured chinese Hamster Ovary (CHO) cells. Racenic methylphenidate in cultured chinese Hamster Ovary CHO) cells.

18-week Continuous breeding study, the series, and Prepnancy Calegory C Instlucties 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 feta 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, postwaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnati 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 throunhout organogenesis.

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

Mothers nown whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, hould 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 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 Qay 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Veeks 13-14), decreased spontaneous to comotor adults (Weeks 10). Observed in mates and females previously freaded with 50 mg/kg/day (approximately 6 limes) the maximum recommended to beerved in metes and termates and termates previously freaded with 50 mg/kg/day (approximately 6 limes) the maximum recommended to beerved in metes and termates previously freaded with 50 mg/kg/day (approximately 6 limes) the maximum recommended limes and termates and termates were started with 50 mg/kg/day (approximately 6 limes). The mate and termates and termates and termates and termates and termates and termates were started with 50 mg/kg/day (approximately 6 limes). The provide the holp-term behavioral effects observed in rats is unknown. ADVERSE REACTIONS

QUVERSE REACTIONS occalm[®] XR (downethylphenidate hydrochloride) extended⊣release capsules was administered to 46 children and 7 adoles-ents with ADHD for up to 7 weeks and 206 adults with ADHD in clinical studies. During the clinical studies, 101 adult adients were treated for at least 6 months.

patients were treated for at least 6 months. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using ter-minology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of indi-viduals 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.

described as the first study aimed at systematically evaluating the association between anxiety disorders and physical conditions in a large epidemiologic sample that included standardized physician-based diagnoses. They used data from the German Health Survey, a nationally representative sample of more than 4,000 members of the German population aged 18-79 years in 1997-1999.

Subjects were assessed for 44 physical conditions and for panic disorder, agoraphobia, social phobia, simple phobia, generalized anxiety disorder, and obsessivecompulsive disorder, Dr. Sareen and his associates reported.

The presence of an anxiety disorder was associated with respiratory diseases such as asthma and chronic bronchitis; gastrointestinal diseases such as gastritis and ulcer; arthritic conditions such as inflammatory joint disease; allergic conditions such as hay fever, eczema, hives, food allergy, and conjunctivitis; thyroid

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, insommia, and tachycardia (approximately 1% each). None of the 53 Focalin XR-treated pediatric patients discontinued to adverse events in the 7-week placebo-controlled study. Adverse Events Occurring at an Incidence of 5% or Marc Among Focalin® XR-treated Patients Table 1 enumerates treatment use to adverse events in the 7-week placebo-controlled, paralle-group study in children and ado-lescents with AbHD at flexible Focalin XR toges 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 AR was at least twice the incidence in placebo-treated platents. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events. 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 prevaled in the chincal tracks. 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 pro-vide the precision playnsicians involving different treatments, uses, and investigators. The cited figures, however, do pro-vide the precision playnsicians involving different treatments, uses, and investigations of drug and non-drug factors to the adverse event incidence rate in the population studied. Table 1

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	38%	19%
Dyspepsia	8%	4%
Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

ancrexia (1,2%, n=2), and anxiety (1,2%, n=2) were the reasons for decontinuation reported by more than 1 patient. Adverse Events Occurring at an Indidence of 5% or More Among Foccurr® XA-Treated Patients Table 2 enumerates treatment-benergent adverse events for the placeb-controlled, paralle-prove study in adults with ADHD at thed focculin XA doess of 20, 30, and 40 mg/day. The table indudes only those events that occurred in 5% or more of with does. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in in the course of usual medical practice where patient characteristics and other factors differ from those which prevaled in the dimical trials. Similarly, the other frequencies cannot be used so biated 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.

12012 Z Treatment-Emergent Adverse Events ¹ Occurring During Double-Blind Treatment – Adults						
	Focalin® XR 20 mg	Focalin® XR 30 mg	Focalin® XR 40 mg	Placebo		
	N=57	N=54	N=54	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%		

 Imaging one ying entities 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 requency 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) Diastolic BP (mmHg) Weight (kg)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{c} 6.0 \pm 10.1 \\ 2.1 \pm 8.0 \\ -1.7 \pm 2.3 \end{array}$	1.4 ± 9.3 0.3 ± 7.8 0.1 ± 3.9

Adverse Events with Other Methylphenidate HCI Dosage Forms Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In chil-dren, loss of appetite, addominal 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 Gastrointestinat: addominal pain, nausea Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multi-forme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura

Immune, hypelsentiological findings of neorbizing vasculitis, and thrombogito, exolutive demanus, eryonenta mutu-forme with histopathological findings of neorbizing vasculitis, and thrombogito, exolutive demanus, eryonenta mutu-Metabolism/Nutrition: anorexia, weight loss during probinged therapy Metabolism/Nutrition: anorexia, weight loss during probinged therapy Nervous System: dizziness, drowsiness, dyskinesia, hadadare, 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: transient depressed mood, aggressive behavior Skin/Subucitameous: scalp hair loss Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were con-currently 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 venetaxine. 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 Focaling' XR (desmethylphenidate products, is classi-fored as Schwithe II. Unorthied but bottore but berdere trevelation causules, like other methylphenidate products, is classi-fored as Costhue II. Unorthied to ubstance but berdere trevelation causules, like other methylphenidate products, is classi-fored as Schwith II. Distributed but bottore but berdere trevelation causules, like other methylphenidate products, is classi-fored as Schwithe II. Onstrolled but bottore but berdere trevelation causules, like other methylphenidate products, is classi-

Drub Rubs Rub Dreferueruc Controlle 3 Ubistance Class Focaline[®] XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classi-fied as a Schedule II controlled substance by Federal regulation. Abuse, Dependence, and Tolerance See WARINNOS for boxed warming 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 tipt container (USP). Focaline[®] XR is a trademark of Novartis AG This product is covered by US patents including 5,837,284, 5,908,850, 6,226,398, 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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diseases; and migraine headaches.

Anxiety disorders were not found to be associated with cardiac disease, hypertension, or diabetes in this study.

In most cases of comorbidity, onset of the anxiety disorder preceded onset of the physical conditions, the investigators said (Arch. Intern. Med. 2006;166:2109-16).

Compared with subjects who had these physical conditions alone, those who had comorbid anxiety disorders were more likely to report a poor quality of life and significant disability because of the physical illness.

"These findings underscore the importance of recognition of comorbidity of anxiety disorders among people who present with these physical health problems," Dr. Sareen and his associates said.

The nature of this link between anxiety disorders and physical illnesses remains unclear. There may be a direct causal relationship mediated by biological mechanisms. Or there may be common genetic, environmental, or personality factors that underlie both types of disorders, the investigators noted.

Depression, Anxiety May Worsen Asthma

he presence of an anxiety or depressive disorder in asthmatic children aged 11-17 years is associated with an increase in asthma symptoms, reported Dr. Laura P. Richardson of the University of Washington, Seattle, and her colleagues.

'We found that youth with an anxiety or depressive disorder reported significantly more asthma symptom days than youth without anxiety or depressive disorders after controlling for asthma severity," reported Dr. Richardson and her associates.

The researchers conducted a telephone survey of 767 children and adolescents aged 11-17 with a history of asthma who belonged to a health maintenance organization in Washington State. The study participants were considered to have asthma if they met certain criteria for the number of office or emergency department visits, hospitalizations, and medication prescriptions for asthma in the 12- to 18-month period preceding the study (Pediatrics 2006;118:1042-51).

Nine percent of the study participants had an anxiety disorder, 2.5% had a depressive disorder, and 4.8% had both.

The results showed that the youth with an anxiety or depressive disorder reported more asthma symptom days in a 2-week period, compared with youth without one of these disorders: 5.4 symptom days, compared with 3.5 symptom days. In addition, compared with youth without an anxiety or depressive disorder, youth with one of these disorders were more likely to be girls, to have a parent without a college education, to have a recent asthma diagnosis, and to be taking one medication to control asthma symptoms.

-Sarah Pressman Lovinger