

From the CDC

All bicyclists should wear helmets

Making the wearing of helmets mandatory for all bicyclists is the best way to reduce bicycle-related injuries and deaths, say agency officials.

Currently, only Georgia and New Jersey have statewide laws requiring children to wear bicycle helmets. Fewer than 10% of all bicyclists in the United States wear a helmet. Children fare even worse: fewer than 2% of all children bicyclists don a helmet.

No link: HIV and CFS

Researchers found no link between the class of retroviruses that causes the acquired immunodeficiency syndrome (AIDS) and chronic fatigue syndrome (CFS). Investigators tested 68 CFS patients for retroviruses and compared the results with test results of 68 healthy persons.

False-positive results may have led scientists to prematurely link HIV and CFS in earlier studies, now say officials.

From the NIH

Vaccines tested in HIV-infected children

For the first time, the efficacy of three experimental vaccines is

being tested in children infected with the human immunodeficiency virus (HIV).

The 90 children participating in the trial range in age from 1 month to 12 years. All of the children are asymptomatic. Once the safety of the vaccines has been determined, future trials will examine whether the vaccines prevent, or at least delay, the progression of the HIV infection to the onset of the acquired immunodeficiency syndrome.

From the FDA

Approvals for MS, AD drugs pending

A medical advisory board has recommended that the genetically engineered drug Betaseron (interferon-beta) be approved for the treatment of multiple sclerosis (MS). In clinical trials, the genetically engineered drug reduced nerve damage and severe attacks associated with MS by 50%.

In a separate review process, an advisory panel unanimously recommended that the drug tacrine be approved for use in treating Alzheimer's disease. This recommendation was made despite less than optimal benefits.

"There is a beneficial effect, but it is not a drug for everyone," says Paul Leber, director of the drug division that supervised the testing of tacrine. About 12% of patients with Alzheimer's disease are expected to benefit from this drug. Side effects associated with tacrine ther-

apy include liver disease.

At presstime, no approval dates for either drug had been set.

Revised CVS sampling guidelines

New guidelines for chorionic villus sampling (CVS) have been established. Physicians are now advised to perform CVS on women no earlier than the 10th week of pregnancy. Previously, physicians were performing this test as early as the eighth week of gestation.

The timetable was revised in response to at least two studies published last year that associated birth defects with this sampling procedure.

"The FDA has to take a conservative approach; we'd be remiss if we didn't," says spokesperson Marcia Meyer.

The agency is also advising that women seek physicians who are experienced in performing CVS, as the risk of miscarriage is greater each time a placental tissue sample must be drawn.

Labeling on contraceptives strengthened

Over-the-counter and prescription contraceptives are required to carry more precise wording. The labeling change is part of an overall effort to educate the public concerning high-risk sexual behavior, particularly among adolescents and young adults.

Oral and injectable contracep-

(continued on page 551)

PAXIL™ (brand of paroxetine hydrochloride)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of depression.

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. See WARNINGS.)

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil* in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting a MAOI.

PRECAUTIONS: As with all antidepressants, use *Paxil* cautiously in patients with a history of mania.

Use *Paxil* cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Write *Paxil* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted.

Clinical experience with *Paxil* in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil* therapy does not affect their ability to engage in such activities. Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking *Paxil*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Concomitant use of *Paxil* with tryptophan is not recommended.

Use cautiously with warfarin. When administering *Paxil* with imipramine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. When co-administering *Paxil* with phenobarbital or phenytoin, no initial *Paxil* dosage adjustment is needed; base subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome P₄₅₀2D₆ (antidepressants such as amitriptyline, nortriptyline, imipramine, desipramine and doxepine; phenothiazines such as thioridazine; Type 1C antiarrhythmics such as propafenone, flecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug; approach concomitant use cautiously. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs. normals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil*. Erogenic compounds are known to affect reproductive function in animals. Impaired reproductive function in rats (i.e., reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups) was found at *Paxil* doses 5 or more times the highest recommended human dose.

Reproduction Category B. Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, there are no adequate and well-controlled studies in pregnant women. *Paxil* should be used in pregnancy only if the benefits outweigh the risks. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering *Paxil* to a nursing woman.

Safety and effectiveness in children have not been established.

In worldwide *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly; however, there were no overall differences in the adverse event profile between older and younger patients.

DIVERSE REACTIONS: Incidence in Controlled Trials—

Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events

associated with the use of *Paxil* (incidence of 5% or greater) were: incidence for *Paxil* at least twice that for placebo: asthenia (5% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (3% vs. 0%) and other male genital disorders (10% vs. 0%). Twenty-one percent (881/4,126) of *Paxil* patients in worldwide clinical trials discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include: somnolence, insomnia, agitation, tremor, anxiety, nausea,

diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating. The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more.

Body as a Whole: headache, asthenia, abdominal pain, fever, chest pain, trauma, back pain. **Cardiovascular:** palpitation, vasodilation, postural hypotension. **Dermatologic:** sweating, rash. **Gastrointestinal:** nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, vomiting, oropharynx disorder, dyspepsia, increased appetite. **Musculoskeletal:** myopathy, myalgia, myasthenia. **Nervous System:** somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, agitation, drugged feeling, myoclonus, CNS stimulation, confusion. **Respiration:** respiratory disorder, yawn, pharyngitis. **Special Senses:** blurred vision, taste perversion. **Urogenital System:** ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders.

Studies show a clear dose dependency for some of the more common adverse events associated with *Paxil* use. There was evidence of adaptation to some adverse events with continued *Paxil* therapy (e.g., nausea and dizziness). Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss. In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

Other Events Observed During the Premarketing Evaluation of Paxil: During premarketing assessment, multiple doses of *Paxil* were administered to 4,126 patients, and the following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions. It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it.

Body as a Whole: frequent: chills, malaise; infrequent: allergic reaction, carcinoma, face edema, moniliasis, neck pain; rare: abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** frequent: hypertension, syncope, tachycardia; infrequent: bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; rare: angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. **Digestive System:** infrequent: bruxism, dysphagia, eructation, gastritis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; rare: aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries. **Endocrine System:** rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** infrequent: anemia, leukopenia, lymphadenopathy, purpura; rare: abnormal erythrocytes, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia. **Metabolic and Nutritional:** frequent: edema, weight gain, weight loss; infrequent: hyperglycemia, peripheral edema, thirst; rare: alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesterolemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, SGOT increased, SGPT increased.

Musculoskeletal System: infrequent: arthralgia, arthritis; rare: arthrosis, bursitis, myositis, osteoporosis, tetany. **Nervous System:** frequent: amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; infrequent: abnormal thinking, akinesia, alcohol abuse, ataxia, convulsions, depersonalization, hallucinations, hyperkinesia, hyper-tonia, incoordination, lack of emotion, manic reaction, paranoid reaction; rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome. **Respiratory System:** frequent: cough increased, rhinitis; infrequent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; rare: carcinoma of lung, hiccups, lung fibrosis, sputum increased. **Skin and Appendages:** frequent: pruritus; infrequent: acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; rare: angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma. **Special Senses:** infrequent: abnormality of accommodation, ear pain, eye pain, mydriasis, otitis media, taste loss, tinnitus; rare: amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia.

Urogenital System: infrequent: abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; rare: breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, prostatic carcinoma, vaginal moniliasis.

Non-U.S. Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and may have no causal relationship with *Paxil* include elevated liver function tests (the most severe case was a death due to liver necrosis, and one other case involving grossly elevated transaminases associated with severe liver dysfunction).

DRUG ABUSE AND DEPENDENCE: Controlled Substance

Class: *Paxil* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, increments of dose, drug-seeking behavior).

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federal update (continued)

tives, birth control implants, intrauterine devices, and condoms are included in this labeling change. Specifically, the new regulations require the packaging to state that the particular product is intended to prevent pregnancy and *not* sexually transmitted diseases (STDs).

"There is a great deal of confusion out there," says Ruth Merkatz, special assistant for women's health at the agency.

Latex condoms are the only contraceptives that can claim efficacy in preventing the transmission of STDs.