

manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dyspnea, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and periparturition disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Post-Marketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Paroxetine hydrochloride is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE: Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdose during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdose include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdose Management: Treatment should consist of those general measures employed in the management of overdose with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CYP2D6*).

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSE AND ADMINISTRATION: Major Depressive Disorder: Usual Initial Dosage: Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics in full prescribing information).

Special Populations: Treatment of Pregnant Women During the Third Trimester: Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.



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short-term data on olanzapine for these two indications, on quetiapine (Seroquel) for treating schizophrenia in adolescents aged 13-17 years and bipolar mania in children and adolescents aged 10-17, and on ziprasidone (Geodon) for manic or mixed episodes associated with bipolar disorder in children and adolescents aged 10-17.

For olanzapine, the panel voted 11 to 5, with 2 abstentions, that the drug had been shown to be an effective treatment for schizophrenia in patients aged 13-17. Ten voted that it had been shown to be "acceptably safe" for this indication.

However, four panelists voted no on the safety question, and four abstained, citing concerns that included the well-known metabolic effects of olanzapine.

The panel also voted 17 to 0, with 1 abstention, that the drug had been shown to be effective for treating bipolar mania for the same age group and 11 to 4, with 3 abstentions, that it had been shown to be acceptably safe in this age

group for this indication. Those voting in the affirmative on safety and efficacy for both indications said they considered the drug as a second-line treatment because of its metabolic effects.

At the June meeting, Dr. Thomas Laughren, head of the FDA's Division of Psychiatry Products, said the olanzapine label would advise clinicians to consider other drugs before this one, because of concerns about its metabolic effects.

At a December meeting of the Pediatric Advisory Committee, Dr. Laughren noted that as a result of a comprehensive review of the weight gain associated with the atypical antipsychotics currently underway at the agency, information about the metabolic effects of the atypical antipsychotics probably would be moved to the boxed warning of the labels.

The panel unanimously agreed at that meeting that the current labeling does not adequately address the risk of weight gain associated with these agents. ■

More Long-Term Data Needed

The FDA's action is consistent with the data presented at the hearing last June. When used appropriately, medications such as olanzapine can be helpful in the treatment of children and adolescents with bipolar disorder or schizophrenia. However, we're well aware that they can also have very significant side effects.

I'm glad to see that the agency's action includes the addition of wording to the prescribing information, which specifically addresses the risk of weight gain and hyperlipidemia. I'm also pleased that it emphasizes the importance of obtaining a thorough diagnostic evaluation before starting medication and that it underscores the need for a comprehensive treatment plan.

My real concern is that the studies reviewed by the FDA were relatively short term. In actual clinical practice, most young people

take these medications for months and often years. Ultimately, physicians and parents need more data on safety and efficacy when medications such as olanzapine are used on a long-term or ongoing basis.

DR. DAVID FASSLER is a child and adolescent psychiatrist who practices in Burlington, Vt., and is clinical professor of psychiatry at the University of Vermont, Burlington. He testified on behalf of the American Psychiatric Association during the open public hearing portion of the June 2009 meeting of the FDA's Psychiatric Drugs Advisory Panel, during which olanzapine, quetiapine, and ziprasidone were reviewed for pediatric indications. He neither receives research or consultation funding from pharmaceutical companies nor participates in speakers bureaus.

Side Effects Vary by Diagnosis

ISTANBUL, TURKEY — The side effects of second-generation antipsychotics in young people vary not just by agent, but also by psychiatric diagnosis.

In a soon-to-be-published study involving 90 young patients on antipsychotic therapy, the 31 who were being treated for bipolar disorder experienced significantly greater weight gain over the course of 3 months than did the 29 patients with other psychotic disorders, who in turn gained significantly more weight than those with

nonpsychotic disorders, Dr. Mara Parellada said at the annual congress of the European College of Neuropsychopharmacology.

In a series of studies conducted by Dr. Parellada and her colleagues at Gregorio Maranon University Hospital, Madrid, patients with a first psychotic episode were randomized to one of several second-generation antipsychotics. The findings showed that the side effect profiles of these antipsychotics in youths differ substantially by diagnosis.

—Bruce Jancin