

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 dysphonia, 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 puerperal 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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Page 3 of 3

Watch for Conduct Disorder Plus ADHD

School-age children with these comorbidities may have elevated risk of later substance use.

BY BETSY BATES

LOS ANGELES — Early conduct disorder in children with ADHD predicts substance use disorders in adolescence and early adulthood, according to researchers who conducted a long-term prospective study on 778 children.

"I'm a child psychiatrist. I treat kids and work with families. I'd like to know in 10-year-olds, whom do I worry about?" said Dr. Timothy E. Wilens, who is a pediatric psychopharmacologist at Massachusetts General Hospital in Boston and lead investigator of a 10-year, prospective study of 361 children with ADHD and 417 matched controls.

Children aged 10-11 years and their families underwent extensive interviews, and at periodic intervals over the subsequent decade, culminating in a follow-up evaluation when subjects were in their early 20s.

His overall hypothesis—that attention-deficit/hyperactivity disorder (ADHD) in school-age children would confer an elevated risk of later substance use—was supported, with significant hazard ratios for any substance use of 2.15; alcohol use or dependence, 2.19; drug use or drug dependence, 4.12; and cigarette smoking, 3.21.

As expected, conduct disorder in a child with ADHD "solidly" and independently predicted substance use (hazard ratio, 5.26), including alcohol use or dependence (2.85), drug use or dependence (2.36), and cigarette smoking (2.74).

"We know conduct disorder is big," he said at the annual meeting of the American Academy of Addiction Psychiatry.

"What you may not know is that you can identify it in a 10-year-old pretty clearly, and if you see it in a 10-year-old, you know you're going to have a problem in adolescence."

What failed to materialize in the study was a hypothesized link to other independent risk factors for eventual substance use in children with ADHD.

Early difficulties with socialization, family environment, school performance, full-scale IQ or the digit span subtest, arithmetic skills, and a family history of ADHD or substance use all failed to significantly increase the risk of substance use over and above the baseline risk faced by children with ADHD.

Similarly, neither depression nor anx-

ety independently increased risk for substance use.

"Remember, we have a bit of a ceiling effect here," cautioned Dr. Wilens, who nonetheless expressed surprise at the results.

One strong trend that failed to reach significance because of a small sample size was a possible link between bipolar disorder and later substance use in children with ADHD.

Previous studies conducted by Dr. Wilens and his group also have drawn associations between substance use among older children with ADHD when they have experienced parental substance use during certain vulnerable

VITALS

Major Finding: Conduct disorder in a child with ADHD "solidly" and "independently" predicted substance use (hazard ratio, 5.26), including alcohol use or dependence (2.85), drug use or dependence (2.36), and cigarette smoking (2.74).

Data Source: Ten-year prospective, longitudinal case-control family study of ADHD youth (n = 361) and controls (n = 417) first assessed by comprehensive interview at about age 11 and, for most recent findings, at about age 20.

Disclosures: The presenter receives research support from numerous pharmaceutical companies that make medications used to treat ADHD. This study was funded exclusively by government grants, including from the National Institute of Mental Health.

developmental stages, he said.

Overall, however, Dr. Wilens said the study suggests that children with ADHD who do not have conduct disorder or severe mood dysregulation face a baseline elevated risk of substance abuse that is not exacerbated by other comorbidities.

He drew attention to a large body of research showing that substance use initiation is delayed if children with ADHD are well managed with medication, although the protective effects of medication are lost in adulthood.

"Aggressively treating the ADHD is really critical," he said.

He also advised careful assessment of potential conduct disorder in young children, which might present as a history of aggressiveness, bullying, a dearth of positive interactions with other children, harm to animals or younger children, a problematic response to parental discipline, and a lack of empathy.

Minor property damage such as breaking windows might be part of the picture in a 10-year-old, but conduct disorder is likely to look different in younger children, Dr. Wilens said.

"You're not going to see them stealing a car."