

POLICY & PRACTICE

Medicaid Limits Curb Rx Access

Medicaid limits on prescription drugs for mental illness often have adverse consequences for patients, according to a survey of 600 psychiatrists and 1,600 patients (Psychiatr. Serv. 2009;60:601-10). Researchers found medication access was a greater problem in states with more limits, such as prior authorization or restrictive formularies. More than a third of respondents said they could not get a therapy because Medicaid would not cover or approve it. About 30% said

the preferred medication could not be prescribed because it was not approved or because the patient could not afford the copay. In addition, the survey found that patients who have problems making a copayment were eight times more likely to suffer an adverse event. Those patients who had trouble accessing a medication experienced a 3.6 times greater likelihood of adverse events, including emergency room visits, hospitalizations, homelessness, suicidal ideation or behavior, or incarceration.

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. **Ritonavir**-Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. **CYP3A4 and -2C19 Inhibitors**-*In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Escitalopram is metabolized by multiple enzymes in humans. Inhibition of any single enzyme may not appreciably decrease escitalopram clearance. **Drugs Metabolized by Cytochrome P4502D6**-*In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. **Metoprolol**-Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)**-There are no clinical studies of the combined use of ECT and escitalopram.

USE IN SPECIFIC POPULATIONS: Pregnancy-Pregnancy Category C-In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy-Nonteratogenic Effects**-Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypoxemia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [see *Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse or major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breast-feeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [see *Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [see *Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [see *Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence-Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, 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, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, 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.

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Insurance Dictates Teens' Care

Health insurance is a major determinant as to whether adolescents with major depressive episodes receive treatment, according to a report by the Substance Abuse and Mental Health Services Administration (SAMHSA). The data are based on SAMHSA's 2007 National Survey on Drug Use and Health, which includes a representative sample of 22,000 adolescents. The survey found that 8% of adolescents aged 12-17 years had experienced at least one major depressive episode in the past year, but only 39% of them had received treatment. When broken down by insurance status, only 17% of uninsured teens got treatment, compared with 43% of those on Medicaid or a State Children's Health Insurance Plan, and 41% of those with private insurance.

Mental Illness Costly For Kids

The most expensive condition to treat in children in 2008 was mental illness, according to the Agency for Healthcare Research and Quality. Treating mental disorders in noninstitutionalized children 17 years or younger cost \$8.9 billion in 2008, according to the agency. The data are taken from the Medical Expenditure Panel Survey. The second-most expensive disorder was asthma, at \$8 billion, followed by trauma, at \$6.1 billion.

Pot Potency Doubles

Marijuana potency keeps rising. The latest figures from the University of Mississippi's Potency Monitoring Project, show tetrahydrocannabinol (THC) levels in marijuana are, for the second year in a row, the highest ever recorded. The project has analyzed marijuana samples for the National Institute on Drug Abuse since 1976. In 2008, an analysis of 1,500 samples found THC levels at 10.1%, a doubling since 1983, but up just slightly from the previous year, when THC levels were about 9.6%. The most potent sample had a THC concentration of 27%. The project also found that samples crossing the Southwest borders are as potent as what has been seen in domestic sources.

—Alicia Ault

Medicare Contractor Program Is Back on Track

The controversial Medicare Recovery Audit Contractor program is continuing as planned after federal officials cleared up some contracting disputes.

The rollout of the permanent, national Recovery Audit Contractor (RAC) program is proceeding, with the full implementation of the program expected across the country by Jan. 1, 2010.

Under the program, Medicare contracts with private companies to identify and correct improper payments made through the Medicare fee-for-service program. The contractors will be paid on a contingency fee basis for both the over- and underpayments that they identify.

During its demonstration phase, the RAC program came under fire from physician testers who said it placed the burden on physicians to prove that payments they received were correct.

Parity Comments Due

The federal government is seeking public comments before implementing the Mental Health Parity and Addiction Equity Act of 2008. The Health and Human Services department and the Labor department said they want to know the financial and treatment limits that health plans currently impose, their practices in determining medical necessity for and denying mental health benefits, and how plans handle out-of-network mental health benefits.

Using Methadone Safely

The Food and Drug Administration and SAMHSA have launched a public outreach program to teach consumers, health professionals, and clinicians on how to safely use methadone for pain and drug addiction treatment. Methadone poisoning deaths have been on the rise, tripling since 2004, according to the Centers for Disease Control and Prevention. FDA and SAMHSA are making available to the public and health professionals a brochure, poster, and fact sheet and have created an information sheet that pharmacies can give to patients.

PhRMA Revises Trial Standards

The Pharmaceutical Research and Manufacturers of America has revised its voluntary standards for how drug manufacturers run clinical trials and communicate trial results. The new standards call on drug makers to register on a public Web site all interventional clinical trials, including some phase I studies. The standards also call for companies to "greatly expand transparency" by providing summaries of results from all interventional clinical trials, regardless of whether the research is discontinued or the medication being studied is ever approved. The standards also call for drug makers to adopt the authorship standards of the International Committee of Medical Journal Editors.

—Alicia Ault

Last November, officials at the Centers for Medicare and Medicaid Services imposed an automatic stay on the program due to protests filed by two contractors who bid unsuccessfully to be part of the program. Under federal statute, the disputes were reviewed by the Government Accountability Office and a decision was issued earlier this year. As part of the settlement, two subcontractors have been retained to work with the four RACs announced last October.

With the RAC program back on track, the CMS will resume provider outreach activities over the next few months.

The demonstration resulted in the return of more than \$900 million in overpayments between 2005 and 2008 and nearly \$38 million in underpayments, according to the CMS.

—Mary Ellen Schneider